HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CYMBALTA safely and effectively. See full prescribing information for CYMBALTA.

CYMBALTA (Duloxetine Delayed-Release Capsules) for Oral Use.
Initial U.S. Approval: 2004

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

- **Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants (5.1)**
- **Monitor for worsening and emergence of suicidal thoughts and behaviors (5.1)**

---------- RECENT MAJOR CHANGES ----------
Warnings and Precautions (5.5) 10/2019

---------- INDICATIONS AND USAGE ----------

CYMBALTA® is a serotonin and norepinephrine reuptake inhibitor (SNRI) indicated for:
- Major Depressive Disorder (MDD) (1)
- Generalized Anxiety Disorder (GAD) (1)
- Diabetic Peripheral Neuropathic Pain (DPNP) (1)
- Fibromyalgia (FM) (1)
- Chronic Musculoskeletal Pain (1)

----------DOSAGE AND ADMINISTRATION----------
- Take CYMBALTA once daily, with or without food. Swallow CYMBALTA whole; do not crush or chew, do not open capsule. Take a missed dose as soon as it is remembered. Do not take two doses of CYMBALTA at the same time (2)

Indication	Starting Dose	Target Dose	Maximum Dose
MDD (2.1)	40 mg/day to 60 mg/day	Acute Treatment: 40 mg/day (20 mg twice daily) to 60 mg/day (once daily or as 30 mg twice daily); Maintenance Treatment: 60 mg/day	120 mg/day
GAD (2.2)			
Adults	60 mg/day	60 mg/day (once daily)	120 mg/day
Elderly	30 mg/day	60 mg/day (once daily)	120 mg/day
Children and Adolescents (7 to 17 years of age)	30 mg/day	30 to 60 mg/day (once daily)	120 mg/day
DPNP (2.3)	60 mg/day	60 mg/day (once daily)	60 mg/day
FM (2.4)	30 mg/day	60 mg/day (once daily)	60 mg/day
Chronic Musculoskeletal Pain (2.5)	30 mg/day	60 mg/day (once daily)	60 mg/day

- Some patients may benefit from starting at 30 mg once daily (2)
- There is no evidence that doses greater than 60 mg/day confers additional benefit, while some adverse reactions were observed to be dose-dependent (2)
- Discontinuing CYMBALTA: Gradually reduce dosage to avoid discontinuation symptoms (2.7, 5.7)
- Hepatic Impairment: Avoid use in patients with chronic liver disease or cirrhosis (5.14)
- Renal Impairment: Avoid use in patients with severe renal impairment, GFR <30 mL/min (5.14)

----------DOSAGE FORMS AND STRENGTHS----------

20 mg, 30 mg, and 60 mg delayed-release capsules (3)

---------- CONTRAINDICATIONS ----------
- Serotonin Syndrome and MAOIs: Do not use MAOIs intended to treat psychiatric disorders with CYMBALTA or within 5 days of stopping treatment with CYMBALTA. Do not use CYMBALTA within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start CYMBALTA in a patient who is being treated with linezolid or intravenous methylene blue (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Hepatotoxicity: Hepatic failure, sometimes fatal, has been reported in patients treated with CYMBALTA. CYMBALTA should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established. CYMBALTA should not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease (5.2)
- Orthostatic Hypotension, Falls and Syncope: Cases have been reported with CYMBALTA therapy (5.3)
- Serotonin Syndrome: Increased risk when co-administered with other serotonergic agents (e.g., SSRIs, SNRIs, triptans), but also when taken alone. If it occurs, discontinue CYMBALTA and initiate supportive treatment (5.4)
- Increased Risk of Bleeding: CYMBALTA may increase the risk of bleeding events. Concomitant use of NSAIDs, aspirin, other antiplatelet drugs, warfarin, and anticoagulants may increase this risk (5.5, 7.4, 8.1)
- Severe Skin Reactions: Severe skin reactions, including erythema multiforme and Stevens-Johnson Syndrome (SJS), can occur with CYMBALTA. CYMBALTA should be discontinued at the first appearance of blisters, peeling rash, mucosal erosions, or any other sign of hypersensitivity if no other etiology can be identified (5.6)
- Discontinuation: Taper dose when possible and monitor for discontinuation symptoms (5.7)
- Activation of mania or hypomania has occurred (5.8)
- Angle-Closure Glaucoma: Angle-closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants (5.9)
- Seizures: Prescribe with care in patients with a history of seizure disorder (5.10)
- Blood Pressure: Monitor blood pressure prior to initiating treatment and periodically throughout treatment (5.11)
- Inhibitors of CYP1A2 or Thioridazine: Should not administer with CYMBALTA (5.12)
- Hyponatremia: Can occur in association with SIADH. Cases of hyponatremia have been reported (5.13)
- Glucose Control in Diabetes: In diabetic peripheral neuropathic pain patients, small increases in fasting blood glucose, and HbA_{1c} have been observed (5.14)
- Conditions that Slow Gastric Emptying: Use cautiously in these patients (5.14)

---------- ADVERSE REACTIONS ----------
- Most common adverse reactions (≥5% and at least twice the incidence of placebo patients): nausea, dry mouth, somnolence, constipation, decreased appetite, and hyperhidrosis (6.3)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------
- Potent inhibitors of CYP1A2 should be avoided (7.1)
- Potent inhibitors of CYP2D6 may increase CYMBALTA concentrations (7.2)
- CYMBALTA is a moderate inhibitor of CYP2D6 (7.9)

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: Third trimester use may increase risk for symptoms of poor adaptation (respiratory distress, temperature instability, feeding difficulty, hypotonia, tremor, irritability) in the neonate (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide.

