

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 Antidepressants
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**-----

WARNING: Suicidality and Antidepressants (*Boxed Warning*) 6/2007
 Indications and Usage, Generalized Anxiety Disorder (1.3) 2/2007
 Warnings and Precautions, Abnormal Bleeding (5.5) MM/2007
 Warnings and Precautions, Clinical Worsening and Suicide Risk (5.1) 6/2007
 Warnings and Precautions, Orthostatic Hypotension and Syncope (5.3), Serotonin Syndrome (5.4), Effect on Blood Pressure (5.9), Hyponatremia (5.11) 10/2006

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

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

- Major Depressive Disorder (1.1)
- Diabetic Peripheral Neuropathic Pain (1.2)
- Generalized Anxiety Disorder (1.3)

-----**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	Recommended Dose
MDD (2.1, 2.2)	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
DPNP (2.1)	60 mg/day (once daily)
GAD (2.1)	60 mg/day (once daily)

- 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 adverse reactions such as dizziness, fatigue, somnolence, constipation, and decreased appetite were observed to be dose-dependent.
- Discontinuing Cymbalta: a gradual dose reduction is recommended.

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

- 20, 30, 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: Elevated transaminases, bilirubin and alkaline phosphatase, some severe, have occurred. Cymbalta should ordinarily 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: Serotonin syndrome has been reported with SSRIs and SNRIs (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).
- Abrupt discontinuation: may result in symptoms, including dizziness, paresthesia, irritability, and headache (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, HbA1c, 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, 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 the FDA approved Medication Guide (17.1)

Revised: MM/YYYY

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

1 **FULL PRESCRIBING INFORMATION**
2

3 **WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS**

4 **Antidepressants increased the risk compared to placebo of suicidal thinking and behavior**
5 **(suicidality) in children, adolescents, and young adults in short-term studies of major depressive**
6 **disorder (MDD) and other psychiatric disorders. Anyone considering the use of Cymbalta or any**
7 **other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical**
8 **need. Short-term studies did not show an increase in the risk of suicidality with antidepressants**
9 **compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants**
10 **compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders**
11 **are themselves associated with increases in the risk of suicide. Patients of all ages who are started on**
12 **antidepressant therapy should be monitored appropriately and observed closely for clinical**
13 **worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of**
14 **the need for close observation and communication with the prescriber. Cymbalta is not approved for**
15 **use in pediatric patients. [see Warnings and Precautions (5.1) Use in Specific Populations (8.4) and**
16 **Information for Patients (17.2).]**

17
18 **1 INDICATIONS AND USAGE**
19

20 **1.1 Major Depressive Disorder**

21 Cymbalta is indicated for the acute and maintenance treatment of major depressive disorder (MDD) [*see*
22 *Clinical Studies (14.1)*].

23 A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every
24 day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning,
25 and includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual
26 activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor
27 agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or
28 impaired concentration, or a suicide attempt or suicidal ideation.
29

30 **1.2 Diabetic Peripheral Neuropathic Pain**

31 Cymbalta is indicated for the management of neuropathic pain associated with diabetic peripheral
32 neuropathy [*see Clinical Studies (14.2)*].
33

34 **1.3 Generalized Anxiety Disorder**

35 Cymbalta is indicated for the acute treatment of generalized anxiety disorder (GAD) [*see Clinical*
36 *Studies (14.3)*].

37 Generalized anxiety disorder is defined by the DSM-IV as excessive anxiety and worry, present
38 more days than not, for at least 6 months. The excessive anxiety and worry must be difficult to control
39 and must cause significant distress or impairment in normal functioning. It must be associated with at
40 least 3 of the following 6 symptoms: restlessness or feeling keyed up or on edge, being easily fatigued,
41 difficulty concentrating or mind going blank, irritability, muscle tension, and/or sleep disturbance.
42

43 **2 DOSAGE AND ADMINISTRATION**

44 Cymbalta should be swallowed whole and should not be chewed or crushed, nor should the capsule be
45 opened and its contents sprinkled on food or mixed with liquids. All of these might affect the enteric
46 coating. Cymbalta should be given without regard to meals.
47

48 **2.1 Initial Treatment**

49 Major Depressive Disorder - Cymbalta should be administered at a total dose of 40 mg/day (given as
50 20 mg twice daily) to 60 mg/day (given either once daily or as 30 mg twice daily). For some patients, it
51 may be desirable to start at 30 mg once daily for 1 week, to allow patients to adjust to the medication
52 before increasing to 60 mg once daily. While a 120 mg/day dose was shown to be effective, there is no
53 evidence that doses greater than 60 mg/day confer any additional benefits. The safety of doses above 120
54 mg once daily has not been adequately evaluated [*see Clinical Studies (14.1)*].

55 Diabetic Peripheral Neuropathic Pain - Cymbalta should be administered at a total dose of 60 mg/day
56 given once a day.

57 While a 120 mg/day dose was shown to be safe and effective, there is no evidence that doses higher
58 than 60 mg confer additional significant benefit, and the higher dose is clearly less well tolerated [*see*
59 *Clinical Studies (14.2)*]. For patients for whom tolerability is a concern, a lower starting dose may be
60 considered. Since diabetes is frequently complicated by renal disease, a lower starting dose and gradual
61 increase in dose should be considered for patients with renal impairment [*see Clinical Pharmacology*
62 *(12.3) and Dosing in Special Populations (2.3)*].

63 Generalized Anxiety Disorder - For most patients, the recommended starting dose for Cymbalta is
64 60 mg administered once daily. For some patients, it may be desirable to start at 30 mg once daily for
65 1 week, to allow patients to adjust to the medication before increasing to 60 mg once daily. While a
66 120 mg once daily dose was shown to be effective, there is no evidence that doses greater than 60
67 mg/day confer additional benefit. Nevertheless, if a decision is made to increase the dose beyond 60
68 mg once daily, dose increases should be in increments of 30 mg once daily. The safety of doses above
69 120 mg once daily has not been adequately evaluated [*see Clinical Studies (14.3)*]
70

71 **2.2 Maintenance/Continuation/Extended Treatment**

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

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

79 Generalized Anxiety Disorder — Generalized anxiety disorder is recognized as a chronic condition. The
80 efficacy of Cymbalta in the treatment of GAD, that is, beyond 10 weeks, has not been systematically
81 studied. The physician who elects to use Cymbalta for extended periods should periodically evaluate the
82 long-term usefulness of the drug for the individual patient.
83

84 **2.3 Dosing in Special Populations**

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

88 Severe Renal Impairment — Cymbalta is not recommended for patients with end-stage renal disease or
89 severe renal impairment (estimated creatinine clearance <30 mL/min) [*see Warnings and Precautions*
90 *(5.12) and Use in Specific Populations (8.10)*].

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

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

97 Nursing Mothers — Because the safety of duloxetine in infants is not known, nursing while on Cymbalta
98 is not recommended [*see Use in Specific Populations (8.3)*].
99

100 **2.4 Discontinuing Cymbalta**

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

104

105 **2.5 Switching Patients to or from a Monoamine Oxidase Inhibitor**

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

109 **3 DOSAGE FORM AND STRENGTHS**

109 Cymbalta is available as:

110 20mg opaque green capsules imprinted with “Lilly 3235 20mg”

111 30mg opaque white and blue capsules imprinted with “Lilly 3240 30mg”

112 60mg opaque green and blue capsules imprinted with “Lilly 3237 60mg”

113

114 **4 CONTRAINDICATIONS**

115

116 **4.1 Monoamine Oxidase Inhibitors**

117 Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated due to
118 the risk of serious, sometimes fatal, drug interactions with serotonergic drugs. These interactions may
119 include hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of
120 vital signs, and mental status changes that include extreme agitation progressing to delirium and coma.
121 These reactions have also been reported in patients who have recently discontinued serotonin reuptake
122 inhibitors and are then started on an MAOI. Some cases presented with features resembling neuroleptic
123 malignant syndrome [*see Dosage and Administration, (2.5) and Warnings and Precautions (5.4)*].
124

125 **4.2 Uncontrolled Narrow-Angle Glaucoma**

126 In clinical trials, Cymbalta use was associated with an increased risk of mydriasis; therefore, its use
127 should be avoided in patients with uncontrolled narrow-angle glaucoma [*see Warnings and*
128 *Precautions (5.12)*].
129

130 **5 WARNINGS AND PRECAUTIONS**

131

132 **5.1 Clinical Worsening and Suicide Risk**

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

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

146 The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive
147 compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9
148 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults
149 with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2
150 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of
151 suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs
152 studied. There were differences in absolute risk of suicidality across the different indications, with the
153 highest incidence in MDD. The risk of differences (drug vs placebo), however, were relatively stable
154 within age strata and across indications. These risk differences (drug-placebo difference in the number
155 of cases of suicidality per 1000 patients treated) are provided in Table 1.
156

157
158

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

159

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

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

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

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

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

180 If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is
181 feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms [*see*
182 *Dosage and Administration (2.4) and Warnings and Precautions (5.6)* for descriptions of the risks of
183 discontinuation of Cymbalta].

