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CYMBALTA[®]

(duloxetine hydrochloride) Delayed-release Capsules

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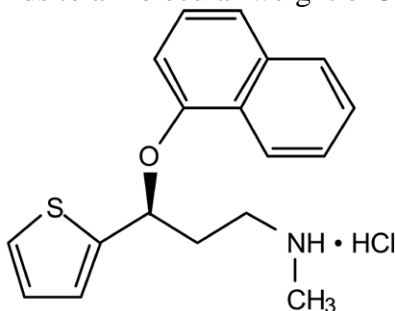
WARNING

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

20

DESCRIPTION

21 Cymbalta[®] (duloxetine hydrochloride) is a selective serotonin and norepinephrine reuptake
22 inhibitor (SSNRI) for oral administration. Its chemical designation is (+)-(S)-N-methyl-γ-(1-
23 naphthoxy)-2-thiophenpropylamine hydrochloride. The empirical formula is
24 C₁₈H₁₉NOS•HCl, which corresponds to a molecular weight of 333.88. The structural formula is:



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

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

CLINICAL PHARMACOLOGY

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35 **Pharmacodynamics**

36 Although the exact mechanisms of the antidepressant, central pain inhibitory and anxiolytic
37 actions of duloxetine in humans are unknown, these actions are believed to be related to its
38 potentiation of serotonergic and noradrenergic activity in the CNS. Preclinical studies have
39 shown that duloxetine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake
40 and a less potent inhibitor of dopamine reuptake. Duloxetine has no significant affinity for
41 dopaminergic, adrenergic, cholinergic, histaminergic, opioid, glutamate, and GABA receptors
42 *in vitro*. Duloxetine does not inhibit monoamine oxidase (MAO). Duloxetine undergoes
43 extensive metabolism, but the major circulating metabolites have not been shown to contribute
44 significantly to the pharmacologic activity of duloxetine.

45 **Pharmacokinetics**

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

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

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

62 Metabolism and Elimination — Biotransformation and disposition of duloxetine in humans
63 have been determined following oral administration of ^{14}C -labeled duloxetine. Duloxetine
64 comprises about 3% of the total radiolabeled material in the plasma, indicating that it undergoes
65 extensive metabolism to numerous metabolites. The major biotransformation pathways for
66 duloxetine involve oxidation of the naphthyl ring followed by conjugation and further oxidation.
67 Both CYP2D6 and CYP1A2 catalyze the oxidation of the naphthyl ring *in vitro*. Metabolites
68 found in plasma include 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine
69 sulfate. Many additional metabolites have been identified in urine, some representing only minor
70 pathways of elimination. Only trace (<1% of the dose) amounts of unchanged duloxetine are
71 present in the urine. Most (about 70%) of the duloxetine dose appears in the urine as metabolites
72 of duloxetine; about 20% is excreted in the feces.

73 **Special Populations**

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

76 Age — The pharmacokinetics of duloxetine after a single dose of 40 mg were compared in
77 healthy elderly females (65 to 77 years) and healthy middle-age females (32 to 50 years). There
78 was no difference in the C_{max} , but the AUC of duloxetine was somewhat (about 25%) higher and

79 the half-life about 4 hours longer in the elderly females. Population pharmacokinetic analyses
80 suggest that the typical values for clearance decrease by approximately 1% for each year of age
81 between 25 to 75 years of age; but age as a predictive factor only accounts for a small percentage
82 of between-patient variability. Dosage adjustment based on the age of the patient is not necessary
83 (*see* DOSAGE AND ADMINISTRATION).

84 Smoking Status — Duloxetine bioavailability (AUC) appears to be reduced by about
85 one-third in smokers. Dosage modifications are not recommended for smokers.

86 Race — No specific pharmacokinetic study was conducted to investigate the effects of race.

87 Renal Insufficiency — Limited data are available on the effects of duloxetine in patients with
88 end-stage renal disease (ESRD). After a single 60-mg dose of duloxetine, C_{max} and AUC values
89 were approximately 100% greater in patients with end-stage renal disease receiving chronic
90 intermittent hemodialysis than in subjects with normal renal function. The elimination half-life,
91 however, was similar in both groups. The AUCs of the major circulating metabolites, 4-hydroxy
92 duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate, largely excreted in urine,
93 were approximately 7- to 9-fold higher and would be expected to increase further with multiple
94 dosing. For this reason, Cymbalta is not recommended for patients with end-stage renal disease
95 (requiring dialysis) or severe renal impairment (estimated creatinine clearance [CrCl]
96 <30 mL/min) (*see* DOSAGE AND ADMINISTRATION). Population PK analyses suggest that
97 mild to moderate degrees of renal dysfunction (estimated CrCl 30-80 mL/min) have no
98 significant effect on duloxetine apparent clearance.

99 Hepatic Insufficiency — Patients with clinically evident hepatic insufficiency have decreased
100 duloxetine metabolism and elimination. After a single 20-mg dose of Cymbalta, 6 cirrhotic
101 patients with moderate liver impairment (Child-Pugh Class B) had a mean plasma duloxetine
102 clearance about 15% that of age- and gender-matched healthy subjects, with a 5-fold increase in
103 mean exposure (AUC). Although C_{max} was similar to normals in the cirrhotic patients, the
104 half-life was about 3 times longer (*see* PRECAUTIONS). It is recommended that duloxetine not
105 be administered to patients with any hepatic insufficiency (*see* DOSAGE AND
106 ADMINISTRATION).

107 Nursing Mothers — The disposition of duloxetine was studied in 6 lactating women who were
108 at least 12-weeks postpartum. Duloxetine 40 mg BID was given for 3.5 days. Lactation did not
109 influence duloxetine pharmacokinetics. Like many other drugs, duloxetine is detected in breast
110 milk, and steady-state concentrations in breast milk are about one-fourth those in plasma. The
111 amount of duloxetine in breast milk is approximately 7 μ g/day while on 40 mg BID dosing. The
112 excretion of duloxetine metabolites into breast milk was not examined. Because the safety of
113 duloxetine in infants is not known, nursing while on Cymbalta is not recommended (*see*
114 DOSAGE AND ADMINISTRATION).

115 **Drug-Drug Interactions (also see PRECAUTIONS, Drug Interactions)**

116 **Potential for Other Drugs to Affect Duloxetine**

117 Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

118 Inhibitors of CYP1A2 — When duloxetine 60 mg was co-administered with fluvoxamine
119 100 mg, a potent CYP1A2 inhibitor, to male subjects (n=14) duloxetine AUC was increased
120 approximately 6-fold, the C_{max} was increased about 2.5-fold, and duloxetine $t_{1/2}$ was increased
121 approximately 3-fold. Other drugs that inhibit CYP1A2 metabolism include cimetidine and
122 quinolone antimicrobials such as ciprofloxacin and enoxacin.

123 Inhibitors of CYP2D6 — Because CYP2D6 is involved in duloxetine metabolism, concomitant
124 use of duloxetine with potent inhibitors of CYP2D6 would be expected to, and does, result in
125 higher concentrations (on average 60%) of duloxetine (*see* PRECAUTIONS, Drug Interactions).

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

129 Studies with Benzodiazepines

130 Lorazepam — Under steady-state conditions for duloxetine (60 mg Q 12 hours) and lorazepam
131 (2 mg Q 12 hours), the pharmacokinetics of duloxetine were not affected by co-administration.

132 Temazepam — Under steady-state conditions for duloxetine (20 mg qhs) and temazepam
133 (30 mg qhs), the pharmacokinetics of duloxetine were not affected by co-administration.