Revised: 10/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older *[see Warnings and Precautions (5.1)]*.

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

CYMBALTA® is indicated for the treatment of:

- Major Depressive Disorder *[see Clinical Studies (14.1)]*
- Generalized Anxiety Disorder *[see Clinical Studies (14.2)]*
- Diabetic Peripheral Neuropathy *[see Clinical Studies (14.3)]*
- Fibromyalgia *[see Clinical Studies (14.4)]*
- Chronic Musculoskeletal Pain *[see Clinical Studies (14.5)]*

2 DOSAGE AND ADMINISTRATION

Swallow CYMBALTA whole. Do not chew or crush. Do not open the capsule and sprinkle its contents on food or mix with liquids. All of these might affect the enteric coating. CYMBALTA can be given without regard to meals. If a dose of CYMBALTA is missed, take the missed dose as soon as it is remembered. If it is almost time for the next dose, skip the missed dose and take the next dose at the regular time. Do not take two doses of CYMBALTA at the same time.

2.1 Dosage for Treatment of Major Depressive Disorder

Administer CYMBALTA at a total dose of 40 mg/day (given as 20 mg twice daily) to 60 mg/day (given either once daily or as 30 mg twice daily). For some patients, it may be desirable to start at 30 mg once daily for 1 week, to allow patients to adjust to the medication before increasing to 60 mg once daily. While a 120 mg/day dose was shown to be effective, there is no evidence that doses greater than 60 mg/day confer any additional benefits. The safety of doses above 120 mg/day has not been adequately evaluated. Periodically reassess to determine the need for maintenance treatment and the appropriate dose for such treatment *[see Clinical Studies (14.1)]*.

2.2 Dosage for Treatment of Generalized Anxiety Disorder

Adults — For most patients, initiate CYMBALTA 60 mg once daily. For some patients, it may be desirable to start at 30 mg once daily for 1 week, to allow patients to adjust to the medication before increasing to 60 mg once daily. While a 120 mg once daily dose was shown to be effective, there is no evidence that doses greater than 60 mg/day confer additional benefit. Nevertheless, if a decision is made to increase the dose beyond 60 mg once daily, increase dose in increments of 30 mg once daily. The safety of doses above 120 mg once daily has not been adequately evaluated. Periodically reassess to determine the continued need for maintenance treatment and the appropriate dose for such treatment *[see Clinical Studies (14.2)]*.

Elderly — Initiate CYMBALTA at a dose of 30 mg once daily for 2 weeks before considering an increase to the target dose of 60 mg. Thereafter, patients may benefit from doses above 60 mg once daily. If a decision is made to increase the dose beyond 60 mg once daily, increase dose in increments of 30 mg once daily. The maximum dose studied was 120 mg per day. Safety of doses above 120 mg once daily has not been adequately evaluated *[see Clinical Studies (14.2)]*.

Children and Adolescents (7 to 17 years of age) — Initiate CYMBALTA at a dose of 30 mg once daily for 2 weeks before considering an increase to 60 mg. The recommended dose range is 30 to 60 mg once daily. Some patients may benefit from doses above 60 mg once daily. If a decision is made to increase the dose beyond 60 mg once daily, increase dose in increments of 30 mg once daily. The maximum dose studied was 120 mg per day. The safety of doses above 120 mg once daily has not been evaluated *[see Clinical Studies (14.2)]*.

2.3 Dosage for Treatment of Diabetic Peripheral Neuropathic Pain

Administer CYMBALTA 60 mg once daily. There is no evidence that doses higher than 60 mg confer additional significant benefit and the higher dose is clearly less well tolerated *[see Clinical Studies (14.3)]*. For patients for whom tolerability is a concern, a lower starting dose may be considered.

Since diabetes is frequently complicated by renal disease, consider a lower starting dose and gradual increase in dose for patients with renal impairment *[see Dosage and Administration (2.6), Use in Specific Populations (8.10), and Clinical Pharmacology (12.3)]*.

2.4 Dosage for Treatment of Fibromyalgia

Administer CYMBALTA 60 mg once daily. Begin treatment at 30 mg once daily for 1 week, to allow patients to adjust to the medication before increasing to 60 mg once daily. Some patients may respond to the starting dose. There is

no evidence that doses greater than 60 mg/day confer additional benefit, even in patients who do not respond to a 60 mg dose, and higher doses are associated with a higher rate of adverse reactions *[see Clinical Studies (14.4)]*.

2.5 Dosage for Treatment of Chronic Musculoskeletal Pain

Administer CYMBALTA 60 mg once daily. Begin treatment at 30 mg for one week, to allow patients to adjust to the medication before increasing to 60 mg once daily. There is no evidence that higher doses confer additional benefit, even in patients who do not respond to a 60 mg dose, and higher doses are associated with a higher rate of adverse reactions *[see Clinical Studies (14.5)]*.

2.6 Dosing in Special Populations

Hepatic Impairment — Avoid use in patients with chronic liver disease or cirrhosis *[see Warnings and Precautions (5.14) and Use in Specific Populations (8.9)]*.

Severe Renal Impairment — Avoid use in patients with severe renal impairment, GFR <30 mL/min *[see Warnings and Precautions (5.14) and Use in Specific Populations (8.10)]*.

