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 hydrochloride) Delayed-Release Capsules for Oral Use.

Initial U.S. Approval: 2004

WARNING: Suicidality and Antidepressant Drugs

See full prescribing information for complete boxed warning.

- **Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders. Cymbalta is not approved for use in pediatric patients (5.1).**

----------RECENT MAJOR CHANGES----------

Indications and Usage, Generalized Anxiety Disorder (1.2)	11/2009
Indications and Usage, Chronic Musculoskeletal Pain (1.5)	10/2010
Dosage and Administration, Chronic Musculoskeletal Pain (2.1, 2.2)	10/2010
Dosage and Administration, Maintenance/Continuation/Extended Treatment (2.2)	11/2009
Warnings and Precautions, Effect on Blood Pressure (5.9)	10/2010

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

Cymbalta® is a serotonin and norepinephrine reuptake inhibitor (SNRI) indicated for:

- Major Depressive Disorder (MDD) (1.1)
  Efficacy was established in four short-term and one maintenance trial in adults (14.1).
- Generalized Anxiety Disorder (GAD) (1.2)
  Efficacy was established in three short-term and one maintenance trial in adults (14.2).
- Diabetic Peripheral Neuropathic Pain (DPNP) (1.3)
- Fibromyalgia (FM) (1.4)
- Chronic Musculoskeletal Pain (1.5)

----------DOSAGE AND ADMINISTRATION----------

- Cymbalta should generally be administered once daily without regard to meals. 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 (2.1).

Indication	Starting Dose	Target Dose	Maximum Dose
MDD (2.1, 2.2)	40mg/day to 60mg/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 (2.1)	60 mg/day	60 mg/day (once daily)	120 mg/day
DPNP (2.1)	60 mg/day	60 mg/day (once daily)	60 mg/day
FM (2.1)	30 mg/day	60 mg/day (once daily)	60 mg/day
Chronic Musculoskeletal Pain (2.1)	30 mg/day	60 mg/day (once daily)	60 mg/day

- Some patients may benefit from starting at 30 mg once daily.
- There is no evidence that doses greater than 60 mg/day confers additional benefit, while some adverse reactions were observed to be dose-dependent.
- Discontinuing Cymbalta: A gradual dose reduction is recommended to avoid discontinuation symptoms (5.6).

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

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

----------CONTRAINDICATIONS----------

- Use of a monoamine oxidase inhibitor concomitantly or in close temporal proximity (4.1)
- Use in patients with uncontrolled narrow-angle glaucoma (4.2)

----------WARNINGS AND PRECAUTIONS----------

- Suicidality: Monitor for clinical worsening and suicide risk (5.1).
- 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 and Syncope: Cases have been reported with duloxetine therapy (5.3).
- Serotonin Syndrome, or Neuroleptic Malignant Syndrome (NMS)-like reactions: Serotonin syndrome or NMS-like reactions have been reported with SSRIs and SNRIs. Discontinue Cymbalta and initiate supportive treatment (5.4, 7.14).
- Abnormal Bleeding: Cymbalta may increase the risk of bleeding events. Patients should be cautioned about the risk of bleeding associated with the concomitant use of duloxetine and NSAIDs, aspirin, or other drugs that affect coagulation (5.5, 7.4).
- Discontinuation: May result in symptoms, including dizziness, nausea, headache, paresthesia, fatigue, vomiting, irritability, insomnia, diarrhea, anxiety, and hyperhidrosis(5.6).
- Activation of mania or hypomania has occurred (5.7).
- Seizures: Prescribe with care in patients with a history of seizure disorder (5.8).
- Blood Pressure: Monitor blood pressure prior to initiating treatment and periodically throughout treatment (5.9).
- Inhibitors of CYP1A2 or Thioridazine: Should not administer with Cymbalta (5.10).
- Hyponatremia: Cases of hyponatremia have been reported (5.11).
- Hepatic Insufficiency and Severe Renal Impairment: Should ordinarily not be administered to these patients (5.12).
- Controlled Narrow-Angle Glaucoma: Use cautiously in these patients (5.12).
- Glucose Control in Diabetes: In diabetic peripheral neuropathic pain patients, small increases in fasting blood glucose, HbA_{1c}, and total cholesterol have been observed (5.12).
- Conditions that Slow Gastric Emptying: Use cautiously in these patients (5.12).
- Urinary Hesitation and Retention (5.13).

----------ADVERSE REACTIONS----------

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

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx 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 duloxetine concentrations (7.2).
- Duloxetine is a moderate inhibitor of CYP2D6 (7.9).

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy and Nursing Mothers: Use only if the potential benefit justifies the potential risk to the fetus or child (2.3, 8.1, 8.3).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 10/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Cymbalta or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. 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 in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Cymbalta is not approved for use in pediatric patients. *[see Warnings and Precautions (5.1), Use in Specific Populations (8.4), and Information for Patients (17.2).]*

1 INDICATIONS AND USAGE

1.1 Major Depressive Disorder

Cymbalta is indicated for the treatment of major depressive disorder (MDD). The efficacy of Cymbalta was established in four short term and one maintenance trial in adults *[see Clinical Studies (14.1)]*.

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, or a suicide attempt or suicidal ideation.

1.2 Generalized Anxiety Disorder

Cymbalta is indicated for the treatment of generalized anxiety disorder (GAD). The efficacy of Cymbalta was established in three short-term trials and one maintenance trial in adults *[see Clinical Studies (14.2)]*.

Generalized anxiety disorder is defined by the DSM-IV as excessive anxiety and worry, present more days than not, for at least 6 months. The excessive anxiety and worry must be difficult to control and must cause significant distress or impairment in normal functioning. It must be associated with at least 3 of the following 6 symptoms: restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, and/or sleep disturbance.