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

192 **Screening Patients for Bipolar Disorder** — A major depressive episode may be the initial
193 presentation of bipolar disorder. It is generally believed (though not established in controlled trials)
194 that treating such an episode with an antidepressant alone may increase the likelihood of precipitation
195 of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms
196 described above represent such a conversion is unknown. However, prior to initiating treatment with
197 an antidepressant, patients with depressive symptoms should be adequately screened to determine if
198 they are at risk for bipolar disorder; such screening should include a detailed psychiatric history,
199 including a family history of suicide, bipolar disorder, and depression. It should be noted that
200 Cymbalta (duloxetine) is not approved for use in treating bipolar depression.
201

202 **5.2 Hepatotoxicity**

203 Cymbalta increases the risk of elevation of serum transaminase levels. Liver transaminase elevations
204 resulted in the discontinuation of 0.3% (73/23,983) of Cymbalta-treated patients. In these patients, the
205 median time to detection of the transaminase elevation was about two months. In placebo-controlled
206 trials in any indication, elevation of ALT >3 times the upper limit of normal occurred in
207 1.1% (75/6871) of Cymbalta-treated patients compared to 0.3% (13/5036) of placebo-treated patients.
208 In placebo-controlled studies using a fixed-dose design, there was evidence of a dose-response
209 relationship for ALT and AST elevation of >3 times the upper limit of normal and >5 times the upper
210 limit of normal, respectively. Postmarketing reports have described cases of hepatitis with abdominal
211 pain, hepatomegaly and elevation of transaminase levels to more than twenty times the upper limit of
212 normal with or without jaundice, reflecting a mixed or hepatocellular pattern of liver injury. Cases of
213 cholestatic jaundice with minimal elevation of transaminase levels have also been reported.

214 The combination of transaminase elevations and elevated bilirubin, without evidence of obstruction, is
215 generally recognized as an important predictor of severe liver injury. In clinical trials, three Cymbalta
216 patients had elevations of transaminases and bilirubin, but also had elevation of alkaline phosphatase,
217 suggesting an obstructive process; in these patients, there was evidence of heavy alcohol use and this may
218 have contributed to the abnormalities seen. Two placebo-treated patients also had transaminase elevations
219 with elevated bilirubin. Postmarketing reports indicate that elevated transaminases, bilirubin and alkaline
220 phosphatase have occurred in patients with chronic liver disease or cirrhosis. Because it is possible that
221 duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate pre-existing liver
222 disease, Cymbalta should ordinarily not be prescribed to patients with substantial alcohol use or evidence
223 of chronic liver disease.
224

225 **5.3 Orthostatic Hypotension and Syncope**

226 Orthostatic hypotension and syncope have been reported with therapeutic doses of duloxetine. Syncope
227 and orthostatic hypotension tend to occur within the first week of therapy but can occur at any time during
228 duloxetine treatment, particularly after dose increases. The risk of blood pressure decreases may be greater
229 in patients taking concomitant medications that induce orthostatic hypotension (such as antihypertensives)
230 or are potent CYP1A2 inhibitors [*see Warnings and Precautions (5.10) and Drug Interactions (7.1)*] and in
231 patients taking duloxetine at doses above 60 mg daily. Consideration should be given to discontinuing
232 duloxetine in patients who experience symptomatic orthostatic hypotension and/or syncope during
233 duloxetine therapy.
234

235 **5.4 Serotonin Syndrome**

236 The development of a potentially life-threatening serotonin syndrome may occur with SNRIs and
237 SSRIs, including Cymbalta treatment, particularly with concomitant use of serotonergic drugs
238 (including triptans) and with drugs which impair metabolism of serotonin (including MAOIs).
239 Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations,
240 coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular
241 aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea,
242 vomiting, diarrhea).

243 The concomitant use of Cymbalta with MAOIs intended to treat depression is contraindicated [*see*
244 *Contraindications (4.1)*].

245 If concomitant treatment of Cymbalta with a 5-hydroxytryptamine receptor agonist (triptan) is
246 clinically warranted, careful observation of the patient is advised, particularly during treatment
247 initiation and dose increases [*see Drug Interactions (7.15)*].

248 The concomitant use of Cymbalta with serotonin precursors (such as tryptophan) is not
249 recommended [*see Drug Interactions (7.14)*].
250

251 **5.5 Abnormal Bleeding**

252 SSRIs and SNRIs, including duloxetine, may increase the risk of bleeding events. Concomitant use of
253 aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anti-coagulants may add to this risk.
254 Case reports and epidemiological studies (case-control and cohort design) have demonstrated an
255 association between use of drugs that interfere with serotonin reuptake and the occurrence of
256 gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses,
257 hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

258 Patients should be cautioned about the risk of bleeding associated with the concomitant use of duloxetine
259 and NSAIDs, aspirin, or other drugs that affect coagulation.

260

261 **5.6 Discontinuation of Treatment with Cymbalta**

262 Discontinuation symptoms have been systematically evaluated in patients taking duloxetine.
263 Following abrupt or tapered discontinuation in placebo-controlled clinical trials, the following
264 symptoms occurred at a rate greater than or equal to 1% and at a significantly higher rate in
265 duloxetine-treated patients compared to those discontinuing from placebo: dizziness, nausea, headache,
266 fatigue, paresthesia, vomiting, irritability, nightmares, insomnia, diarrhea, anxiety, hyperhidrosis and
267 vertigo.

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

274 Patients should be monitored for these symptoms when discontinuing treatment with Cymbalta. A
275 gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If
276 intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then
277 resuming the previously prescribed dose may be considered. Subsequently, the physician may continue
278 decreasing the dose but at a more gradual rate [*see Dosage and Administration (2.4)*].

279

280 **5.7 Activation of Mania/Hypomania**

281 In placebo-controlled trials in patients with major depressive disorder, activation of mania or
282 hypomania was reported in 0.1% (2/2327) of duloxetine-treated patients and 0.1% (1/1460) of
283 placebo-treated patients. No activation of mania or hypomania was reported in DPNP or GAD
284 placebo-controlled trials. Activation of mania or hypomania has been reported in a small proportion of
285 patients with mood disorders who were treated with other marketed drugs effective in the treatment of
286 major depressive disorder. As with these other agents, Cymbalta should be used cautiously in patients
287 with a history of mania.

288

289 **5.8 Seizures**

290 Duloxetine has not been systematically evaluated in patients with a seizure disorder, and such
291 patients were excluded from clinical studies. In placebo-controlled clinical trials, seizures/convulsions
292 occurred in 0.04% (3/8504) of patients treated with duloxetine and 0.02% (1/6123) of patients treated
293 with placebo. Cymbalta should be prescribed with care in patients with a history of a seizure disorder.

294

295 **5.9 Effect on Blood Pressure**

296 In clinical trials across indications, relative to placebo, duloxetine treatment was associated with a
297 mean increases of up to 2.1 mm Hg in systolic blood pressure and up to 2.3 mm Hg in diastolic blood
298 pressure. There was no significant difference in the frequency of sustained (3 consecutive visits)
299 elevated blood pressure. In a clinical pharmacology study designed to evaluate the effects of
300 duloxetine on various parameters, including blood pressure at supratherapeutic doses with an
301 accelerated dose titration, there was evidence of increases in supine blood pressure at doses up to 200
302 mg BID. At the highest 200 mg BID dose, the increase in mean pulse rate was 5.0 to 6.8 beats and
303 increases in mean blood pressure were 4.7 to 6.8 mm Hg (systolic) and 4.5 to 7 mm Hg (diastolic) up
304 to 12 hours after dosing.

305 Blood pressure should be measured prior to initiating treatment and periodically measured
306 throughout treatment [*see Adverse Reactions (6.6)*].

307

308 **5.10 Clinically Important Drug Interactions**

309 Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

310 Potential for Other Drugs to Affect Cymbalta

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

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

316 Potential for Cymbalta to Affect Other Drugs

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

325 Other Clinically Important Drug Interactions

326 *Alcohol* —Use of Cymbalta concomitantly with heavy alcohol intake may be associated with severe
327 liver injury. For this reason, Cymbalta should ordinarily not be prescribed for patients with substantial
328 alcohol use [*see Warnings and Precautions (5.2) and Drug Interactions (7.16)*].

329 *CNS Acting Drugs* — Given the primary CNS effects of Cymbalta, it should be used with caution
330 when it is taken in combination with or substituted for other centrally acting drugs, including those
331 with a similar mechanism of action [*see Warnings and Precautions (5.10) and Drug Interactions*
332 *(7.17)*].

333

334 **5.11 Hyponatremia**

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

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

346

347 **5.12 Use in Patients with Concomitant Illness**

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

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

356 Hepatic Insufficiency - Cymbalta should ordinarily not be used in patients with hepatic insufficiency [*see*
357 *Dosage and Administration (2.3), Warnings and Precautions (5.2), and Use in Specific Populations (8.9)*].