134 Potential for Duloxetine to Affect Other Drugs

135 Drugs Metabolized by CYP1A2 — *In vitro* drug interaction studies demonstrate that
136 duloxetine does not induce CYP1A2 activity. Therefore, an increase in the metabolism of
137 CYP1A2 substrates (e.g., theophylline, caffeine) resulting from induction is not anticipated,
138 although clinical studies of induction have not been performed. Duloxetine is an inhibitor of the
139 CYP1A2 isoform in *in vitro* studies, and in two clinical studies the average (90% confidence
140 interval) increase in theophylline AUC was 7% (1%-5%) and 20% (13%-27%) when
141 co-administered with duloxetine (60 mg BID).

142 Drugs Metabolized by CYP2D6 — Duloxetine is a moderate inhibitor of CYP2D6 and
143 increases the AUC and C_{max} of drugs metabolized by CYP2D6 (*see* PRECAUTIONS).
144 Therefore, co-administration of Cymbalta with other drugs that are extensively metabolized by
145 this isozyme and that have a narrow therapeutic index should be approached with caution (*see*
146 PRECAUTIONS, Drug Interactions).

147 Drugs Metabolized by CYP2C9 — Duloxetine does not inhibit the *in vitro* enzyme activity of
148 CYP2C9. Inhibition of the metabolism of CYP2C9 substrates is therefore not anticipated,
149 although clinical studies have not been performed.

150 Drugs Metabolized by CYP3A — Results of *in vitro* studies demonstrate that duloxetine does
151 not inhibit or induce CYP3A activity. Therefore, an increase or decrease in the metabolism of
152 CYP3A substrates (e.g., oral contraceptives and other steroidal agents) resulting from induction
153 or inhibition is not anticipated, although clinical studies have not been performed.

154 Drugs Metabolized by CYP2C19 — Results of *in vitro* studies demonstrate that duloxetine
155 does not inhibit CYP2C19 activity at therapeutic concentrations. Inhibition of the metabolism of
156 CYP2C19 substrates is therefore not anticipated, although clinical studies have not been
157 performed.

158 Studies with Benzodiazepines

159 Lorazepam — Under steady-state conditions for duloxetine (60 mg Q 12 hours) and lorazepam
160 (2 mg Q 12 hours), the pharmacokinetics of lorazepam were not affected by co-administration.

161 Temazepam — Under steady-state conditions for duloxetine (20 mg qhs) and temazepam
162 (30 mg qhs), the pharmacokinetics of temazepam were not affected by co-administration.

163 Drugs Highly Bound to Plasma Protein — Because duloxetine is highly bound to plasma
164 protein, administration of Cymbalta to a patient taking another drug that is highly protein bound
165 may cause increased free concentrations of the other drug, potentially resulting in adverse events.

166

CLINICAL STUDIES

167 **Major Depressive Disorder**

168 The efficacy of Cymbalta as a treatment for depression was established in 4 randomized,
169 double-blind, placebo-controlled, fixed-dose studies in adult outpatients (18 to 83 years) meeting
170 DSM-IV criteria for major depression. In 2 studies, patients were randomized to Cymbalta 60 mg
171 once daily (N=123 and N=128, respectively) or placebo (N=122 and N=139, respectively) for
172 9 weeks; in the third study, patients were randomized to Cymbalta 20 or 40 mg twice daily
173 (N=86 and N=91, respectively) or placebo (N=89) for 8 weeks; in the fourth study, patients were
174 randomized to Cymbalta 40 or 60 mg twice daily (N=95 and N=93, respectively) or
175 placebo (N=93) for 8 weeks. There is no evidence that doses greater than 60 mg/day confer any
176 additional benefit.

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

179 Analyses of the relationship between treatment outcome and age, gender, and race did not
180 suggest any differential responsiveness on the basis of these patient characteristics.

181 **Diabetic Peripheral Neuropathic Pain**

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

191 Both studies compared Cymbalta 60 mg once daily or 60 mg twice daily with placebo. Study 1
192 additionally compared Cymbalta 20 mg with placebo. A total of 457 patients (342 Cymbalta,
193 115 placebo) were enrolled in Study 1 and a total of 334 patients (226 Cymbalta, 108 placebo)
194 were enrolled in Study 2. Treatment with Cymbalta 60 mg one or two times a day statistically
195 significantly improved the endpoint mean pain scores from baseline and increased the proportion
196 of patients with at least a 50% reduction in pain score from baseline. For various degrees of
197 improvement in pain from baseline to study endpoint, Figures 1 and 2 show the fraction of
198 patients achieving that degree of improvement. The figures are cumulative, so that patients
199 whose change from baseline is, for example, 50%, are also included at every level of
200 improvement below 50%. Patients who did not complete the study were assigned 0%
201 improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted
202 throughout the study.

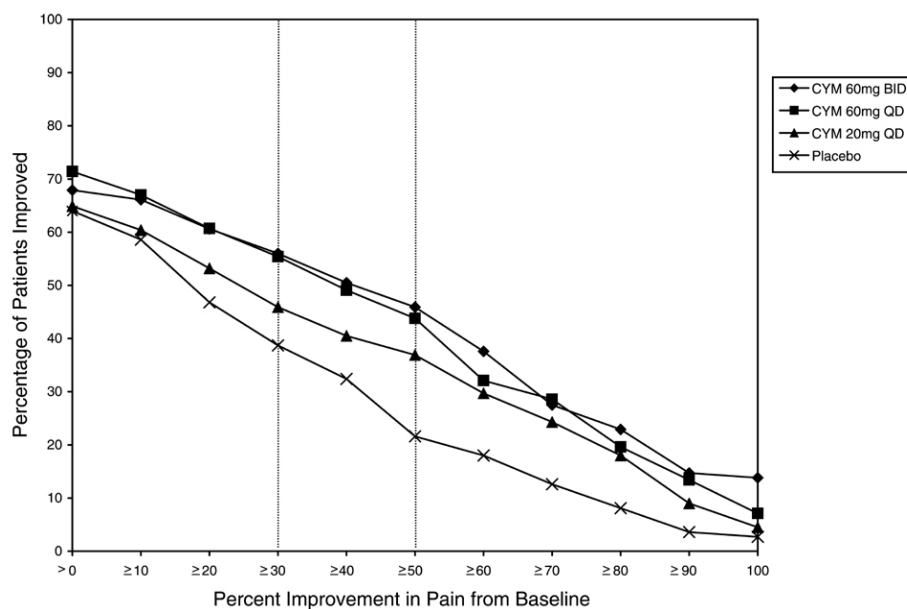


Figure 1: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity - Study 1

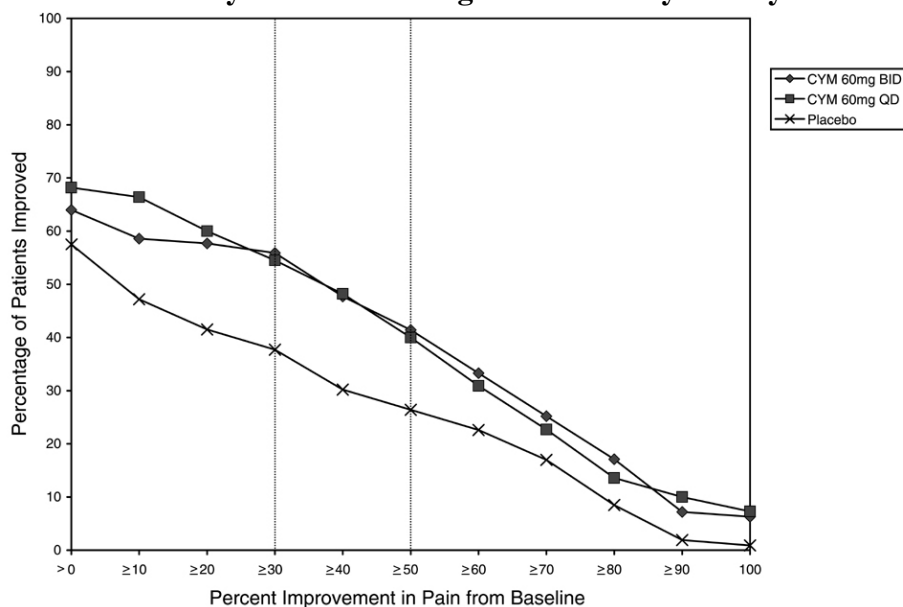


Figure 2: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity - Study 2

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211 Generalized Anxiety Disorder