2.7 Discontinuing CYMBALTA

Adverse reactions after discontinuation of CYMBALTA, after abrupt or tapered discontinuation, include: dizziness, headache, nausea, diarrhea, paresthesia, irritability, vomiting, insomnia, anxiety, hyperhidrosis, and fatigue. A gradual reduction in dosage rather than abrupt cessation is recommended whenever possible *[see Warnings and Precautions (5.7)]*.

2.8 Switching a Patient to or from a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders

At least 14 days should elapse between discontinuation of an MAOI intended to treat psychiatric disorders and initiation of therapy with CYMBALTA. Conversely, at least 5 days should be allowed after stopping CYMBALTA before starting an MAOI intended to treat psychiatric disorders *[see Contraindications (4)].*

2.9 Use of CYMBALTA with Other MAOIs such as Linezolid or Methylene Blue

Do not start CYMBALTA in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome. In a patient who requires more urgent treatment of a psychiatric condition, other interventions, including hospitalization, should be considered *[see Contraindications (4)].*

In some cases, a patient already receiving CYMBALTA therapy may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of linezolid or intravenous methylene blue treatment are judged to outweigh the risks of serotonin syndrome in a particular patient, CYMBALTA should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for 5 days or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with CYMBALTA may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue *[see Warnings and Precautions (5.4)]*.

The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg/kg with CYMBALTA is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use *[see Warnings and Precautions (5.4)]*.

3 DOSAGE FORMS AND STRENGTHS

CYMBALTA is available as delayed release capsules:
20 mg opaque green capsules imprinted with “Lilly 3235 20mg”
30 mg opaque white and blue capsules imprinted with “Lilly 3240 30mg”
60 mg opaque green and blue capsules imprinted with “Lilly 3270 60mg”

4 CONTRAINDICATIONS

Monoamine Oxidase Inhibitors (MAOIs) — The use of MAOIs intended to treat psychiatric disorders with CYMBALTA or within 5 days of stopping treatment with CYMBALTA is contraindicated because of an increased risk of serotonin syndrome. The use of CYMBALTA within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated *[see Dosage and Administration (2.8) and Warnings and Precautions (5.4)]*.

Starting CYMBALTA in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome *[see Dosage and Administration (2.9) and Warnings and Precautions (5.4)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.

Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk of differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

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

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

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that discontinuation can be associated with certain symptoms *[see Dosage and Administration (2.7) and Warnings and Precautions (5.7) for descriptions of the risks of discontinuation of CYMBALTA]*.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for CYMBALTA should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder — A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that CYMBALTA is not approved for use in treating bipolar depression.

5.2 Hepatotoxicity

There have been reports of hepatic failure, sometimes fatal, in patients treated with CYMBALTA. These cases have presented as hepatitis with abdominal pain, hepatomegaly, and elevation of transaminase levels to more than twenty times the upper limit of normal with or without jaundice, reflecting a mixed or hepatocellular pattern of liver injury. CYMBALTA should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established.

Cases of cholestatic jaundice with minimal elevation of transaminase levels have also been reported. Other postmarketing reports indicate that elevated transaminases, bilirubin, and alkaline phosphatase have occurred in patients with chronic liver disease or cirrhosis.

CYMBALTA increased the risk of elevation of serum transaminase levels in development program clinical trials. Liver transaminase elevations resulted in the discontinuation of 0.3% (92/34,756) of CYMBALTA-treated patients. In most patients, the median time to detection of the transaminase elevation was about two months. In adult placebo-controlled trials in any indication, for patients with normal and abnormal baseline ALT values, elevation of ALT >3 times the upper limit of normal occurred in 1.25% (144/11,496) of CYMBALTA-treated patients compared to 0.45% (39/8716) of placebo-treated patients. In adult placebo-controlled studies using a fixed dose design, there was evidence of a dose response relationship for ALT and AST elevation of >3 times the upper limit of normal and >5 times the upper limit of normal, respectively.

Because it is possible that CYMBALTA and alcohol may interact to cause liver injury or that CYMBALTA may aggravate pre-existing liver disease, CYMBALTA should not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

5.3 Orthostatic Hypotension, Falls and Syncope

Orthostatic hypotension, falls and syncope have been reported with therapeutic doses of CYMBALTA. Syncope and orthostatic hypotension tend to occur within the first week of therapy but can occur at any time during CYMBALTA treatment, particularly after dose increases. The risk of falling appears to be related to the degree of orthostatic decrease in blood pressure as well as other factors that may increase the underlying risk of falls.

In an analysis of patients from all placebo-controlled trials, patients treated with CYMBALTA reported a higher rate of falls compared to patients treated with placebo. Risk appears to be related to the presence of orthostatic decrease in blood pressure. The risk of blood pressure decreases may be greater in patients taking concomitant medications that induce orthostatic hypotension (such as antihypertensives) or are potent CYP1A2 inhibitors *[see Warnings and Precautions (5.12) and Drug Interactions (7.1)]* and in patients taking CYMBALTA at doses above 60 mg daily. Consideration should be given to dose reduction or discontinuation of CYMBALTA in patients who experience symptomatic orthostatic hypotension, falls and/or syncope during CYMBALTA therapy.

Risk of falling also appeared to be proportional to a patient's underlying risk for falls and appeared to increase steadily with age. As elderly patients tend to have a higher underlying risk for falls due to a higher prevalence of risk factors such as use of multiple medications, medical comorbidities and gait disturbances, the impact of increasing age by itself is unclear. Falls with serious consequences including bone fractures and hospitalizations have been reported *[see Adverse Reactions (6.10) and Patient Counseling Information (17)]*.