358 Severe Renal Impairment - Cymbalta should ordinarily not be used in patients with end-stage renal
359 disease or severe renal impairment (creatinine clearance <30 mL/min). Increased plasma concentration of
360 duloxetine, and especially of its metabolites, occur in patients with end-stage renal disease (requiring
361 dialysis). [*see Dosage and Administration (2.3) and Use in Specific Populations (8.10)*].

362 Controlled Narrow-Angle Glaucoma - In clinical trials, Cymbalta was associated with an increased risk
363 of mydriasis; therefore, it should be used cautiously in patients with controlled narrow-angle glaucoma [*see*
364 *Contraindications (4.2)*].

365 Glycemic Control in Patients with Diabetes - As observed in DPNP trials, Cymbalta treatment worsens
366 glycemic control in some patients with diabetes. In three clinical trials of Cymbalta for the management of
367 neuropathic pain associated with diabetic peripheral neuropathy, the mean duration of diabetes was
368 approximately 12 years, the mean baseline fasting blood glucose was 176 mg/dL, and the mean baseline

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

374

375 **5.13 Urinary Hesitation and Retention**

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

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

382

383 **5.14 Laboratory Tests**

384 No specific laboratory tests are recommended.

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386 **6 ADVERSE REACTIONS**

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388 **6.1 Clinical Trial Data Sources**

389 The data described below reflect exposure to duloxetine in placebo-controlled trials for MDD (N=2327),
390 DPNP (N=568) and GAD (N=668). The population studied was 17 to 89 years of age; 64.8%, 38.7%, and
391 64.7% female; and 85.5%, 77.6%, and 84.6% Caucasian for MDD, DPNP, and GAD, respectively. Most
392 patients received doses of a total of 60 to 120 mg per day [*see Clinical Studies (14)*].

393 The stated frequencies of adverse reactions represent the proportion of individuals who experienced,
394 at least once, a treatment-emergent adverse reaction of the type listed. A reaction was considered
395 treatment-emergent if it occurred for the first time or worsened while receiving therapy following
396 baseline evaluation. Reactions reported during the studies were not necessarily caused by the therapy,
397 and the frequencies do not reflect investigator impression (assessment) of causality.

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

401

402 **6.2 Adverse Reactions Reported as Reasons for Discontinuation of Treatment in Placebo-Controlled 403 Trials**

404 Major Depressive Disorder — Approximately 9% (209/2327) of the patients who received duloxetine in
405 placebo-controlled trials for MDD discontinued treatment due to an adverse reaction, compared with 4.7%
406 (68/1460) of the patients receiving placebo. Nausea (duloxetine 1.3%, placebo 0.5%) was the only common
407 adverse reaction reported as a reason for discontinuation and considered to be drug-related (i.e.,
408 discontinuation occurring in at least 1% of the duloxetine-treated patients and at a rate of at least twice that
409 of placebo).

410 Diabetic Peripheral Neuropathic Pain — Approximately 14.3% (81/568) of the patients who received
411 duloxetine in placebo-controlled trials for DPNP discontinued treatment due to an adverse reaction,
412 compared with 7.2% (16/223) for placebo. Common adverse reactions reported as a reason for
413 discontinuation and considered to be drug-related (as defined above) were nausea (duloxetine 3.5%,
414 placebo 0.4%), dizziness (duloxetine 1.6%, placebo 0.4%), somnolence (duloxetine 1.6%, placebo 0.0%),
415 and fatigue (duloxetine 1.1%, placebo 0.0%).

416 Generalized Anxiety Disorder — Approximately 15.3% (102/668) of the patients who received
417 duloxetine in placebo-controlled trials for GAD discontinued treatment due to an adverse reaction,
418 compared with 4.0% (20/495) for placebo. Common adverse reactions reported as a reason for
419 discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine 3.7%,
420 placebo 0.2%), vomiting (duloxetine 1.3%, placebo 0.0%), and dizziness (duloxetine 1.0%, placebo 0.2%).

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6.3 Adverse Reactions Occurring at an Incidence of 5% or More among Duloxetine-Treated Patients in Placebo-Controlled Trials

Table 2 gives the incidence of treatment-emergent adverse reactions in placebo-controlled trials for approved indications that occurred in 5% or more of patients treated with duloxetine and with an incidence greater than placebo. The most commonly observed adverse reactions in duloxetine-treated patients (incidence of 5% or greater and at least twice the incidence in placebo patients) were nausea, dry mouth, somnolence, constipation, decreased appetite, and hyperhidrosis.

Table 2: Treatment-Emergent Adverse Reactions: Incidence of 5% or More in Placebo-Controlled Trials of Approved Indications¹

Adverse Reaction	Percentage of Patients Reporting Reaction	
	Cymbalta (N=3563)	Placebo (N=2178)
Nausea	25	9
Dry mouth	14	6
Diarrhea	10	7
Dizziness*	11	6
Insomnia ^a	10	6
Fatigue* ^b	10	6
Somnolence* ^c	11	4
Constipation*	10	4
Decreased appetite* ^d	8	2
Hyperhidrosis	7	2

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¹ Events reported by at least 5% of patients treated with Cymbalta and more often than with placebo.
* Events for which there was a significant dose-dependent relationship in fixed-dose studies, excluding three MDD studies which did not have a placebo lead-in period or dose titration.
^a Also includes middle insomnia, early morning awakening, and initial insomnia
^b Also includes asthenia
^c Also includes hypersomnia and sedation
^d Also includes anorexia

6.4 Adverse Reactions Occurring at an Incidence of 2% or More among Duloxetine-Treated Patients in Placebo-Controlled Trials

Pooled MDD and GAD trials

Table 3 gives the incidence of treatment-emergent adverse reactions in MDD and GAD placebo-controlled trials for approved indications that occurred in 2% or more of patients treated with duloxetine and with an incidence greater than placebo. The most commonly observed adverse reactions in duloxetine-treated MDD/GAD patients (incidence of 5% or greater and at least twice the incidence in placebo patients) were nausea, dry mouth, constipation, somnolence, decreased appetite, and hyperhidrosis.

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Table 3: Treatment-Emergent Adverse Reactions: Incidence of 2% or More in MDD and GAD Placebo-Controlled Trials¹

System Organ Class / Adverse Reaction	Percentage of Patients Reporting Reaction	
	Cymbalta (N=2995)	Placebo (N=1955)
Cardiac Disorders		
Palpitations	2	2
Eye Disorders		
Vision blurred	3	2
Gastrointestinal Disorders		
Nausea	25	9
Dry mouth	15	6
Diarrhea	10	7
Constipation*	10	4
Abdominal pain ^a	4	4
Vomiting	5	2
General Disorders and Administration Site Conditions		
Fatigue ^b	10	6
Investigations		
Weight decreased*	2	<1
Metabolism and Nutrition Disorders		
Decreased appetite ^c	7	2
Nervous System Disorders		
Dizziness	10	6
Somnolence ^d	10	4
Tremor	3	<1
Psychiatric Disorders		
Insomnia ^e	10	6
Agitation ^f	5	3
Anxiety	3	2
Libido decreased ^g	4	1
Orgasm abnormal ^h	3	<1
Abnormal dreams ⁱ	2	1
Reproductive System and Breast Disorders		
Erectile dysfunction ^j	5	1
Ejaculation delayed* ^j	3	<1
Ejaculation disorder ^{i,k}	2	<1
Respiratory, Thoracic, and Mediastinal Disorders		
Yawning	2	<1
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	6	2
Vascular Disorders		
Hot flush	2	<1

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¹ Events reported by at least 2% of patients treated with Cymbalta and more often than with placebo.
* Events for which there was a significant dose-dependent relationship in fixed-dose studies, excluding three MDD studies which did not have a placebo lead-in period or dose titration.
^a Also includes abdominal pain upper, abdominal pain lower, abdominal tenderness, abdominal discomfort, and gastrointestinal pain
^b Also includes asthenia
^c Also includes anorexia

459 ^d Also includes hypersomnia and sedation
 460 ^e Also includes middle insomnia, early morning awakening, and initial insomnia
 461 ^f Also includes feeling jittery, nervousness, restlessness, tension, and psychomotor agitation
 462 ^g Also includes loss of libido
 463 ^h Also includes anorgasmia
 464 ⁱ Also includes nightmare
 465 ^j Males patients only
 466 ^k Also includes ejaculation failure and ejaculation dysfunction
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468 **Diabetic Peripheral Neuropathic Pain**

469 Table 4 gives the incidence of treatment-emergent adverse events that occurred in 2% or more of
 470 patients treated with Cymbalta in the premarketing acute phase of DPNP placebo-controlled trials
 471 (doses of 20 to 120 mg/day) and with an incidence greater than placebo. The most commonly observed
 472 adverse events in Cymbalta-treated DPNP patients (incidence of 5% or greater and at least twice the
 473 incidence in placebo patients) were: nausea; somnolence; dizziness; constipation; dry mouth;
 474 hyperhidrosis; decreased appetite; and asthenia (*see* Table 4).
 475