212 The efficacy of Cymbalta in the treatment of generalized anxiety disorder (GAD) was
213 established in 1 fixed-dose randomized, double-blind, placebo-controlled trial and
214 2 flexible-dose randomized, double-blind, placebo-controlled trials in adult outpatients between
215 18 and 83 years of age meeting the DSM-IV criteria for GAD.

216 In 1 flexible-dose study and in the fixed-dose study, the starting dose was 60 mg once daily
217 where down titration to 30 mg once daily was allowed for tolerability reasons before increasing

218 it to 60 mg once daily. Fifteen percent of patients were down titrated. One flexible-dose study
219 had a starting dose of 30 mg once daily for 1 week before increasing it to 60 mg once daily.

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

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

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

234

INDICATIONS AND USAGE

235 **Major Depressive Disorder**

236 Cymbalta is indicated for the treatment of major depressive disorder (MDD).

237 The efficacy of Cymbalta has been established in 8- and 9-week placebo-controlled trials of
238 outpatients who met DSM-IV diagnostic criteria for major depressive disorder (*see CLINICAL*
239 *STUDIES*).

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

247 The effectiveness of Cymbalta in hospitalized patients with major depressive disorder has not
248 been studied.

249 The effectiveness of Cymbalta in long-term use for major depressive disorder, that is, for more
250 than 9 weeks, has not been systematically evaluated in controlled trials. The physician who elects
251 to use Cymbalta for extended periods should periodically evaluate the long-term usefulness of
252 the drug for the individual patient.

253 **Diabetic Peripheral Neuropathic Pain**

254 Cymbalta is indicated for the management of neuropathic pain associated with diabetic
255 peripheral neuropathy (*see CLINICAL STUDIES*).

256 **Generalized Anxiety Disorder**

257 Cymbalta is indicated for the treatment of generalized anxiety disorder (GAD).

258 The efficacy of Cymbalta has been established in three 9- or 10-week placebo-controlled trials
259 of outpatients who met DSM-IV diagnostic criteria for generalized anxiety disorder (*see*
260 *CLINICAL STUDIES*).

261 Generalized anxiety disorder is defined by the DSM-IV as excessive anxiety and worry,
262 present more days than not, for at least 6 months. The excessive anxiety and worry must be

263 difficult to control and must cause significant distress or impairment in normal functioning. It
264 must be associated with at least 3 of the following 6 symptoms: restlessness or feeling keyed up
265 or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability,
266 muscle tension, and/or sleep disturbance.

267 The effectiveness of Cymbalta in long-term use for GAD, that is, for more than 10 weeks, has
268 not been systematically evaluated in controlled trials. The physician who elects to use Cymbalta
269 for extended periods should periodically evaluate the long-term usefulness of the drug for the
270 individual patient.

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CONTRAINDICATIONS

272 **Hypersensitivity**

273 Cymbalta is contraindicated in patients with a known hypersensitivity to duloxetine or any of
274 the inactive ingredients.

275 **Monoamine Oxidase Inhibitors**

276 Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated
277 (*see* WARNINGS).

278 **Uncontrolled Narrow-Angle Glaucoma**

279 In clinical trials, Cymbalta use was associated with an increased risk of mydriasis; therefore, its
280 use should be avoided in patients with uncontrolled narrow-angle glaucoma.

281

WARNINGS

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

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

296 The pooled analyses of placebo-controlled trials in children and adolescents with MDD,
297 obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24
298 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of
299 placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of
300 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000
301 patients. There was considerable variation in risk of suicidality among drugs, but a tendency
302 toward an increase in the younger patients for almost all drugs studied. There were differences in
303 absolute risk of suicidality across the different indications, with the highest incidence in MDD.
304 The risk of differences (drug vs placebo), however, were relatively stable within age strata and
305 across indications. These risk differences (drug-placebo difference in the number of cases of
306 suicidality per 1000 patients treated) are provided in Table 1.

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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

309

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

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

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

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

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

331 If the decision has been made to discontinue treatment, medication should be tapered, as
332 rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with
333 certain symptoms (*see* PRECAUTIONS *and* DOSAGE AND ADMINISTRATION,
334 Discontinuation of Treatment with Cymbalta, for a description of the risks of discontinuation of
335 Cymbalta).

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

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

354 **Monoamine Oxidase Inhibitors (MAOI)** — **In patients receiving a serotonin reuptake**
355 **inhibitor in combination with a monoamine oxidase inhibitor, there have been reports of**
356 **serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic**
357 **instability with possible rapid fluctuations of vital signs, and mental status changes that**
358 **include extreme agitation progressing to delirium and coma. These reactions have also**
359 **been reported in patients who have recently discontinued serotonin reuptake inhibitors and**
360 **are then started on an MAOI. Some cases presented with features resembling neuroleptic**
361 **malignant syndrome. The effects of combined use of Cymbalta and MAOIs have not been**
362 **evaluated in humans or animals. Therefore, because Cymbalta is an inhibitor of both**
363 **serotonin and norepinephrine reuptake, it is recommended that Cymbalta not be used in**
364 **combination with an MAOI, or within at least 14 days of discontinuing treatment with an**
365 **MAOI. Based on the half-life of Cymbalta, at least 5 days should be allowed after stopping**
366 **Cymbalta before starting an MAOI.**

367 **Serotonin Syndrome** — The development of a potentially life-threatening serotonin syndrome
368 may occur with SNRIs and SSRIs, including Cymbalta treatment, particularly with concomitant
369 use of serotonergic drugs (including triptans) and with drugs which impair metabolism of
370 serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes
371 (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood
372 pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or
373 gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

374 The concomitant use of Cymbalta with MAOIs intended to treat depression is contraindicated
375 (*see* CONTRAINDICATIONS and WARNINGS, Potential for Interaction with Monoamine
376 Oxidase Inhibitors).

377 If concomitant treatment of Cymbalta with a 5-hydroxytryptamine receptor agonist (triptan) is
378 clinically warranted, careful observation of the patient is advised, particularly during treatment
379 initiation and dose increases (*see* PRECAUTIONS, Drug Interactions).

380 The concomitant use of Cymbalta with serotonin precursors (such as tryptophan) is not
381 recommended (*see* PRECAUTIONS, Drug Interactions).