5.4 Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs and SSRIs, including CYMBALTA, alone but particularly with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, and St. John's Wort) and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Serotonin syndrome symptoms 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 symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of CYMBALTA with MAOIs intended to treat psychiatric disorders is contraindicated. CYMBALTA should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking CYMBALTA. CYMBALTA should be discontinued before initiating treatment with the MAOI *[see Dosage and Administration (2.8, 2.9), and Contraindications (4)]*.

If concomitant use of CYMBALTA with other serotonergic drugs including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan, amphetamines, and St. John's Wort is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases. Treatment with CYMBALTA and any concomitant serotonergic agents, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

5.5 Increased Risk of Bleeding

Drugs that interfere with serotonin reuptake inhibition, including CYMBALTA, may increase the risk of bleeding events. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. A post-marketing study showed a higher incidence of postpartum hemorrhage in mothers taking duloxetine. Other bleeding events related to SSRI and SNRI use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anti-coagulants may add to this risk.

Inform patients about the risk of bleeding associated with the concomitant use of CYMBALTA and NSAIDs, aspirin, or other drugs that affect coagulation *[see Drug Interactions (7.4)]*.

5.6 Severe Skin Reactions

Severe skin reactions, including erythema multiforme and Stevens-Johnson Syndrome (SJS), can occur with CYMBALTA. The reporting rate of SJS associated with CYMBALTA use exceeds the general population background incidence rate for this serious skin reaction (1 to 2 cases per million person years). The reporting rate is generally accepted to be an underestimate due to underreporting.

CYMBALTA should be discontinued at the first appearance of blisters, peeling rash, mucosal erosions, or any other sign of hypersensitivity if no other etiology can be identified.

5.7 Discontinuation of Treatment with CYMBALTA

Discontinuation symptoms have been systematically evaluated in patients taking CYMBALTA. Following abrupt or tapered discontinuation in adult placebo-controlled clinical trials, the following symptoms occurred at 1% or greater and at a significantly higher rate in CYMBALTA-treated patients compared to those discontinuing from placebo: dizziness, headache, nausea, diarrhea, paresthesia, irritability, vomiting, insomnia, anxiety, hyperhidrosis, and fatigue.

During marketing of other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Although these events are generally self-limiting, some have been reported to be severe.

Patients should be monitored for these symptoms when discontinuing treatment with CYMBALTA. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate *[see Dosage and Administration (2.7)]*.

5.8 Activation of Mania/Hypomania

In adult placebo-controlled trials in patients with major depressive disorder, activation of mania or hypomania was reported in 0.1% (4/3779) of CYMBALTA-treated patients and 0.04% (1/2536) of placebo-treated patients. No activation of mania or hypomania was reported in DPNP, GAD, fibromyalgia, or chronic musculoskeletal pain placebo-controlled trials. Activation of mania or hypomania has been reported in a small proportion of patients with mood disorders who were treated with other marketed drugs effective in the treatment of major depressive disorder. As with these other agents, CYMBALTA should be used cautiously in patients with a history of mania.

5.9 Angle-Closure Glaucoma

The pupillary dilation that occurs following use of many antidepressant drugs including CYMBALTA may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

5.10 Seizures

CYMBALTA has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. In adult placebo-controlled clinical trials, seizures/convulsions occurred in 0.02% (3/12,722) of patients treated with CYMBALTA and 0.01% (1/9513) of patients treated with placebo. CYMBALTA should be prescribed with care in patients with a history of a seizure disorder.

5.11 Effect on Blood Pressure

In adult placebo-controlled clinical trials across indications from baseline to endpoint, CYMBALTA treatment was associated with mean increases of 0.5 mm Hg in systolic blood pressure and 0.8 mm Hg in diastolic blood pressure compared to mean decreases of 0.6 mm Hg systolic and 0.3 mm Hg diastolic in placebo-treated patients. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure. In a clinical pharmacology study designed to evaluate the effects of CYMBALTA on various parameters, including blood pressure at supratherapeutic doses with an accelerated dose titration, there was evidence of increases in supine blood pressure at doses up to 200 mg twice daily. At the highest 200 mg twice daily dose, the increase in mean pulse rate was 5.0 to 6.8 beats and increases in mean blood pressure were 4.7 to 6.8 mm Hg (systolic) and 4.5 to 7 mm Hg (diastolic) up to 12 hours after dosing.

Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment *[see Adverse Reactions (6.7)]*.

5.12 Clinically Important Drug Interactions

Both CYP1A2 and CYP2D6 are responsible for CYMBALTA metabolism.

Potential for Other Drugs to Affect CYMBALTA

CYP1A2 Inhibitors — Co-administration of CYMBALTA with potent CYP1A2 inhibitors should be avoided *[see Drug Interactions (7.1)]*.

CYP2D6 Inhibitors — Because CYP2D6 is involved in CYMBALTA metabolism, concomitant use of CYMBALTA with potent inhibitors of CYP2D6 would be expected to, and does, result in higher concentrations (on average of 60%) of CYMBALTA *[see Drug Interactions (7.2)]*.

Potential for CYMBALTA to Affect Other Drugs

Drugs Metabolized by CYP2D6 — Co-administration of CYMBALTA with drugs that are extensively metabolized by CYP2D6 and that have a narrow therapeutic index, including certain antidepressants (tricyclic antidepressants [TCAs], such as nortriptyline, amitriptyline, and imipramine), phenothiazines and Type 1C antiarrhythmics (e.g., propafenone, flecainide), should be approached with caution. Plasma TCA concentrations may need to be monitored and the dose of the TCA may need to be reduced if a TCA is co-administered with CYMBALTA. Because of the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, CYMBALTA and thioridazine should not be co-administered *[see Drug Interactions (7.9)]*.