476 **Table 4: Treatment-Emergent Adverse Reactions Incidence of 2% or More**
 477 **in DPNP Placebo-Controlled Trials**

System Organ Class / Adverse Reaction	Percentage of Patients Reporting Reaction			
	Cymbalta 60 mg BID (N=225)	Cymbalta 60 mg QD (N=228)	Cymbalta 20 mg QD (N=115)	Placebo (N=223)
Gastrointestinal Disorders				
Nausea	30	22	14	9
Constipation	15	11	5	3
Diarrhea	7	11	13	6
Dry mouth	12	7	5	4
Vomiting	5	5	6	4
Dyspepsia	4	4	4	3
Loose stools	2	3	2	1
General Disorders and Administration Site Conditions				
Fatigue	12	10	2	5
Asthenia	8	4	2	1
Pyrexia	3	1	2	1
Infections and Infestations				
Nasopharyngitis	9	7	9	5
Metabolism and Nutrition Disorders				
Decreased appetite	11	4	3	<1
Anorexia	5	3	3	<1
Musculoskeletal and Connective Tissue Disorders				
Muscle cramp	4	4	5	3
Myalgia	4	1	3	<1
Nervous System Disorders				
Somnolence	21	15	7	5
Headache	15	13	13	10
Dizziness	17	14	6	6
Tremor	5	1	0	0
Psychiatric Disorders				
Insomnia	13	8	9	7
Renal and Urinary Disorders				
Pollakiuria	5	1	3	2
Reproductive System and Breast Disorders				

Erectile dysfunction ¹	4	1	0	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	5	3	6	4
Pharyngolaryngeal pain	6	1	3	1
Skin and Subcutaneous Tissue Disorders				
Hyperhidrosis	8	6	6	2

¹-Male patients only.

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6.5 Effects on Male and Female Sexual Function

Changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of psychiatric disorders or diabetes, but they may also be a consequence of pharmacologic treatment. Because adverse sexual reactions are presumed to be voluntarily underreported, the Arizona Sexual Experience Scale (ASEX), a validated measure designed to identify sexual side effects, was used prospectively in 4 MDD placebo-controlled trials. In these trials, as shown in Table 5 below, patients treated with Cymbalta experienced significantly more sexual dysfunction, as measured by the total score on the ASEX, than did patients treated with placebo. Gender analysis showed that this difference occurred only in males. Males treated with Cymbalta experienced more difficulty with ability to reach orgasm (ASEX Item 4) than males treated with placebo. Females did not experience more sexual dysfunction on Cymbalta than on placebo as measured by ASEX total score. Negative numbers signify an improvement from a baseline level of dysfunction, which is commonly seen in depressed patients. Physicians should routinely inquire about possible sexual side effects.

Table 5: Mean Change in ASEX Scores by Gender in MDD Placebo-Controlled Trials

	Male Patients ^a		Female Patients ^a	
	Cymbalta (n=175)	Placebo (n=83)	Cymbalta (n=241)	Placebo (n=126)
ASEX Total (Items 1-5)	0.56 ^b	-1.07	-1.15	-1.07
Item 1 — Sex drive	-0.07	-0.12	-0.32	-0.24
Item 2 — Arousal	0.01	-0.26	-0.21	-0.18
Item 3 — Ability to achieve erection (men); Lubrication (women)	0.03	-0.25	-0.17	-0.18
Item 4 — Ease of reaching orgasm	0.40 ^c	-0.24	-0.09	-0.13
Item 5 — Orgasm satisfaction	0.09	-0.13	-0.11	-0.17

^a n=Number of patients with non-missing change score for ASEX total

^b p=0.013 versus placebo

^c p<0.001 versus placebo

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6.6 Vital Sign Changes

In clinical trials across indications, relative to placebo, duloxetine treatment was associated with a mean increase of up to 2.1 mm Hg in systolic blood pressure and up to 2.3 mm Hg in diastolic blood pressure. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure [see *Warnings and Precautions (5.3 and 5.9)*].

Duloxetine treatment, for up to 13-weeks in placebo-controlled trials typically caused a small increase in heart rate compared to placebo of up to 3 beats per minute.

6.7 Weight Changes

In placebo-controlled clinical trials, MDD and GAD patients treated with Cymbalta for up to 10-weeks experienced a mean weight loss of approximately 0.5 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients. In DPN placebo-controlled clinical trials, patients treated with Cymbalta for up to 13-weeks experienced a mean weight loss of approximately 1.1 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients.

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515 **6.8 Laboratory Changes**

516 Cymbalta treatment in placebo-controlled clinical trials, was associated with small mean increases
517 from baseline to endpoint in ALT, AST, CPK, and alkaline phosphatase; infrequent, modest, transient,
518 abnormal values were observed for these analytes in Cymbalta-treated patients when compared with
519 placebo-treated patients [*see Warnings and Precautions (5.2)*].

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521 **6.9 Electrocardiogram Changes**

522 Electrocardiograms were obtained from duloxetine-treated patients and placebo-treated patients in
523 clinical trials lasting up to 13-weeks. No clinically significant differences were observed for QTc, QT,
524 PR, and QRS intervals between duloxetine-treated and placebo-treated patients. There were no
525 differences in clinically meaningful QTcF elevations between duloxetine and placebo. In a
526 positive-controlled study in healthy volunteers using duloxetine up to 200 mg BID, no prolongation of
527 the corrected QT interval was observed.

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529 **6.10 Other Adverse Reactions Observed During the Premarketing and Postmarketing Clinical Trial**
530 **Evaluation of Duloxetine**

531 Following is a list of treatment-emergent adverse reactions reported by patients treated with duloxetine in
532 clinical trials. In clinical trials of all indications, 23,983 patients were treated with duloxetine. Of these,
533 6,702 took duloxetine for at least 6 months, and 3,006 for at least one year. The following listing is not
534 intended to include reactions (1) already listed in previous tables or elsewhere in labeling, (2) for which a
535 drug cause was remote, (3) which were so general as to be uninformative, (4) which were not considered to
536 have significant clinical implications, or (5) which occurred at a rate equal to or less than placebo.

537 Reactions are categorized by body system according to the following definitions: frequent adverse
538 reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring
539 in 1/100 to 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients.

540 **Cardiac Disorders** — *Frequent*: palpitations; *Infrequent*: myocardial infarction and tachycardia.

541 **Ear and Labyrinth Disorders** — *Frequent*: vertigo; *Infrequent*: ear pain.

542 **Endocrine Disorders** — *Infrequent*: Hypothyroidism.

543 **Eye Disorders** — *Frequent*: vision blurred; *Infrequent*: diplopia and visual disturbance.

544 **Gastrointestinal Disorders** — *Frequent*: flatulence; *Infrequent*: eructation, gastritis, halitosis, and
545 stomatitis; *Rare*: gastric ulcer, hemochezia, and melena.

546 **General Disorders and Administration Site Conditions** — *Frequent*: chills/rigors;

547 *Infrequent*: feeling abnormal, feeling hot and/or cold, malaise, and thirst.

548 **Infections and Infestations** — *Infrequent*: gastroenteritis and laryngitis.

549 **Investigations** — *Frequent*: weight increased; *Infrequent*: blood cholesterol increased.

550 **Metabolism and Nutrition Disorders** — *Infrequent*: dehydration and hyperlipidemia;

551 *Rare*: dyslipidemia.

552 **Musculoskeletal and Connective Tissue Disorders** — *Frequent*: musculoskeletal pain;

553 *Infrequent*: muscle tightness and muscle twitching.

554 **Nervous System Disorders** — *Frequent*: dysgeusia, lethargy, and parasthesia/hypoesthesia;

555 *Infrequent*: disturbance in attention, dyskinesia, and myoclonus; *Rare*: dysarthria.

556 **Psychiatric Disorders** — *Frequent*: abnormal dreams and sleep disorder; *Infrequent*: apathy,

557 bruxism, disorientation/confusional state, irritability, mood swings, and suicide attempt;

558 *Rare*: completed suicide.

559 **Renal and Urinary Disorders** — *Infrequent*: dysuria, micturition urgency, nocturia, and urine odor
560 abnormal.

561 **Reproductive System and Breast Disorders** — *Frequent*: anorgasmia/orgasm abnormal;

562 *Infrequent*: menopausal symptoms.

563 **Respiratory, Thoracic and Mediastinal Disorders** — *Frequent*: yawning; *Infrequent*: throat

564 tightness.

565 **Skin and Subcutaneous Tissue Disorders** — *Infrequent*: cold sweat, erythema, increased tendency
566 to bruise, night sweats, and photosensitivity reaction; *Rare*: ecchymosis.

567 **Vascular Disorders** — *Frequent*: hot flush; *Infrequent*: flushing, orthostatic hypotension, and
568 peripheral coldness.