382

PRECAUTIONS

General

384 **Hepatotoxicity** — Cymbalta increases the risk of elevation of serum transaminase levels. Liver
385 transaminase elevations resulted in the discontinuation of 0.4% (31/8454) of Cymbalta-treated
386 patients. In these patients, the median time to detection of the transaminase elevation was about
387 two months. In controlled trials in MDD, elevations of alanine transaminase (ALT) to >3 times
388 the upper limit of normal occurred in 0.9% (8/930) of Cymbalta-treated patients and in
389 0.3% (2/652) of placebo-treated patients. In controlled trials in DPN, elevations of ALT to

390 >3 times the upper limit of normal occurred in 1.68% (8/477) of Cymbalta-treated patients and in
391 0% (0/187) of placebo-treated patients. In the full cohort of placebo-controlled trials in any
392 indication, elevation of ALT >3 times the upper limit of normal occurred in 1% (39/3732) of
393 Cymbalta-treated patients compared to 0.2% (6/2568) of placebo-treated patients. In
394 placebo-controlled studies using a fixed-dose design, there was evidence of a dose-response
395 relationship for ALT and AST elevation of >3 times the upper limit of normal and >5 times the
396 upper limit of normal, respectively. Postmarketing reports have described cases of hepatitis with
397 abdominal pain, hepatomegaly and elevation of transaminase levels to more than twenty times
398 the upper limit of normal with or without jaundice, reflecting a mixed or hepatocellular pattern of
399 liver injury. Cases of cholestatic jaundice with minimal elevation of transaminase levels have
400 also been reported.

401 The combination of transaminase elevations and elevated bilirubin, without evidence of
402 obstruction, is generally recognized as an important predictor of severe liver injury. In clinical
403 trials, three Cymbalta patients had elevations of transaminases and bilirubin, but also had
404 elevation of alkaline phosphatase, suggesting an obstructive process; in these patients, there was
405 evidence of heavy alcohol use and this may have contributed to the abnormalities seen.
406 Two placebo-treated patients also had transaminase elevations with elevated bilirubin.
407 Postmarketing reports indicate that elevated transaminases, bilirubin and alkaline phosphatase
408 have occurred in patients with chronic liver disease or cirrhosis. Because it is possible that
409 duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate
410 pre-existing liver disease, Cymbalta should ordinarily not be prescribed to patients with
411 substantial alcohol use or evidence of chronic liver disease.

412 Orthostatic Hypotension and Syncope — Orthostatic hypotension and syncope have been
413 reported with therapeutic doses of duloxetine. Syncope and orthostatic hypotension tend to occur
414 within the first week of therapy but can occur at any time during duloxetine treatment,
415 particularly after dose increases. The risk of blood pressure decreases may be greater in patients
416 taking concomitant medications that induce orthostatic hypotension (such as antihypertensives)
417 or are potent CYP1A2 inhibitors (*see* CLINICAL PHARMACOLOGY, Drug-Drug Interactions,
418 *and* PRECAUTIONS, Drug Interactions) and in patients taking duloxetine at doses above 60 mg
419 daily. Consideration should be given to discontinuing duloxetine in patients who experience
420 symptomatic orthostatic hypotension and/or syncope during duloxetine therapy.

421 Effect on Blood Pressure — In clinical trials across indications, relative to placebo, duloxetine
422 treatment was associated with mean increases of up to 2.1 mm Hg in systolic blood pressure and
423 up to 2.3 mm Hg in diastolic blood pressure. There was no significant difference in the frequency
424 of sustained (3 consecutive visits) elevated blood pressure. In a clinical pharmacology study
425 designed to evaluate the effects of duloxetine on various parameters, including blood pressure at
426 supratherapeutic doses with an accelerated dose titration, there was evidence of increases in
427 supine blood pressure at doses up to 200 mg BID. At the highest 200 mg BID dose, the increase
428 in mean pulse rate was 5.0-6.8 bpm and increases in mean blood pressure were 4.7-6.8 mm Hg
429 (systolic) and 4.5-7 mm Hg (diastolic) up to 12 hours after dosing.

430 Blood pressure should be measured prior to initiating treatment and periodically measured
431 throughout treatment (*see* ADVERSE REACTIONS, Vital Sign Changes).

432 Activation of Mania/Hypomania — In placebo-controlled trials in patients with major
433 depressive disorder, activation of mania or hypomania was reported in 0.1% (2/2327) of
434 duloxetine-treated patients and 0.1% (1/1460) of placebo-treated patients. No activation of mania
435 or hypomania was reported in DPNP or GAD placebo-controlled trials. Activation of

436 mania/hypomania has been reported in a small proportion of patients with mood disorders who
437 were treated with other marketed drugs effective in the treatment of major depressive disorder.
438 As with these other agents, Cymbalta should be used cautiously in patients with a history of
439 mania.

440 Seizures — Duloxetine has not been systematically evaluated in patients with a seizure
441 disorder, and such patients were excluded from clinical studies. In placebo-controlled clinical
442 trials, seizures/convulsions occurred in 0.04% (3/8504) of patients treated with duloxetine and
443 0.02% (1/6123) of patients treated with placebo. Cymbalta should be prescribed with care in
444 patients with a history of a seizure disorder.

445 Hyponatremia — Cases of hyponatremia (some with serum sodium lower than 110 mmol/L)
446 have been reported and appeared to be reversible when Cymbalta was discontinued. Some cases
447 were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH).
448 The majority of these occurrences have been in elderly individuals, some in patients taking
449 diuretics or who were otherwise volume depleted.

450 Controlled Narrow-Angle Glaucoma — In clinical trials, Cymbalta was associated with an
451 increased risk of mydriasis; therefore, it should be used cautiously in patients with controlled
452 narrow-angle glaucoma (*see* CONTRAINDICATIONS, Uncontrolled Narrow-Angle Glaucoma).

453 Discontinuation of Treatment with Cymbalta — Discontinuation symptoms have been
454 systematically evaluated in patients taking duloxetine. Following abrupt discontinuation in
455 placebo-controlled clinical trials, the following symptoms occurred at a rate greater than or equal
456 to 1% and at a significantly higher rate in duloxetine-treated patients compared to those
457 discontinuing from placebo: dizziness; nausea; headache; paresthesia; vomiting; irritability;
458 nightmares; insomnia; diarrhea; anxiety; hyperhidrosis; and vertigo.

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

466 Patients should be monitored for these symptoms when discontinuing treatment with
467 Cymbalta. A gradual reduction in the dose rather than abrupt cessation is recommended
468 whenever possible. If intolerable symptoms occur following a decrease in the dose or upon
469 discontinuation of treatment, then resuming the previously prescribed dose may be considered.
470 Subsequently, the physician may continue decreasing the dose but at a more gradual rate (*see*
471 DOSAGE AND ADMINISTRATION).

472 Use in Patients with Concomitant Illness — Clinical experience with Cymbalta in patients with
473 concomitant systemic illnesses is limited. There is no information on the effect that alterations in
474 gastric motility may have on the stability of Cymbalta's enteric coating. As duloxetine is rapidly
475 hydrolyzed in acidic media to naphthol, caution is advised in using Cymbalta in patients with
476 conditions that may slow gastric emptying (e.g., some diabetics).

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

480 As observed in DPNP trials, Cymbalta treatment worsens glycemic control in some patients
481 with diabetes. In three clinical trials of Cymbalta for the management of neuropathic pain

482 associated with diabetic peripheral neuropathy, the mean duration of diabetes was approximately
483 12 years, the mean baseline fasting blood glucose was 176 mg/dL, and the mean baseline
484 hemoglobin A_{1c} (HbA_{1c}) was 7.8%. In the 12-week acute treatment phase of these studies,
485 Cymbalta was associated with a small increase in mean fasting blood glucose as compared to
486 placebo. In the extension phase of these studies, which lasted up to 52 weeks, mean fasting blood
487 glucose increased by 12 mg/dL in the Cymbalta group and decreased by 11.5 mg/dL in the
488 routine care group. HbA_{1c} increased by 0.5% in the Cymbalta and by 0.2% in the routine care
489 groups.