Other Clinically Important Drug Interactions

Alcohol — Use of CYMBALTA concomitantly with heavy alcohol intake may be associated with severe liver injury. For this reason, CYMBALTA should not be prescribed for patients with substantial alcohol use *[see Warnings and Precautions (5.2) and Drug Interactions (7.15)]*.

CNS Acting Drugs — Given the primary CNS effects of CYMBALTA, it should be used with caution when it is taken in combination with or substituted for other centrally acting drugs, including those with a similar mechanism of action *[see Warnings and Precautions (5.12) and Drug Interactions (7.16)]*.

5.13 Hyponatremia

Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including CYMBALTA. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported and appeared to be reversible when CYMBALTA was discontinued. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk *[see Use in Specific Populations (8.5)]*. Discontinuation of CYMBALTA should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. More severe and/or acute cases have been associated with hallucination, syncope, seizure, coma, respiratory arrest, and death.

5.14 Use in Patients with Concomitant Illness

Clinical experience with CYMBALTA in patients with concomitant systemic illnesses is limited. There is no information on the effect that alterations in gastric motility may have on the stability of CYMBALTA's enteric coating. In extremely acidic conditions, CYMBALTA, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using CYMBALTA in patients with conditions that may slow gastric emptying (e.g., some diabetics).

CYMBALTA has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable coronary artery disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing.

Hepatic Impairment — Avoid use in patients with chronic liver disease or cirrhosis *[see Dosage and Administration (2.6), Warnings and Precautions (5.2), and Use in Specific Populations (8.9)]*.

Severe Renal Impairment — Avoid use in patients with severe renal impairment, GFR <30 mL/min. Increased plasma concentration of CYMBALTA, and especially of its metabolites, occur in patients with end-stage renal disease (requiring dialysis) *[see Dosage and Administration (2.6) and Use in Specific Populations (8.10)]*.

Glycemic Control in Patients with Diabetes — As observed in DPNP trials, CYMBALTA treatment worsens glycemic control in some patients with diabetes. In three clinical trials of CYMBALTA for the management of neuropathic pain associated with diabetic peripheral neuropathy, the mean duration of diabetes was approximately 12 years, the mean baseline fasting blood 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 and by 0.2% in the routine care groups.

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)]*
- Abnormal Bleeding *[see Warnings and Precautions (5.5)]*
- Severe Skin Reactions *[see Warnings and Precautions (5.6)]*
- Discontinuation of Treatment with CYMBALTA *[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)]*
- Effect on 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 Studies 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 individuals who experienced, at least once, a 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. Reactions reported during the studies were not necessarily caused by the therapy, and the frequencies do not reflect investigator impression (assessment) of causality.

Adults — The data described below reflect exposure to CYMBALTA in placebo-controlled trials for MDD (N=3779), GAD (N=1018), OA (N=503), CLBP (N=600), DPNP (N=906), and FM (N=1294). The population studied was 17 to 89 years of age; 65.7%, 60.8%, 60.6%, 42.9%, and 94.4% female; and 81.8%, 72.6%, 85.3%, 74.0%, and 85.7% Caucasian for MDD, GAD, OA and CLBP, DPNP, and FM, respectively. Most patients received doses of a total of 60 to 120 mg per day *[see Clinical Studies (14)]*.The data below do not include results of the trial examining the efficacy of CYMBALTA in patients ≥ 65 years old for the treatment of generalized anxiety disorder; however, the adverse reactions observed in this geriatric sample were generally similar to adverse reactions in the overall adult population.

Children and Adolescents — The data described below reflect exposure to CYMBALTA in pediatric, 10-week, placebo-controlled trials for MDD (N=341) and GAD (N=135). The population studied (N=476) was 7 to 17 years of age with 42.4% children age 7 to 11 years of age, 50.6% female, and 68.6% white. Patients received 30-120 mg per day during placebo-controlled acute treatment studies. Additional data come from the overall total of 822 pediatric patients (age 7 to 17 years of age) with 41.7% children age 7 to 11 years of age and 51.8% female exposed to CYMBALTA in MDD and GAD clinical trials up to 36-weeks in length, in which most patients received 30-120 mg per day.

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

Major Depressive Disorder — Approximately 8.4% (319/3779) of the patients who received CYMBALTA in placebo-controlled trials for MDD discontinued treatment due to an adverse reaction, compared with 4.6% (117/2536) of the patients receiving placebo. Nausea (CYMBALTA 1.1%, placebo 0.4%) was the only common 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).

Generalized Anxiety Disorder — Approximately 13.7% (139/1018) of the patients who received CYMBALTA in placebo-controlled trials for GAD discontinued treatment due to an adverse reaction, compared with 5.0% (38/767) for placebo. 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 patients who received CYMBALTA in placebo-controlled trials for DPNP discontinued treatment due to an adverse reaction, compared with 5.1% (23/448) for placebo. 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 0.0%).

Fibromyalgia — Approximately 17.5% (227/1294) of the patients who received CYMBALTA in 3 to 6 month placebo-controlled trials for FM discontinued treatment due to an adverse reaction, compared with 10.1% (96/955) for placebo. Common 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 0.0%), and fatigue (CYMBALTA 1.1%, placebo 0.1%).