1.3 Diabetic Peripheral Neuropathic Pain

Cymbalta is indicated for the management of neuropathic pain (DPNP) associated with diabetic peripheral neuropathy *[see Clinical Studies (14.3)]*.

1.4 Fibromyalgia

Cymbalta is indicated for the management of fibromyalgia (FM) *[see Clinical Studies (14.4)]*.

1.5 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 *[see Clinical Studies (14.5)]*.

2 DOSAGE AND ADMINISTRATION

Cymbalta should be swallowed whole and should not be chewed or crushed, nor should the capsule be opened and its contents sprinkled on food or mixed with liquids. All of these might affect the enteric coating. Cymbalta can be given without regard to meals.

2.1 Initial Treatment

Major Depressive Disorder — Cymbalta should be administered 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 *[see Clinical Studies (14.1)]*.

Generalized Anxiety Disorder — For most patients, the recommended starting dose for Cymbalta is 60 mg administered 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, dose increases should be in increments of 30 mg once daily. The safety of doses above 120 mg once daily has not been adequately evaluated *[see Clinical Studies (14.2)]*.

Diabetic Peripheral Neuropathic Pain — The recommended dose for Cymbalta is 60 mg administered 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, a lower starting dose and gradual increase in dose should be considered for patients with renal impairment *[see Clinical Pharmacology (12.3) and Dosage and Administration (2.3)]*.

Fibromyalgia — The recommended dose for Cymbalta is 60 mg administered once daily. Treatment should begin 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)]*.

Chronic Musculoskeletal Pain — The recommended dose for Cymbalta is 60 mg once daily. Dosing may be started 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)]*.

2.2 Maintenance/Continuation/Extended Treatment

Major Depressive Disorder — It is generally agreed that acute episodes of major depression require several months or longer of sustained pharmacologic therapy. Maintenance of efficacy in MDD was demonstrated with Cymbalta as monotherapy. Cymbalta should be administered at a total dose of 60 mg once daily. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment *[see Clinical Studies (14.1)]*.

Generalized Anxiety Disorder — It is generally agreed that episodes of generalized anxiety disorder require several months or longer of sustained pharmacological therapy. Maintenance of efficacy in GAD was demonstrated with Cymbalta as monotherapy. Cymbalta should be administered in a dose range of 60-120 mg once daily. Patients should be periodically reassessed to determine the continued need for maintenance treatment and the appropriate dose for such treatment *[see Clinical Studies (14.2)]*.

Diabetic Peripheral Neuropathic Pain — As the progression of diabetic peripheral neuropathy is highly variable and management of pain is empirical, the effectiveness of Cymbalta must be assessed individually. Efficacy beyond 12 weeks has not been systematically studied in placebo-controlled trials.

Fibromyalgia — Fibromyalgia is recognized as a chronic condition. The efficacy of Cymbalta in the management of fibromyalgia has been demonstrated in placebo-controlled studies up to 3 months. The efficacy of Cymbalta was not demonstrated in longer studies; however, continued treatment should be based on individual patient response.

Chronic Musculoskeletal Pain — The efficacy of Cymbalta has not been established in placebo-controlled studies beyond 13 weeks.

2.3 Dosing in Special Populations

Hepatic Insufficiency — It is recommended that Cymbalta should ordinarily not be administered to patients with any hepatic insufficiency *[see Warnings and Precautions (5.12) and Use in Specific Populations (8.9)]*.

Severe Renal Impairment — Cymbalta is not recommended for patients with end-stage renal disease or severe renal impairment (estimated creatinine clearance <30 mL/min) *[see Warnings and Precautions (5.12) and Use in Specific Populations (8.10)]*.

Elderly Patients — No dose adjustment is recommended for elderly patients on the basis of age. As with any drug, caution should be exercised in treating the elderly. When individualizing the dosage in elderly patients, extra care should be taken when increasing the dose *[see Use in Specific Populations (8.5)]*.

Pregnant Women — There are no adequate and well-controlled studies in pregnant women; therefore, Cymbalta should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus *[see Use in Specific Populations (8.1)]*.

Nursing Mothers — Because the safety of duloxetine in infants is not known, nursing while on Cymbalta is not recommended *[see Use in Specific Populations (8.3)]*.

2.4 Discontinuing Cymbalta

Symptoms associated with discontinuation of Cymbalta and other SSRIs and SNRIs have been reported. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible *[see Warnings and Precautions (5.6)]*.

2.5 Switching Patients to or from a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Cymbalta. In addition, at least 5 days should be allowed after stopping Cymbalta before starting an MAOI *[see Contraindications (4.1) and Warnings and Precautions (5.4)]*.

3 DOSAGE FORMS AND STRENGTHS

Cymbalta is available as delayed release capsules:
20mg opaque green capsules imprinted with “Lilly 3235 20mg”
30mg opaque white and blue capsules imprinted with “Lilly 3240 30mg”
60mg opaque green and blue capsules imprinted with “Lilly 3237 60mg”
60mg opaque green and blue capsules imprinted with “Lilly 3270 60mg”

4 CONTRAINDICATIONS

4.1 Monoamine Oxidase Inhibitors

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated due to the risk of serious, sometimes fatal, drug interactions with serotonergic drugs. These interactions may include hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued serotonin reuptake inhibitors and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome *[see Dosage and Administration (2.5) and Warnings and Precautions (5.4)]*.

4.2 Uncontrolled Narrow-Angle Glaucoma

In clinical trials, Cymbalta use was associated with an increased risk of mydriasis; therefore, its use should be avoided in patients with uncontrolled narrow-angle glaucoma *[see Warnings and Precautions (5.12)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant 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

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