490 Increased plasma concentrations of duloxetine, and especially of its metabolites, occur in
491 patients with end-stage renal disease (requiring dialysis). For this reason, Cymbalta is not
492 recommended for patients with end-stage renal disease or severe renal impairment (creatinine
493 clearance <30 mL/min) (*see CLINICAL PHARMACOLOGY and DOSAGE AND*
494 *ADMINISTRATION*).

495 Markedly increased exposure to duloxetine occurs in patients with hepatic insufficiency and
496 Cymbalta should not be administered to these patients (*see CLINICAL PHARMACOLOGY and*
497 *DOSAGE AND ADMINISTRATION*).

498 **Information for Patients**

499 Prescribers or other health professionals should inform patients, their families, and their
500 caregivers about the benefits and risks associated with treatment with Cymbalta and should
501 counsel them in its appropriate use. A patient Medication Guide about “Antidepressant
502 Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions” is
503 available for Cymbalta. The prescriber or health professional should instruct patients, their
504 families, and their caregivers to read the Medication Guide and should assist them in
505 understanding its contents. Patients should be given the opportunity to discuss the contents of the
506 Medication Guide and to obtain answers to any questions they may have. The complete text of
507 the Medication Guide is reprinted at the end of this document.

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

510 Clinical Worsening and Suicide Risk — Patients, their families, and their caregivers should be
511 encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability,
512 hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania,
513 other unusual changes in behavior, worsening of depression, and suicidal ideation, especially
514 early during antidepressant treatment and when the dose is adjusted up or down. Families and
515 caregivers of patients should be advised to look for the emergence of such symptoms on a
516 day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the
517 patient’s prescriber or health professional, especially if they are severe, abrupt in onset, or were
518 not part of the patient’s presenting symptoms. Symptoms such as these may be associated with
519 an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring
520 and possibly changes in the medication.

521 Cymbalta should be swallowed whole and should not be chewed or crushed, nor should the
522 contents be sprinkled on food or mixed with liquids. All of these might affect the enteric coating.

523 Any psychoactive drug may impair judgment, thinking, or motor skills. Although in controlled
524 studies Cymbalta has not been shown to impair psychomotor performance, cognitive function, or
525 memory, it may be associated with sedation and dizziness. Therefore, patients should be
526 cautioned about operating hazardous machinery including automobiles, until they are reasonably
527 certain that Cymbalta therapy does not affect their ability to engage in such activities.

528 Patients should be advised to inform their physicians if they are taking, or plan to take, any
529 prescription or over-the-counter medications, since there is a potential for interactions.

530 Although Cymbalta does not increase the impairment of mental and motor skills caused by
531 alcohol, use of Cymbalta concomitantly with heavy alcohol intake may be associated with severe
532 liver injury. For this reason, Cymbalta should ordinarily not be prescribed for patients with
533 substantial alcohol use.

534 Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of
535 Cymbalta and triptans, tramadol or other serotonergic agents.

536 Orthostatic Hypotension and Syncope — Patients should be advised of the risk of orthostatic
537 hypotension and syncope, especially during the period of initial use and subsequent dose
538 escalation, and in association with the use of concomitant drugs that might potentiate the
539 orthostatic effect of duloxetine.

540 Patients should be advised to notify their physician if they become pregnant or intend to
541 become pregnant during therapy.

542 Patients should be advised to notify their physician if they are breast-feeding.

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

545 **Laboratory Tests**

546 No specific laboratory tests are recommended.

547 **Drug Interactions (also see CLINICAL PHARMACOLOGY, Drug-Drug Interactions)**

548 Potential for Other Drugs to Affect Cymbalta

549 Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

550 Inhibitors of CYP1A2 — Concomitant use of duloxetine with fluvoxamine, an inhibitor of
551 CYP1A2, results in approximately a 6-fold increase in AUC and about a 2.5-fold increase in
552 C_{max} of duloxetine. Some quinolone antibiotics would be expected to have similar effects and
553 these combinations should be avoided.

554 Inhibitors of CYP2D6 — Because CYP2D6 is involved in duloxetine metabolism, concomitant
555 use of duloxetine with potent inhibitors of CYP2D6 may result in higher concentrations of
556 duloxetine. Paroxetine (20 mg QD) increased the concentration of duloxetine (40 mg QD) by
557 about 60%, and greater degrees of inhibition are expected with higher doses of paroxetine.
558 Similar effects would be expected with other potent CYP2D6 inhibitors (e.g., fluoxetine,
559 quinidine).

560 Potential for Duloxetine to Affect Other Drugs

561 Drugs Metabolized by CYP1A2 — *In vitro* drug interaction studies demonstrate that
562 duloxetine does not induce CYP1A2 activity, and it is unlikely to have a clinically significant
563 effect on the metabolism of CYP1A2 substrates (*see* CLINICAL PHARMACOLOGY, Drug
564 Interactions).

565 Drugs Metabolized by CYP2D6 — Duloxetine is a moderate inhibitor of CYP2D6. When
566 duloxetine was administered (at a dose of 60 mg BID) in conjunction with a single 50-mg dose
567 of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold. Therefore,
568 co-administration of Cymbalta with other drugs that are extensively metabolized by this isozyme
569 and which have a narrow therapeutic index, including certain antidepressants (tricyclic
570 antidepressants [TCAs], such as nortriptyline, amitriptyline, and imipramine), phenothiazines
571 and Type 1C antiarrhythmics (e.g., propafenone, flecainide), should be approached with caution.
572 Plasma TCA concentrations may need to be monitored and the dose of the TCA may need to be

573 reduced if a TCA is co-administered with Cymbalta. Because of the risk of serious ventricular
574 arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine,
575 Cymbalta and thioridazine should not be co-administered.

576 Drugs Metabolized by CYP3A — Results of *in vitro* studies demonstrate that duloxetine does
577 not inhibit or induce CYP3A activity (*see* CLINICAL PHARMACOLOGY, Drug Interactions).

578 **Cymbalta May Have a Clinically Important Interaction with the Following Other Drugs:**

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

582 In the Cymbalta clinical trials database, three Cymbalta-treated patients had liver injury as
583 manifested by ALT and total bilirubin elevations, with evidence of obstruction. Substantial
584 intercurrent ethanol use was present in each of these cases, and this may have contributed to the
585 abnormalities seen (*see* PRECAUTIONS, Hepatotoxicity).

586 CNS Acting Drugs — Given the primary CNS effects of Cymbalta, it should be used with
587 caution when it is taken in combination with or substituted for other centrally acting drugs,
588 including those with a similar mechanism of action.

589 Serotonergic Drugs — Based on the mechanism of action of SNRIs and SSRIs, including
590 Cymbalta and the potential for serotonin syndrome, caution is advised when Cymbalta is
591 coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such
592 as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol,
593 or St. John's Wort (*see* WARNINGS, Serotonin Syndrome). The concomitant use of Cymbalta
594 with other SSRIs, SNRIs or tryptophan is not recommended (*see* PRECAUTIONS, Drug
595 Interactions).