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6.11 Postmarketing Spontaneous Reports

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The following adverse reactions have been identified during postapproval use of Cymbalta. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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Adverse reactions reported since market introduction that were temporally related to duloxetine therapy and not mentioned elsewhere in labeling include: anaphylactic reaction, angioneurotic edema, erythema multiforme, extrapyramidal disorder, glaucoma, hallucinations, hyperglycemia, hypersensitivity, hypertensive crisis, rash, supraventricular arrhythmia, trismus, and urticaria.

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Serious skin reactions including Stevens-Johnson Syndrome that have required drug discontinuation and/or hospitalization have been reported with duloxetine.

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7 DRUG INTERACTIONS

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Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

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7.1 Inhibitors of CYP1A2

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When duloxetine 60 mg was co-administered with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to male subjects (n=14) duloxetine AUC was increased approximately 6-fold, the C_{max} was increased about 2.5-fold, and duloxetine $t_{1/2}$ was increased approximately 3-fold. Other drugs that inhibit CYP1A2 metabolism include cimetidine and quinolone antimicrobials such as ciprofloxacin and enoxacin [*see Warnings and Precautions (5.10)*].

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7.2 Inhibitors of CYP2D6

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Concomitant use of duloxetine (40 mg QD) with paroxetine (20 mg QD) increased the concentration of duloxetine AUC by about 60%, and greater degrees of inhibition are expected with higher doses of paroxetine. Similar effects would be expected with other potent CYP2D6 inhibitors (e.g., fluoxetine, quinidine) [*see Warnings and Precautions (5.10)*].

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7.3 Dual Inhibition of CYP1A2 and CYP2D6

Concomitant administration of duloxetine 40 mg BID with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to CYP2D6 poor metabolizer subjects (n=14) resulted in a 6-fold increase in duloxetine AUC and C_{max} .

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7.4 Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)

Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs or SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when duloxetine is initiated or discontinued [*see Warnings and Precautions (5.5)*].

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7.5 Lorazepam

Under steady-state conditions for duloxetine (60 mg Q 12 hours) and lorazepam (2 mg Q 12 hours), the pharmacokinetics of duloxetine were not affected by co-administration.

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7.6 Temazepam

Under steady-state conditions for duloxetine (20 mg qhs) and temazepam (30 mg qhs), the pharmacokinetics of duloxetine were not affected by co-administration.

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7.7 Drugs that Affect Gastric Acidity

Cymbalta has an enteric coating that resists dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. In extremely acidic conditions, Cymbalta, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using Cymbalta

624 in patients with conditions that may slow gastric emptying (e.g., some diabetics). Drugs that raise the
625 gastrointestinal pH may lead to an earlier release of duloxetine. However, co-administration of
626 Cymbalta with aluminum- and magnesium-containing antacids (51 mEq) or Cymbalta with famotidine,
627 had no significant effect on the rate or extent of duloxetine absorption after administration of a 40-mg
628 oral dose. It is unknown whether the concomitant administration of proton pump inhibitors affects
629 duloxetine absorption [*see Warnings and Precautions (5.12)*].
630

631

7.8 Drugs Metabolized by CYP1A2

632

In vitro drug interaction studies demonstrate that duloxetine does not induce CYP1A2 activity.
633 Therefore, an increase in the metabolism of CYP1A2 substrates (e.g., theophylline, caffeine) resulting from
634 induction is not anticipated, although clinical studies of induction have not been performed. Duloxetine is
635 an inhibitor of the CYP1A2 isoform in *in vitro* studies, and in two clinical studies the average (90%
636 confidence interval) increase in theophylline AUC was 7% (1%-15%) and 20% (13%-27%) when
637 co-administered with duloxetine (60 mg BID).
638

639

7.9 Drugs Metabolized by CYP2D6

640

Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered (at a dose of
641 60 mg BID) in conjunction with a single 50-mg dose of desipramine, a CYP2D6 substrate, the AUC of
642 desipramine increased 3-fold [*see Warnings and Precautions (5.10)*].
643

644

7.10 Drugs Metabolized by CYP2C9

645

Duloxetine does not inhibit the *in vitro* enzyme activity of CYP2C9. Inhibition of the metabolism of
646 CYP2C9 substrates is therefore not anticipated, although clinical studies have not been performed.
647

648

7.11 Drugs Metabolized by CYP3A

649

Results of *in vitro* studies demonstrate that duloxetine does not inhibit or induce CYP3A activity.
650 Therefore, an increase or decrease in the metabolism of CYP3A substrates (e.g., oral contraceptives
651 and other steroidal agents) resulting from induction or inhibition is not anticipated, although clinical
652 studies have not been performed.
653

654

7.12 Drugs Metabolized by CYP2C19

655

Results of *in vitro* studies demonstrate that duloxetine does not inhibit CYP2C19 activity at
656 therapeutic concentrations. Inhibition of the metabolism of CYP2C19 substrates is therefore not
657 anticipated, although clinical studies have not been performed.
658

659

7.13 Monoamine Oxidase Inhibitors

660

[*see Dosage and Administration (2.5), Contraindications (4.1), and Warnings and Precautions*
661 (5.4)].
662

663

7.14 Serotonergic Drugs

664

Based on the mechanism of action of SNRIs and SSRIs, including Cymbalta, and the potential for
665 serotonin syndrome, caution is advised when Cymbalta is co-administered with other drugs that may affect
666 the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible
667 non-selective MAOI), lithium, tramadol, or St. John's Wort. The concomitant use of Cymbalta with other
668 SSRIs, SNRIs or tryptophan is not recommended [*see Warnings and Precautions (5.4)*].
669

670

7.15 Triptans

671

There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If
672 concomitant treatment of Cymbalta with a triptan is clinically warranted, careful observation of the patient
673 is advised, particularly during treatment initiation and dose increases [*see Warnings and Precautions (5.4)*].
674

675

7.16 Alcohol

676

When Cymbalta and ethanol were administered several hours apart so that peak concentrations of
677 each would coincide, Cymbalta did not increase the impairment of mental and motor skills caused by
678 alcohol.

679 In the Cymbalta clinical trials database, three Cymbalta-treated patients had liver injury as
680 manifested by ALT and total bilirubin elevations, with evidence of obstruction. Substantial intercurrent
681 ethanol use was present in each of these cases, and this may have contributed to the abnormalities seen
682 [*see Warnings and Precautions (5.2 and 5.10)*].

683

684 **7.17 CNS Drugs**

685 [*see Warnings and Precautions (5.10)*].

686

687 **7.18 Drugs Highly Bound to Plasma Protein**

688 Because duloxetine is highly bound to plasma protein, administration of Cymbalta to a patient taking
689 another drug that is highly protein bound may cause increased free concentrations of the other drug,
690 potentially resulting in adverse reactions.

691

692 **8 USE IN SPECIFIC POPULATIONS**

693

694 **8.1 Pregnancy**

695 Teratogenic Effects, Pregnancy Category C — In animal reproduction studies, duloxetine has been
696 shown to have adverse effects on embryo/fetal and postnatal development.

697 When duloxetine was administered orally to pregnant rats and rabbits during the period of
698 organogenesis, there was no evidence of teratogenicity at doses up to 45 mg/kg/day (7 times the
699 maximum recommended human dose [MRHD, 60 mg/day] and 4 times the human dose of 120 mg/day
700 on a mg/m² basis, in rat; 15 times the MRHD and 7 times the human dose of 120 mg/day on a mg/m²
701 basis in rabbit). However, fetal weights were decreased at this dose, with a no-effect dose of
702 10 mg/kg/day (2 times the MRHD and ≈1 times the human dose of 120 mg/day on a mg/m² basis in
703 rat; 3 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m² basis in rabbits).

704 When duloxetine was administered orally to pregnant rats throughout gestation and lactation, the
705 survival of pups to 1 day postpartum and pup body weights at birth and during the lactation period
706 were decreased at a dose of 30 mg/kg/day (5 times the MRHD and 2 times the human dose of
707 120 mg/day on a mg/m² basis); the no-effect dose was 10 mg/kg/day. Furthermore, behaviors
708 consistent with increased reactivity, such as increased startle response to noise and decreased
709 habituation of locomotor activity, were observed in pups following maternal exposure to
710 30 mg/kg/day. Post-weaning growth and reproductive performance of the progeny were not affected
711 adversely by maternal duloxetine treatment.

712 There are no adequate and well-controlled studies in pregnant women; therefore, duloxetine should be
713 used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

714 Nonteratogenic Effects — Neonates exposed to SSRIs or serotonin and norepinephrine reuptake
715 inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged
716 hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon
717 delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures,
718 temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia,
719 tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic
720 effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some
721 cases, the clinical picture is consistent with serotonin syndrome [*see Warnings and Precautions (5.4)*].

722 When treating pregnant women with Cymbalta during the third trimester, the physician should
723 carefully consider the potential risks and benefits of treatment. The physician may consider tapering
724 Cymbalta in the third trimester [*see Dosage and Administration (2.3)*].