Chronic Pain due to Osteoarthritis — Approximately 15.7% (79/503) of the patients who received CYMBALTA in 13-week, placebo-controlled trials for chronic pain due to OA discontinued treatment due to an adverse reaction,

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. The figures are cumulative so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as week 1, which persisted throughout the study. Improvement was also demonstrated on measures of function (Fibromyalgia Impact Questionnaires) and patient global impression of change (PGI). Neither study demonstrated a benefit of 120 mg compared to 60 mg, and a higher dose was associated with more adverse reactions and premature discontinuations of treatment.

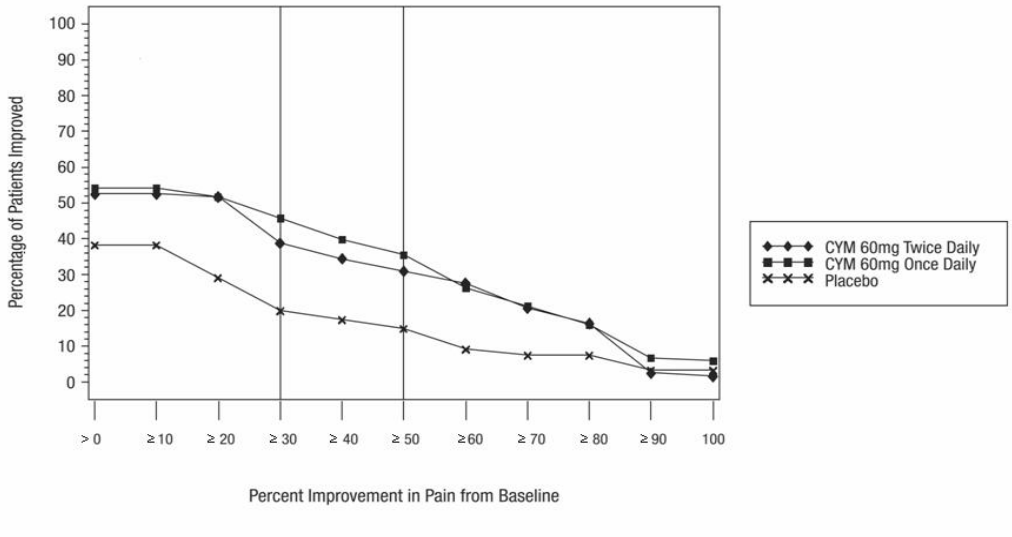

Figure 5: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity - FM-1

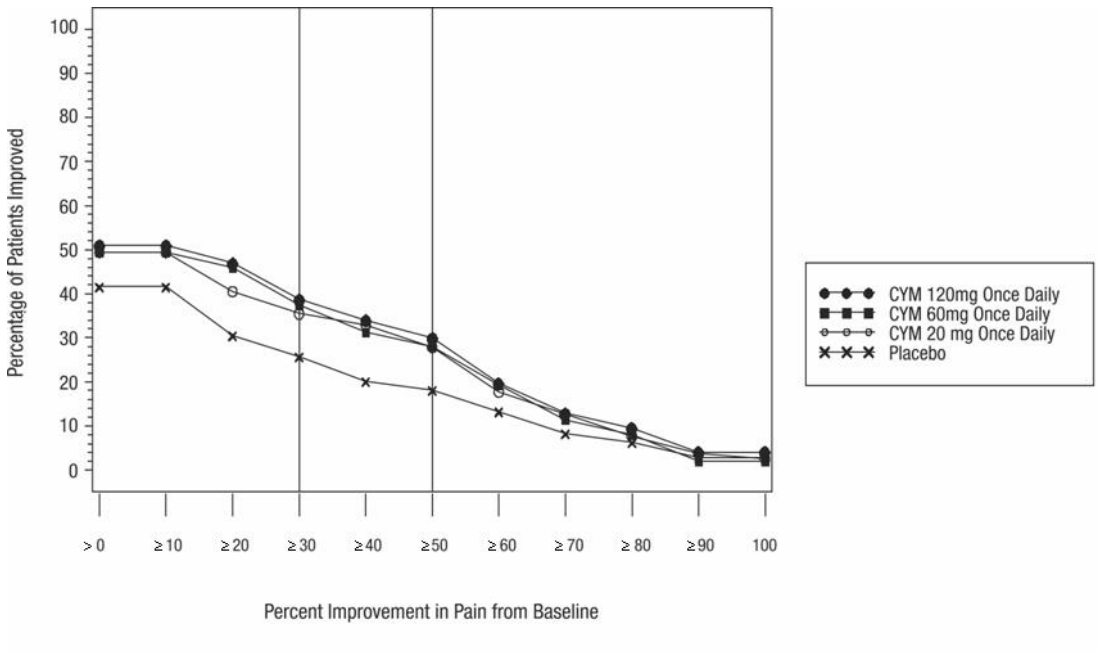

Figure 6: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity - FM-2

Additionally, the benefit of up-titration in non-responders to CYMBALTA at 60 mg/day was evaluated in a separate study. 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. Those patients who were considered non-responders, where response was defined as at least a 30% reduction in pain score from baseline at the end of the 8-week treatment, 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.

14.5 Chronic Musculoskeletal Pain

CYMBALTA is indicated for the management of chronic musculoskeletal pain. This has been established in studies in patients with chronic low back pain and chronic pain due to osteoarthritis.