596 Triptans — There have been rare postmarketing reports of serotonin syndrome with use of an
597 SSRI and a triptan. If concomitant treatment of Cymbalta with a triptan is clinically warranted,
598 careful observation of the patient is advised, particularly during treatment initiation and dose
599 increases (*see* WARNINGS, Serotonin Syndrome).

600 Potential for Interaction with Drugs that Affect Gastric Acidity — Cymbalta has an enteric
601 coating that resists dissolution until reaching a segment of the gastrointestinal tract where the pH
602 exceeds 5.5. In extremely acidic conditions, Cymbalta, unprotected by the enteric coating, may
603 undergo hydrolysis to form naphthol. Caution is advised in using Cymbalta in patients with
604 conditions that may slow gastric emptying (e.g., some diabetics). Drugs that raise the
605 gastrointestinal pH may lead to an earlier release of duloxetine. However, co-administration of
606 Cymbalta with aluminum- and magnesium-containing antacids (51 mEq) or Cymbalta with
607 famotidine, had no significant effect on the rate or extent of duloxetine absorption after
608 administration of a 40-mg oral dose. It is unknown whether the concomitant administration of
609 proton pump inhibitors affects duloxetine absorption.

610 Monoamine Oxidase Inhibitors — *See* CONTRAINDICATIONS and WARNINGS.

611 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

618 100 mg/kg/day (8 times the MRHD and 4 times the human dose of 120 mg/day on a mg/m²
619 basis).

620 In rats, dietary doses of duloxetine up to 27 mg/kg/day in females (4 times the MRHD and
621 2 times the human dose of 120 mg/day on a mg/m² basis) and up to 36 mg/kg/day in males
622 (6 times the MRHD and 3 times the human dose of 120 mg/day on a mg/m² basis) did not
623 increase the incidence of tumors.

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

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

634 **Pregnancy**

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

637 When duloxetine was administered orally to pregnant rats and rabbits during the period of
638 organogenesis, there was no evidence of teratogenicity at doses up to 45 mg/kg/day (7 times the
639 maximum recommended human dose [MRHD, 60 mg/day] and 4 times the human dose of
640 120 mg/day on a mg/m² basis, in rat; 15 times the MRHD and 7 times the human dose of
641 120 mg/day on a mg/m² basis in rabbit). However, fetal weights were decreased at this dose,
642 with a no-effect dose of 10 mg/kg/day (2 times the MRHD and ≈1 times the human dose of
643 120 mg/day on a mg/m² basis in rat; 3 times the MRHD and 2 times the human dose of
644 120 mg/day on a mg/m² basis in rabbits).

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

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

656 Nonteratogenic Effects — Neonates exposed to SSRIs or serotonin and norepinephrine
657 reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring
658 prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise
659 immediately upon delivery. Reported clinical findings have included respiratory distress,
660 cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia,
661 hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These
662 features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug
663 discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent

664 with serotonin syndrome (*see* WARNINGS, Monoamine Oxidase Inhibitors). When treating a
665 pregnant woman with Cymbalta during the third trimester, the physician should carefully
666 consider the potential risks and benefits of treatment (*see* DOSAGE AND
667 ADMINISTRATION).

668 **Labor and Delivery**

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

671 **Nursing Mothers**

672 Duloxetine is excreted into the milk of lactating women. The estimated daily infant dose on a
673 mg/kg basis is approximately 0.14% of the maternal dose. Because the safety of duloxetine in
674 infants is not known, nursing while on Cymbalta is not recommended.

675 **Pediatric Use**

676 Safety and effectiveness in the pediatric population have not been established (*see* BOX
677 WARNING *and* WARNINGS, Clinical Worsening and Suicide Risk). Anyone considering the
678 use of Cymbalta in a child or adolescent must balance the potential risks with the clinical need.

679 **Geriatric Use**

680 Of the 2418 patients in premarketing clinical studies of Cymbalta for MDD, 5.9% (143) were
681 65 years of age or over. Of the 1074 patients in the DPN premarketing studies, 33% (357) were
682 65 years of age or over. Premarketing clinical studies of GAD did not include sufficient numbers
683 of subjects age 65 or over to determine whether they respond differently from younger subjects.
684 In the MDD and DPN studies, no overall differences in safety or effectiveness were observed
685 between these subjects and younger subjects, and other reported clinical experience has not
686 identified differences in responses between the elderly and younger patients, but greater
687 sensitivity of some older individuals cannot be ruled out. As with other antidepressants,
688 Cymbalta has been associated with cases of clinically significant hyponatremia (*see*
689 Hyponatremia, under PRECAUTIONS).

690 **ADVERSE REACTIONS**

691 Cymbalta has been evaluated for safety in 2418 patients diagnosed with major depressive
692 disorder who participated in multiple-dose premarketing trials, representing 1099 patient-years
693 of exposure. Among these 2418 Cymbalta-treated patients, 1139 patients participated in
694 eight 8- or 9-week, placebo-controlled trials at doses ranging from 40 to 120 mg/day, while the
695 remaining 1279 patients were followed for up to 1 year in an open-label safety study using
696 flexible doses from 80 to 120 mg/day. Two placebo-controlled studies with doses of 80 and
697 120 mg/day had 6-month maintenance extensions. Of these 2418 patients, 993 Cymbalta-treated
698 patients were exposed for at least 180 days and 445 Cymbalta-treated patients were exposed for
699 at least 1 year.

700 Cymbalta has also been evaluated for safety in 1074 patients with diabetic peripheral
701 neuropathy representing 472 patient-years of exposure. Among these 1074 Cymbalta-treated
702 patients, 568 patients participated in two 12- to 13-week, placebo-controlled trials at doses
703 ranging from 20 to 120 mg/day. An additional 449 patients were enrolled in an open-label safety
704 study using 120 mg/day for a duration of 6 months. Another 57 patients, originally treated with
705 placebo, were exposed to Cymbalta for up to 12 months at 60 mg twice daily in an extension
706 phase. Among these 1074 patients, 484 had 6 months of exposure to Cymbalta, and 220 had
707 12 months of exposure.

708 Cymbalta has also been evaluated for safety in 668 patients with generalized anxiety disorder
709 representing 95 patient-years of exposure. These 668 patients participated in 9- or 10-week
710 placebo-controlled trials at doses ranging from 60 mg once daily to 120 mg once daily. Of these
711 668 patients, 449 were exposed for at least 2 months to Cymbalta.

712 In the full cohort of placebo-controlled clinical trials for any indication, safety has been
713 evaluated in 8504 patients treated with duloxetine and 6123 patients treated with placebo. In
714 clinical trials, a total of 23,983 patients have been exposed to duloxetine. In duloxetine clinical
715 trials, adverse reactions were assessed by collecting adverse events, results of physical
716 examinations, vital signs, weights, laboratory analyses, and ECGs.

717 Clinical investigators recorded adverse events using descriptive terminology of their own
718 choosing. To provide a meaningful estimate of the proportion of individuals experiencing
719 adverse events, grouping similar types of events into a smaller number of standardized event
720 categories is necessary. In the tables and tabulations that follow, MedDRA terminology has been
721 used to classify reported adverse events.

722 The stated frequencies of adverse events represent the proportion of individuals who
723 experienced, at least once, a treatment-emergent adverse event of the type listed. An event was
724 considered treatment-emergent if it occurred for the first time or worsened while receiving
725 therapy following baseline evaluation. Events reported during the studies were not necessarily
726 caused by the therapy, and the frequencies do not reflect investigator impression (assessment) of
727 causality.