725

726 **8.2 Labor and Delivery**

727 The effect of duloxetine on labor and delivery in humans is unknown. Duloxetine should be used during
728 labor and delivery only if the potential benefit justifies the potential risk to the fetus.

729

730 **8.3 Nursing Mothers**

731 Duloxetine is excreted into the milk of lactating women. The estimated daily infant dose on a mg/kg
732 basis is approximately 0.14% of the maternal dose. Because the safety of duloxetine in infants is not
733 known, nursing while on Cymbalta is not recommended. However, if the physician determines that the

734 benefit of duloxetine therapy for the mother outweighs any potential risk to the infant, no dosage
735 adjustment is required as lactation did not influence duloxetine pharmacokinetics.

736 The disposition of duloxetine was studied in 6 lactating women who were at least 12 weeks
737 postpartum. Duloxetine 40 mg BID was given for 3.5 days. Like many other drugs, duloxetine is
738 detected in breast milk, and steady state concentrations in breast milk are about one-fourth those in
739 plasma. The amount of duloxetine in breast milk is approximately 7 µg/day while on 40 mg BID
740 dosing. The excretion of duloxetine metabolites into breast milk was not examined. Because the safety
741 of duloxetine in infants is not known, nursing while on Cymbalta is not recommended [(see *Dosing*
742 *and Administration* (2.3)].

743 744 **8.4 Pediatric Use**

745 Safety and effectiveness in the pediatric population have not been established [see *Boxed Warning and*
746 *Warnings and Precautions* (5.1)]. Anyone considering the use of Cymbalta in a child or adolescent must
747 balance the potential risks with the clinical need.

748 749 **8.5 Geriatric Use**

750 Of the 2418 patients in premarketing clinical studies of Cymbalta for MDD, 5.9% (143) were
751 65 years of age or over. Of the 1074 patients in the DPNP premarketing studies, 33% (357) were
752 65 years of age or over. Premarketing clinical studies of GAD did not include sufficient numbers of
753 subjects age 65 or over to determine whether they respond differently from younger subjects. In the
754 MDD and DPNP studies, no overall differences in safety or effectiveness were observed between these
755 subjects and younger subjects, and other reported clinical experience has not identified differences in
756 responses between the elderly and younger patients, but greater sensitivity of some older individuals
757 cannot be ruled out. SSRIs and SNRIs, including Cymbalta have been associated with cases of
758 clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event
759 [see *Warnings and Precautions* (5.11)].

760 The pharmacokinetics of duloxetine after a single dose of 40 mg were compared in healthy elderly
761 females (65 to 77 years) and healthy middle-age females (32 to 50 years). There was no difference in
762 the C_{max} , but the AUC of duloxetine was somewhat (about 25%) higher and the half-life about 4 hours
763 longer in the elderly females. Population pharmacokinetic analyses suggest that the typical values for
764 clearance decrease by approximately 1% for each year of age between 25 to 75 years of age; but age as
765 a predictive factor only accounts for a small percentage of between-patient variability. Dosage
766 adjustment based on the age of the patient is not necessary [see *Dosage and Administration* (2.3)].

767 768 **8.6 Gender**

769 Duloxetine's half-life is similar in men and women. Dosage adjustment based on gender is not necessary.

770 771 **8.7 Smoking Status**

772 Duloxetine bioavailability (AUC) appears to be reduced by about one-third in smokers. Dosage
773 modifications are not recommended for smokers.

774 775 **8.8 Race**

776 No specific pharmacokinetic study was conducted to investigate the effects of race.

777 778 **8.9 Hepatic Insufficiency**

779 Patients with clinically evident hepatic insufficiency have decreased duloxetine metabolism and
780 elimination. After a single 20-mg dose of Cymbalta, 6 cirrhotic patients with moderate liver
781 impairment (Child-Pugh Class B) had a mean plasma duloxetine clearance about 15% that of age- and
782 gender-matched healthy subjects, with a 5-fold increase in mean exposure (AUC). Although C_{max} was
783 similar to normals in the cirrhotic patients, the half-life was about 3 times longer [see *Dosage and*
784 *Administration* (2.3) *and Warnings and Precautions* (5.12)].

785 786 **8.10 Severe Renal Impairment**

787 Limited data are available on the effects of duloxetine in patients with end-stage renal
788 disease (ESRD). After a single 60-mg dose of duloxetine, C_{max} and AUC values were approximately
789 100% greater in patients with end-stage renal disease receiving chronic intermittent hemodialysis than

790 in subjects with normal renal function. The elimination half-life, however, was similar in both groups.
791 The AUCs of the major circulating metabolites, 4-hydroxy duloxetine glucuronide and 5-hydroxy,
792 6-methoxy duloxetine sulfate, largely excreted in urine, were approximately 7- to 9-fold higher and
793 would be expected to increase further with multiple dosing. Population PK analyses suggest that mild
794 to moderate degrees of renal dysfunction (estimated CrCl 30-80 mL/min) have no significant effect on
795 duloxetine apparent clearance [*see Dosage and Administration (2.3) and Warnings and Precautions*
796 *(5.12)*].

797

798 **9 DRUG ABUSE AND DEPENDENCE**

799

800 **9.2 Abuse**

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

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

808

809 **9.3 Dependence**

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

811

812 **10 OVERDOSAGE**

813

814 **10.1 Signs and Symptoms**

815 In postmarketing experience, fatal outcomes have been reported for acute overdoses, primarily with
816 mixed overdoses, but also with duloxetine only, at doses as low as 1000 mg. Signs and symptoms of
817 overdose (duloxetine alone or with mixed drugs) included somnolence, coma, serotonin syndrome,
818 seizures, syncope, tachycardia, hypotension, hypertension and vomiting.

819

820 **10.2 Management of Overdose**

821 There is no specific antidote to Cymbalta, but if serotonin syndrome ensues, specific treatment (such
822 as with cyproheptadine and/or temperature control) may be considered. In case of acute overdose,
823 treatment should consist of those general measures employed in the management of overdose with any
824 drug.

825 An adequate airway, oxygenation, and ventilation should be assured, and cardiac rhythm and vital
826 signs should be monitored. Induction of emesis is not recommended. Gastric lavage with a large-bore
827 orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after
828 ingestion or in symptomatic patients.

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

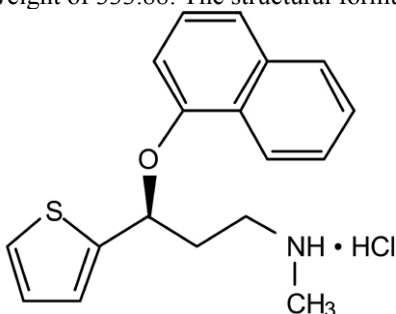
834 In managing overdose, the possibility of multiple drug involvement should be considered. A specific
835 caution involves patients who are taking or have recently taken Cymbalta and might ingest excessive
836 quantities of a TCA. In such a case, decreased clearance of the parent tricyclic and/or its active
837 metabolite may increase the possibility of clinically significant sequelae and extend the time needed
838 for close medical observation [*see Warnings and Precautions (5.4) and Drug Interactions (7)*]. The
839 physician should consider contacting a poison control center for additional information on the
840 treatment of any overdose. Telephone numbers for certified poison control centers are listed in the
841 *Physicians' Desk Reference (PDR)*.

842

843 **11 DESCRIPTION**

844 Cymbalta[®] (duloxetine hydrochloride) is a selective serotonin and norepinephrine reuptake
845 inhibitor (SSNRI) for oral administration. Its chemical designation is (+)-(S)-N-methyl-γ-(1-

846 naphthoxy)-2-thiophenepropylamine hydrochloride. The empirical formula is $C_{18}H_{19}NOS \cdot HCl$,
847 which corresponds to a molecular weight of 333.88. The structural formula is:



848
849 Duloxetine hydrochloride is a white to slightly brownish white solid, which is slightly soluble in
850 water.

851 Each capsule contains enteric-coated pellets of 22.4, 33.7, or 67.3 mg of duloxetine hydrochloride
852 equivalent to 20, 30, or 60 mg of duloxetine, respectively. These enteric-coated pellets are designed to
853 prevent degradation of the drug in the acidic environment of the stomach. Inactive ingredients include
854 FD&C Blue No. 2, gelatin, hypromellose, hydroxypropyl methylcellulose acetate succinate, sodium lauryl
855 sulfate, sucrose, sugar spheres, talc, titanium dioxide, and triethyl citrate. The 20 and 60 mg capsules also
856 contain iron oxide yellow.

857

858 12 CLINICAL PHARMACOLOGY

859

860 12.1 Mechanism of Action

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

864

865 12.2 Pharmacodynamics

866 Preclinical studies have shown that duloxetine is a potent inhibitor of neuronal serotonin and
867 norepinephrine reuptake and a less potent inhibitor of dopamine reuptake. Duloxetine has no significant
868 affinity for dopaminergic, adrenergic, cholinergic, histaminergic, opioid, glutamate, and GABA receptors
869 *in vitro*. Duloxetine does not inhibit monoamine oxidase (MAO).