Studies in Chronic Low Back Pain

The efficacy of CYMBALTA in chronic low back pain (CLBP) was assessed in two double-blind, placebo-controlled, randomized clinical trials of 13-weeks duration (Study CLBP-1 and Study CLBP-2), and one of 12-weeks duration (CLBP-3). CLBP-1 and CLBP-3 demonstrated efficacy of CYMBALTA in the treatment of chronic low back pain. Patients in all studies 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 patients with less than 30% reduction in average daily pain and who were able to tolerate CYMBALTA 60 mg once daily had their dose of CYMBALTA, in a double-blinded fashion, increased to 120 mg once daily for the remainder of the study. 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 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 doses 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 study. After 13 weeks of treatment, none of the three CYMBALTA doses 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 study. 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 placebo.

For various degrees of improvement in pain from baseline to study endpoint, Figures 7 and 8 show the fraction of patients in CLBP-1 and CLBP-3 achieving that degree of improvement. The figures are cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned the value of 0% improvement.

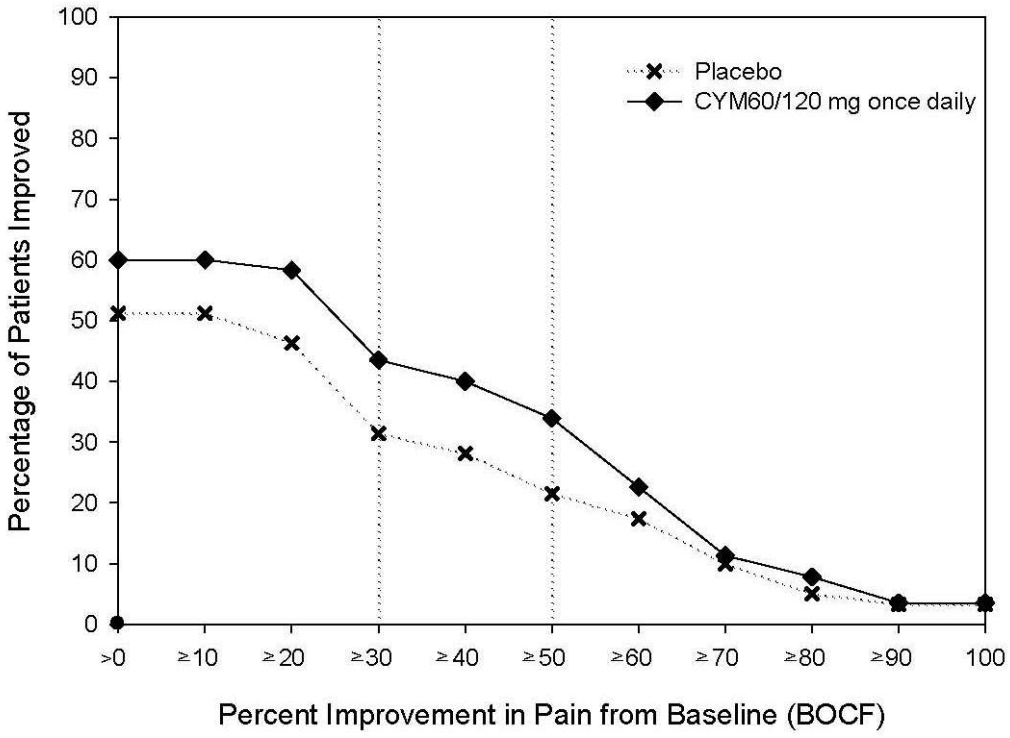

Figure 7: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity – CLBP-1

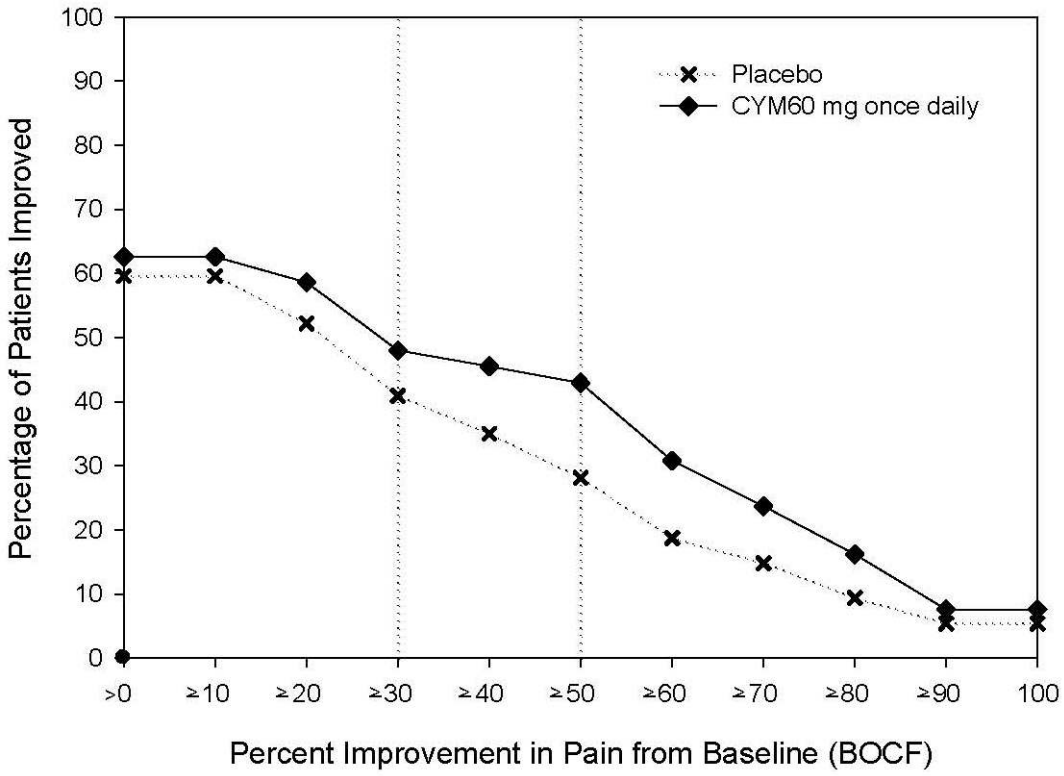

Figure 8: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity – CLBP-3

Studies in Chronic Pain Due to Osteoarthritis

The efficacy of CYMBALTA in chronic pain due to osteoarthritis 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 studies fulfilled the ACR clinical and radiographic criteria for classification of idiopathic osteoarthritis of the knee. Randomization was stratified by the patients' baseline NSAIDs-use status. Patients assigned to CYMBALTA started treatment in both studies 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 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 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 dose increased to 120 mg once daily for the remainder of the study. Patients in the placebo treatment groups in both studies received a matching placebo for the entire duration of studies. For both studies, 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 study. 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. 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 study. 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.