728 The cited figures provide the prescriber with some basis for estimating the relative contribution
729 of drug and non-drug factors to the adverse event incidence rate in the population studied. The
730 prescriber should be aware that the figures in the tables and tabulations cannot be used to predict
731 the incidence of adverse events in the course of usual medical practice where patient
732 characteristics and other factors differ from those that prevailed in the clinical trials. Similarly,
733 the cited frequencies cannot be compared with figures obtained from other clinical investigations
734 involving different treatments, uses, and investigators.

735 **Adverse Events Reported as Reasons for Discontinuation of Treatment in** 736 **Placebo-Controlled Trials**

737 **Major Depressive Disorder**

738 Approximately 10% of the 1139 patients who received Cymbalta in the MDD
739 placebo-controlled trials discontinued treatment due to an adverse event, compared with 4% of
740 the 777 patients receiving placebo. Nausea (Cymbalta 1.4%, placebo 0.1%) was the only
741 common adverse event reported as reason for discontinuation and considered to be drug-related
742 (i.e., discontinuation occurring in at least 1% of the Cymbalta-treated patients and at a rate of at
743 least twice that of placebo).

744 **Diabetic Peripheral Neuropathic Pain**

745 Approximately 14% of the 568 patients who received Cymbalta in the DPN placebo-controlled
746 trials discontinued treatment due to an adverse event, compared with 7% of the 223 patients
747 receiving placebo. Nausea (Cymbalta 3.5%, placebo 0.4%), dizziness (Cymbalta 1.6%,
748 placebo 0.4%), somnolence (Cymbalta 1.6%, placebo 0%) and fatigue (Cymbalta 1.1%,
749 placebo 0%) were the common adverse events reported as reasons for discontinuation and
750 considered to be drug-related (i.e., discontinuation occurring in at least 1% of the
751 Cymbalta-treated patients and at a rate of at least twice that of placebo).

752 **Generalized Anxiety Disorder**

753 Approximately 16% of the 668 patients who received Cymbalta in the GAD placebo-controlled
 754 trials discontinued treatment due to an adverse event, compared with 4% of the 495 patients
 755 receiving placebo. Nausea (Cymbalta 3.7%, placebo 0.2%), vomiting (Cymbalta 1.4%,
 756 placebo 0%) and dizziness (Cymbalta 1.2%, placebo 0.2%) were the common adverse events
 757 reported as reasons for discontinuation and considered to be drug-related (i.e., discontinuation
 758 occurring in at least 1% of the Cymbalta-treated patients and at a rate of at least twice that of
 759 placebo).

760 **Adverse Events Occurring at an Incidence of 2% or More Among Cymbalta-**
 761 **Treated Patients in Placebo-Controlled Trials**

762 **Major Depressive Disorder**

763 Table 2 gives the incidence of treatment-emergent adverse events that occurred in 2% or more
 764 of patients treated with Cymbalta in the premarketing acute phase of MDD placebo-controlled
 765 trials and with an incidence greater than placebo. The most commonly observed adverse events
 766 in Cymbalta-treated MDD patients (incidence of 5% or greater and at least twice the incidence in
 767 placebo patients) were: nausea; dry mouth; constipation; decreased appetite; fatigue;
 768 somnolence; and increased sweating (*see* Table 2).

769
 770 **Table 2: Treatment-Emergent Adverse Events Incidence**
 771 **in MDD Placebo-Controlled Trials¹**

System Organ Class / Adverse Event	Percentage of Patients Reporting Event	
	Cymbalta (N=1139)	Placebo (N=777)
Gastrointestinal Disorders		
Nausea	20	7
Dry mouth	15	6
Constipation	11	4
Diarrhea	8	6
Vomiting	5	3
Metabolism and Nutrition Disorders		
Appetite decreased ²	8	2
Investigations		
Weight decreased	2	1
General Disorders and Administration Site Conditions		
Fatigue	8	4
Nervous System Disorders		
Dizziness	9	5
Somnolence	7	3
Tremor	3	1
Skin and Subcutaneous Tissue Disorders		
Sweating increased	6	2
Vascular Disorders		
Hot flushes	2	1
Eye Disorders		
Vision blurred	4	1
Psychiatric Disorders		
Insomnia ³	11	6
Anxiety	3	2
Libido decreased	3	1

Orgasm abnormal ⁴	3	1
Reproductive System and Breast Disorders		
Erectile dysfunction ⁵	4	1
Ejaculation delayed ⁵	3	1
Ejaculatory dysfunction ^{5,6}	3	1

¹ Events reported by at least 2% of patients treated with Cymbalta and more often with placebo. The following events were reported by at least 2% of patients treated with Cymbalta for MDD and had an incidence equal to or less than placebo: upper abdominal pain, palpitations, dyspepsia, back pain, arthralgia, headache, pharyngitis, cough, nasopharyngitis, and upper respiratory tract infection.

² Term includes anorexia.

³ Term includes middle insomnia.

⁴ Term includes anorgasmia.

⁵ Male patients only.

⁶ Term includes ejaculation disorder and ejaculation failure.

Diabetic Peripheral Neuropathic Pain

Table 3 gives the incidence of treatment-emergent adverse events that occurred in 2% or more of patients treated with Cymbalta in the premarketing acute phase of DPN placebo-controlled trials (doses of 20 to 120 mg/day) and with an incidence greater than placebo. The most commonly observed adverse events in Cymbalta-treated DPN patients (incidence of 5% or greater and at least twice the incidence in placebo patients) were: nausea; somnolence; dizziness; constipation; dry mouth; hyperhidrosis; decreased appetite; and asthenia (*see* Table 3).

Table 3: Treatment-Emergent Adverse Events Incidence in DPN Placebo-Controlled Trials¹

System Organ Class / Adverse Event	Percentage of Patients Reporting Event			
	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 ²	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 Events reported by at least 2% of patients treated with Cymbalta and more often than placebo. The following events were reported by at least 2% of patients treated with Cymbalta for DPN and had an incidence equal to or less than placebo: edema peripheral, influenza, upper respiratory tract infection, back pain, arthralgia, pain in extremity, and pruritus.

² Male patients only.

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798 Generalized Anxiety Disorder

799 Table 4 gives the incidence of treatment-emergent adverse events that occurred in 2% or more
800 of patients treated with Cymbalta in the premarketing acute phase of GAD placebo-controlled
801 trials (doses of 60 to 120 mg once daily) and with an incidence greater than placebo. The most
802 commonly observed adverse events in Cymbalta-treated GAD patients (incidence of 5% or
803 greater and at least twice the incidence in placebo patients) were: nausea; fatigue; dry mouth;
804 somnolence; constipation; insomnia; appetite decreased; hyperhidrosis; libido decreased;
805 vomiting; ejaculation delayed; and erectile dysfunction (*see* Table 4).