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

873

874 12.3 Pharmacokinetics

875 Duloxetine has an elimination half-life of about 12 hours (range 8 to 17 hours) and its
876 pharmacokinetics are dose proportional over the therapeutic range. Steady-state plasma concentrations
877 are typically achieved after 3 days of dosing. Elimination of duloxetine is mainly through hepatic
878 metabolism involving two P450 isozymes, CYP1A2 and CYP2D6.

879 Absorption and Distribution — Orally administered duloxetine hydrochloride is well absorbed. There is a
880 median 2-hour lag until absorption begins (T_{lag}), with maximal plasma concentrations (C_{max}) of duloxetine
881 occurring 6 hours post dose. Food does not affect the C_{max} of duloxetine, but delays the time to reach peak
882 concentration from 6 to 10 hours and it marginally decreases the extent of absorption (AUC) by about 10%.
883 There is a 3-hour delay in absorption and a one-third increase in apparent clearance of duloxetine after an
884 evening dose as compared to a morning dose.

885 The apparent volume of distribution averages about 1640 L. Duloxetine is highly bound (>90%) to
886 proteins in human plasma, binding primarily to albumin and α_1 -acid glycoprotein. The interaction
887 between duloxetine and other highly protein bound drugs has not been fully evaluated. Plasma protein
888 binding of duloxetine is not affected by renal or hepatic impairment.

889 Metabolism and Elimination — Biotransformation and disposition of duloxetine in humans have been
890 determined following oral administration of ^{14}C -labeled duloxetine. Duloxetine comprises about 3% of the
891 total radiolabeled material in the plasma, indicating that it undergoes extensive metabolism to numerous
892 metabolites. The major biotransformation pathways for duloxetine involve oxidation of the naphthyl ring

893 followed by conjugation and further oxidation. Both CYP1A2 and CYP2D6 catalyze the oxidation of the
894 naphthyl ring *in vitro*. Metabolites found in plasma include 4-hydroxy duloxetine glucuronide and
895 5-hydroxy, 6-methoxy duloxetine sulfate. Many additional metabolites have been identified in urine, some
896 representing only minor pathways of elimination. Only trace (<1% of the dose) amounts of unchanged
897 duloxetine are present in the urine. Most (about 70%) of the duloxetine dose appears in the urine as
898 metabolites of duloxetine; about 20% is excreted in the feces. Duloxetine undergoes extensive metabolism,
899 but the he major circulating metabolites have not been shown to contribute significantly to the
900 pharmacologic activity of duloxetine.

901

902 **13 NONCLINICAL TOXICOLOGY**

903

904 **13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility**

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

906 In female mice receiving duloxetine at 140 mg/kg/day (11 times the maximum recommended human
907 dose [MRHD, 60 mg/day] and 6 times the human dose of 120 mg/day on a mg/m² basis), there was an
908 increased incidence of hepatocellular adenomas and carcinomas. The no-effect dose was 50 mg/kg/day
909 (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m² basis). Tumor incidence
910 was not increased in male mice receiving duloxetine at doses up to 100 mg/kg/day (8 times the MRHD
911 and 4 times the human dose of 120 mg/day on a mg/m² basis).

912 In rats, dietary doses of duloxetine up to 27 mg/kg/day in females (4 times the MRHD and 2 times
913 the human dose of 120 mg/day on a mg/m² basis) and up to 36 mg/kg/day in males (6 times the MRHD
914 and 3 times the human dose of 120 mg/day on a mg/m² basis) did not increase the incidence of tumors.

915 Mutagenesis — Duloxetine was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames
916 test) and was not clastogenic in an *in vivo* chromosomal aberration test in mouse bone marrow cells.

917 Additionally, duloxetine was not genotoxic in an *in vitro* mammalian forward gene mutation assay in
918 mouse lymphoma cells or in an *in vitro* unscheduled DNA synthesis (UDS) assay in primary rat
919 hepatocytes, and did not induce sister chromatid exchange in Chinese hamster bone marrow *in vivo*.

920 Impairment of Fertility — Duloxetine administered orally to either male or female rats prior to and
921 throughout mating at doses up to 45 mg/kg/day (7 times the maximum recommended human dose of
922 60 mg/day and 4 times the human dose of 120 mg/day on a mg/m² basis) did not alter mating or fertility.

923

924 **14 CLINICAL STUDIES**

925

926 **14.1 Major Depressive Disorder**

927 The efficacy of Cymbalta as a treatment for depression was established in 4 randomized,
928 double-blind, placebo-controlled, fixed-dose studies in adult outpatients (18 to 83 years) meeting
929 DSM-IV criteria for major depression. In 2 studies, patients were randomized to Cymbalta 60 mg
930 once daily (N=123 and N=128, respectively) or placebo (N=122 and N=139, respectively) for 9 weeks;
931 in the third study, patients were randomized to Cymbalta 20 or 40 mg twice daily (N=86 and N=91,
932 respectively) or placebo (N=89) for 8 weeks; in the fourth study, patients were randomized to
933 Cymbalta 40 or 60 mg twice daily (N=95 and N=93, respectively) or placebo (N=93) for 8 weeks.
934 There is no evidence that doses greater than 60 mg/day confer additional benefits.

935 In all 4 studies, Cymbalta demonstrated superiority over placebo as measured by improvement in the
936 17-item Hamilton Depression Rating Scale (HAM-D-17) total score.

937 In all of these clinical studies, analyses of the relationship between treatment outcome and age,
938 gender, and race did not suggest any differential responsiveness on the basis of these patient
939 characteristics.

940 In another study, 533 patients meeting DSM-IV criteria for MDD received Cymbalta 60 mg once daily
941 during an initial 12-week open-label treatment phase. Two hundred and seventy-eight patients who
942 responded to open label treatment (defined as meeting the following criteria at weeks 10 and 12: a
943 HAM-D-17 total score ≤ 9 , Clinical Global Impressions of Severity (CGI-S) ≤ 2 , and not meeting the DSM-
944 IV criteria for MDD) were randomly assigned to continuation of Cymbalta at the same dose (N=136) or to
945 placebo (N=142) for 6 months. Patients on Cymbalta experienced a statistically significantly longer time to
946 relapse of depression than did patients on placebo. Relapse was defined as an increase in the CGI-S score
947 of ≥ 2 points compared with that obtained at week 12, as well as meeting the DSM-IV criteria for MDD at 2

948 consecutive visits at least 2 weeks apart, where the 2-week temporal criterion had to be satisfied at only the
949 second visit. The effectiveness of Cymbalta in hospitalized patients with major depressive disorder has not
950 been studied.

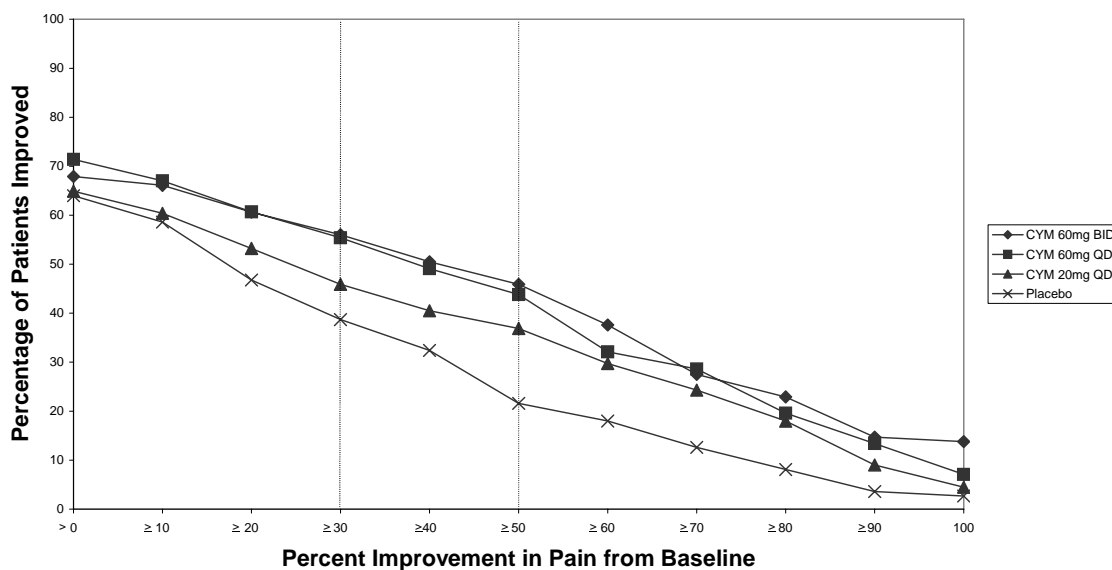
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952 **14.2 Diabetic Peripheral Neuropathic Pain**