In Study OA-1, for various degrees of improvement in pain from baseline to study endpoint, Figure 7 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 study were assigned the value of 0% improvement.

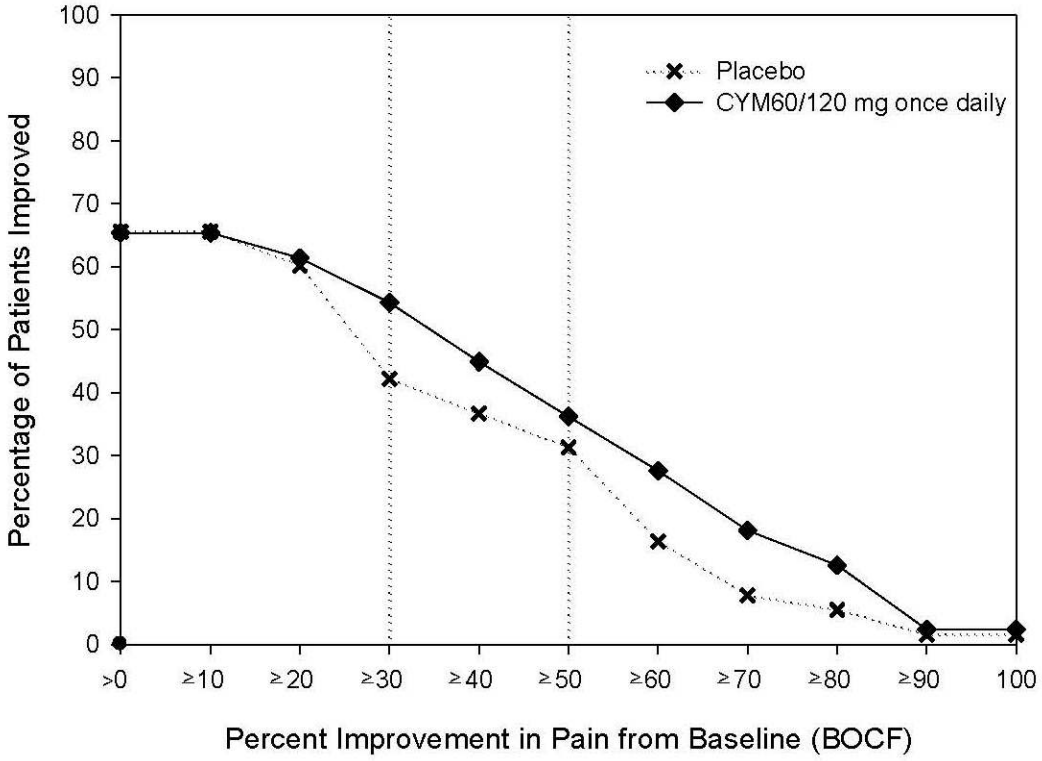

Figure 9: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity – OA-1

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

CYMBALTA is available as delayed release capsules 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)]*.
- CYMBALTA should be swallowed whole and should not be chewed or crushed, nor should the capsule be opened and its contents be sprinkled on food or mixed with liquids. All of these 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. For this reason, CYMBALTA should not be prescribed for patients with substantial alcohol use *[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.
- Abnormal 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 physician *[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 physician 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 physicians 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 (2.8, 2.9), 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 physicians about all of their medical conditions *[see Warnings and Precautions (5.14)]*.
- 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 pregnant women to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with CYMBALTA.
  - Advise patients 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)]*.
- Pediatric Use — Safety and efficacy of CYMBALTA in patients 7 to 17 years of age have been established for the treatment of GAD. The types of adverse reactions observed with CYMBALTA in children and adolescents were generally similar to those observed in adults. The safety and effectiveness of CYMBALTA have not been established in pediatric patients less than 18 years of age with other indications. *[See Use in Specific Populations (8.4)]*.
- Interference with Psychomotor Performance — Any psychoactive drug may impair judgment, thinking, or motor skills. Although in controlled studies CYMBALTA has not been shown to impair psychomotor performance, cognitive function, or memory, it may be associated with sedation and dizziness. Therefore, 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.

Marketed by: Lilly USA, LLC, Indianapolis, IN 46285, USA

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A4.0-CYM-0009-USPI-20191004

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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