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

962 Both studies compared Cymbalta 60 mg once daily or 60 mg twice daily with placebo. Study 1
963 additionally compared Cymbalta 20 mg with placebo. A total of 457 patients (342 Cymbalta, 115 placebo)
964 were enrolled in Study 1 and a total of 334 patients (226 Cymbalta, 108 placebo) were enrolled in Study 2.
965 Treatment with Cymbalta 60 mg one or two times a day statistically significantly improved the endpoint
966 mean pain scores from baseline and increased the proportion of patients with at least a 50% reduction in
967 pain score from baseline. For various degrees of improvement in pain from baseline to study endpoint,
968 Figures 1 and 2 show the fraction of patients achieving that degree of improvement. The figures are
969 cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every
970 level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement.
971 Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

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

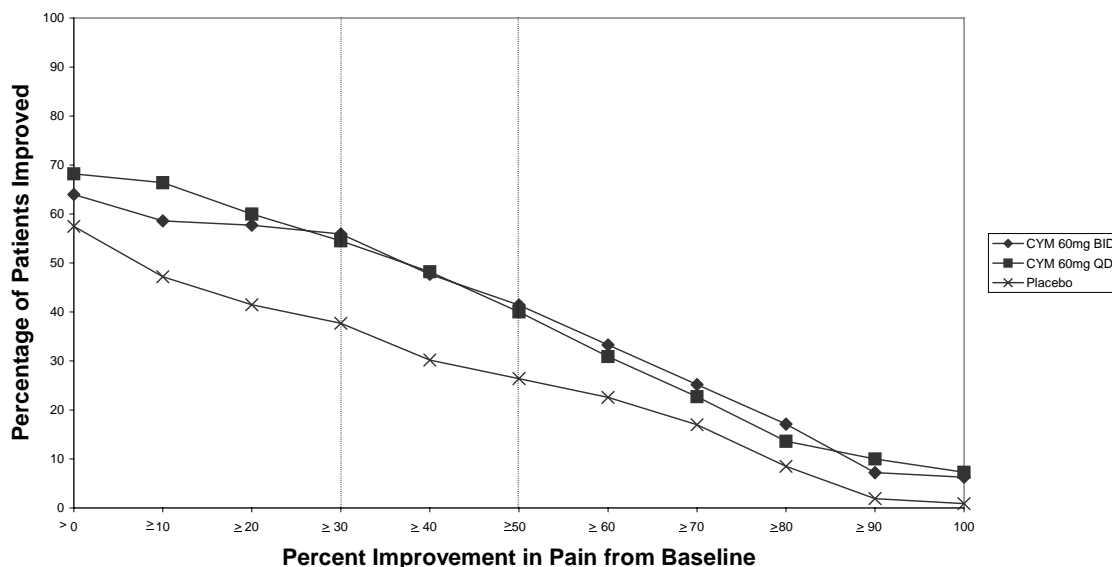


Figure 2: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity - Study 2

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14.3 Generalized Anxiety Disorder

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

In 1 flexible-dose study and in the fixed-dose study, the starting dose was 60 mg once daily where down titration to 30 mg once daily was allowed for tolerability reasons before increasing it to 60 mg once daily. Fifteen percent of patients were down titrated. One flexible-dose study had a starting dose of 30 mg once daily for 1 week before increasing it to 60 mg once daily.

The 2 flexible-dose studies involved dose titration with Cymbalta doses ranging from 60 mg once daily to 120 mg once daily (N=168 and N=162) compared to placebo (N=159 and N=161) over a 10-week treatment period. The mean dose for completers at endpoint in the flexible-dose studies was 104.75 mg/day. The fixed-dose study evaluated Cymbalta doses of 60 mg once daily (N=168) and 120 mg once daily (N=170) compared to placebo (N=175) over a 9-week treatment period. While a 120 mg/day dose was shown to be effective, there is no evidence that doses greater than 60 mg/day confer additional benefit.

In all 3 studies, Cymbalta demonstrated superiority over placebo as measured by greater improvement in the Hamilton Anxiety Scale (HAM-A) total score and by the Sheehan Disability Scale (SDS) global functional impairment score. The SDS is a widely used and well-validated scale that measures the extent emotional symptoms disrupt patient functioning in 3 life domains: work/school, social life/leisure activities and family life/home responsibilities.

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

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16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Cymbalta[®] is available as capsules in the following strengths, colors, imprints, and presentations:

Features	Strengths		
	20 mg*	30 mg*	60 mg*
Body color	Opaque green	Opaque white	Opaque green

Cap color	Opaque green	Opaque blue	Opaque blue
Cap imprint	Lilly 3235	Lilly 3240	Lilly 3237
Body imprint	20mg	30mg	60mg
Capsule number	PU3235	PU3240	PU3237
Presentations and NDC Codes			
Bottles of 30	NA	0002-3240-30	0002-3237-30
Bottles of 60	0002-3235-60	NA	NA
Bottles of 90	NA	0002-3240-90	0002-3237-90
Bottles of 1000	NA	0002-3240-04	0002-3237-04
Blisters ID†100	0002-3235-33	0002-3240-33	0002-3237-33

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* equivalent to duloxetine base
† Identi-Dose® (unit dose medication, Lilly)

16.2 Storage

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved Medication Guide

17.1 Information on Medication Guide

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Cymbalta and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for Cymbalta. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Cymbalta.

17.2 Clinical Worsening and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient’s prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient’s presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication [see *Boxed Warning, and Warning and Precautions (5.1)*].

17.3 Medication Administration

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.

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17.4 Continuing the Therapy Prescribed

While patients may notice improvement with Cymbalta therapy in 1 to 4 weeks, they should be advised to continue therapy as directed.

17.5 Abnormal Bleeding

Patients should be cautioned about the concomitant use of duloxetine 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)*].

17.6 Concomitant Medications

Patients should be advised 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 (2.5), Contraindications (4.1), Warnings and Precautions (5.4 and 5.10), and Drug Interactions (7)*].

17.7 Serotonin Syndrome

Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of Cymbalta and triptans, tramadol or other serotonergic agents [*see Warnings and Precautions (5.4) and Drug Interactions (7.14)*].

17.8 Pregnancy and Breast Feeding

Patients should be advised to notify their physician if they

- become pregnant during therapy
- intend to become pregnant during therapy
- are breast-feeding [*see Dosage and Administration (2.3) and Use in Specific Populations (8.1, 8.2, and 8.3)*].

17.9 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 ordinarily not be prescribed for patients with substantial alcohol use [*see Warnings and Precautions (5.2) and Drug Interactions (7.16)*].

17.10 Orthostatic Hypotension and Syncope

Patients should be advised of the risk of orthostatic hypotension 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 duloxetine [*see Warnings and Precautions (5.3)*].

17.11 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, patients should be cautioned about operating hazardous machinery including automobiles, until they are reasonably certain that Cymbalta therapy does not affect their ability to engage in such activities.

Literature revised: mmm dd, yyyy

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Indianapolis, IN 46285, USA
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Medication Guide

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Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions

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Read the Medication Guide that comes with your or your family member's antidepressant medicine.

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This Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant

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medicines. **Talk to your, or your family member's, healthcare provider about:**

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- all risks and benefits of treatment with antidepressant medicines

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- all treatment choices for depression or other serious mental illness

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

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1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**

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2. **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and 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

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(also called manic-depressive illness) or suicidal thoughts or actions.

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3. **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**

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- Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.

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- Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.

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- Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

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Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

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- thoughts about suicide or dying

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- attempts to commit suicide

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- new or worse depression

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- new or worse anxiety

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- feeling very agitated or restless

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- panic attacks

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- trouble sleeping (insomnia)

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- new or worse irritability

- 1138 • acting aggressive, being angry, or violent
- 1139 • acting on dangerous impulses
- 1140 • an extreme increase in activity and talking (mania)
- 1141 • other unusual changes in behavior or mood

1142 **What else do I need to know about antidepressant medicines?**

- 1143 • **Never stop an antidepressant medicine without first talking to a healthcare**
1144 **provider.** Stopping an antidepressant medicine suddenly can cause other
1145 symptoms.
- 1146 • **Antidepressants are medicines used to treat depression and other illnesses.** It is
1147 important to discuss all the risks of treating depression and also the risks of not
1148 treating it. Patients and their families or other caregivers should discuss all
1149 treatment choices with the healthcare provider, not just the use of antidepressants.
- 1150 • **Antidepressant medicines have other side effects.** Talk to the healthcare provider
1151 about the side effects of the medicine prescribed for you or your family member.
- 1152 • **Antidepressant medicines can interact with other medicines.** Know all of the
1153 medicines that you or your family member takes. Keep a list of all medicines to
1154 show the healthcare provider. Do not start new medicines without first checking
1155 with your healthcare provider.
- 1156 • **Not all antidepressant medicines prescribed for children are FDA approved**
1157 **for use in children.** Talk to your child's healthcare provider for more information.

1158 *This Medication Guide has been approved by the US Food and Drug*
1159 *Administration for all antidepressants.*

1160 Patient Information revised June 21, 2007

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