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**Table 4: Treatment-Emergent Adverse Events Incidence
in GAD Placebo-Controlled Trials¹**

System Organ Class / Adverse Event	Percentage of Patients Reporting Event	
	Cymbalta (N=668)	Placebo (N=495)
Eye Disorders		
Vision blurred	4	2
Gastrointestinal Disorders		
Nausea	38	10
Dry mouth	12	4
Constipation	10	3
Diarrhea	8	6
Vomiting	5	2
Abdominal pain ²	4	3
Dyspepsia ³	4	3
General Disorders and Administration Site Conditions		
Fatigue ⁴	13	5
Metabolism and Nutrition Disorders		
Appetite decreased ⁵	8	3
Nervous System Disorders		

Dizziness	15	8
Somnolence ⁶	12	3
Tremor	4	1
Paraesthesia ⁷	2	1
Psychiatric Disorders		
Insomnia ⁸	9	4
Libido decreased ⁹	7	2
Agitation ¹⁰	4	2
Orgasm abnormal ¹¹	3	0
Reproductive System and Breast Disorders		
Ejaculation delayed ¹²	5	1
Erectile dysfunction ¹²	5	1
Respiratory, Thoracic and Mediastinal Disorders		
Yawning	3	0
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	7	2
Vascular Disorders		
Hot flushes	3	1

809 ¹ Events reported by at least 2% of patients treated with Cymbalta and more often with placebo. The following
810 events were reported by at least 2% of patients treated with Cymbalta for GAD and had an incidence equal to or
811 less than placebo: nasopharyngitis, upper respiratory tract infection, headache, pollakiuria, and musculoskeletal
812 pain (includes myalgia, neck pain).

813 ² Term includes abdominal pain upper, abdominal pain lower, abdominal tenderness, abdominal discomfort, and
814 gastrointestinal pain.

815 ³ Term includes stomach discomfort.

816 ⁴ Term includes asthenia.

817 ⁵ Term includes anorexia.

818 ⁶ Term includes hypersomnia and sedation.

819 ⁷ Term includes hypoaesthesia.

820 ⁸ Term includes initial insomnia, middle insomnia, and early morning awakening.

821 ⁹ Term includes loss of libido.

822 ¹⁰ Term includes feeling jittery, nervousness, restlessness, tension, and psychomotor agitation.

823 ¹¹ Term includes anorgasmia.

824 ¹² Male patients only.

825
826 Adverse events seen in men and women were generally similar except for effects on sexual
827 function (described below). Clinical studies of Cymbalta did not suggest a difference in adverse
828 event rates in people over or under 65 years of age. There were too few non-Caucasian patients
829 studied to determine if these patients responded differently from Caucasian patients.

830 **Effects on Male and Female Sexual Function**

831 Although changes in sexual desire, sexual performance and sexual satisfaction often occur as
832 manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic
833 treatment. Reliable estimates of the incidence and severity of untoward experiences involving
834 sexual desire, performance and satisfaction are difficult to obtain, however, in part because
835 patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence
836 of untoward sexual experience and performance cited in product labeling are likely to
837 underestimate their actual incidence. Table 5 displays the incidence of sexual side effects
838 spontaneously reported by at least 2% of either male or female patients taking Cymbalta in MDD
839 placebo-controlled trials.

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842**Table 5: Treatment-Emergent Sexual Dysfunction-Related Adverse Events Incidence in MDD Placebo-Controlled Trials¹**

Adverse Event	Percentage of Patients Reporting Event ⁴			
	% Male Patients		% Female Patients	
	Cymbalta (N=378)	Placebo (N=247)	Cymbalta (N=761)	Placebo (N=530)
Orgasm abnormal ²	4	1	2	0
Ejaculatory dysfunction ³	3	1	NA	NA
Libido decreased	6	2	1	0
Erectile dysfunction	4	1	NA	NA
Ejaculation delayed	3	1	NA	NA

¹ Events reported by at least 2% of patients treated with Cymbalta and more often than with placebo.

² Term includes anorgasmia.

³ Term includes ejaculation disorder and ejaculation failure.

⁴ NA=Not applicable.

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848 Because adverse sexual events are presumed to be voluntarily underreported, the Arizona
849 Sexual Experience Scale (ASEX), a validated measure designed to identify sexual side effects,
850 was used prospectively in 4 MDD placebo-controlled trials. In these trials, as shown in Table 6
851 below, patients treated with Cymbalta experienced significantly more sexual dysfunction, as
852 measured by the total score on the ASEX, than did patients treated with placebo. Gender analysis
853 showed that this difference occurred only in males. Males treated with Cymbalta experienced
854 more difficulty with ability to reach orgasm (ASEX Item 4) than males treated with placebo.
855 Females did not experience more sexual dysfunction on Cymbalta than on placebo as measured
856 by ASEX total score. These studies did not, however, include an active control drug with known
857 effects on female sexual dysfunction, so that there is no evidence that its effects differ from other
858 antidepressants. Negative numbers signify an improvement from a baseline level of dysfunction,
859 which is commonly seen in depressed patients. Physicians should routinely inquire about
860 possible sexual side effects.

861
862
863**Table 6: Mean Change in ASEX Scores by Gender in MDD Placebo-Controlled Trials**

	Male Patients***		Female Patients***	
	Cymbalta (n***=175)	Placebo (n=83)	Cymbalta (n=241)	Placebo (n=126)
ASEX Total (Items 1-5)	0.56*	-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**	-0.24	-0.09	-0.13
Item 5 — Orgasm satisfaction	0.09	-0.13	-0.11	-0.17

864 *** n=Number of patients with non-missing change score for ASEX total.

865 * p=0.013 versus placebo.

866 ** p<0.001 versus placebo.

867

868 **Urinary Hesitation**

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

872 **Laboratory Changes**

873 Cymbalta treatment, for up to 9-weeks in MDD, 9-10 weeks in GAD or 13-weeks in DPN
874 placebo-controlled clinical trials, was associated with small mean increases from baseline to
875 endpoint in ALT, AST, CPK, and alkaline phosphatase; infrequent, modest, transient, abnormal
876 values were observed for these analytes in Cymbalta-treated patients when compared with
877 placebo-treated patients (*see* PRECAUTIONS).

878 **Vital Sign Changes**

879 In clinical trials across indications, relative to placebo, duloxetine treatment was associated
880 with mean increases of up to 2.1 mm Hg in systolic blood pressure and up to 2.3 mm Hg in
881 diastolic blood pressure, averaging up to 2 mm Hg. There was no significant difference in the
882 frequency of sustained (3 consecutive visits) elevated blood pressure (*see* PRECAUTIONS).

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

885 **Weight Changes**

886 In placebo-controlled clinical trials, MDD and GAD patients treated with Cymbalta for up to
887 10-weeks experienced a mean weight loss of approximately 0.5 kg, compared with a mean
888 weight gain of approximately 0.2 kg in placebo-treated patients. In DPN placebo-controlled
889 clinical trials, patients treated with Cymbalta for up to 13-weeks experienced a mean weight loss
890 of approximately 1.1 kg, compared with a mean weight gain of approximately 0.2 kg in
891 placebo-treated patients.

892 **Electrocardiogram Changes**

893 Electrocardiograms were obtained from duloxetine-treated patients and placebo-treated
894 patients in clinical trials lasting up to 13-weeks. No clinically significant differences were
895 observed for QTc, QT, PR, and QRS intervals between duloxetine-treated and placebo-treated
896 patients. There were no differences in clinically meaningful QTcF elevations between duloxetine
897 and placebo. In a positive-controlled study in healthy volunteers using duloxetine up to
898 200 mg BID, no prolongation of the corrected QT interval was observed.

899 **Other Adverse Events Observed During the Premarketing and Postmarketing 900 Clinical Trial Evaluation of Duloxetine**

901 Following is a list of MedDRA terms that reflect treatment-emergent adverse events as defined
902 in the introduction to the ADVERSE REACTIONS section reported by patients treated with
903 duloxetine at multiple doses throughout the dose range studied during any phase of a clinical trial
904 within the premarketing and postmarketing database (23,983 patients, 10,649.5 patient-years of
905 exposure). The events included are those not already listed in Tables 2 through 4 and not
906 considered in the WARNINGS and PRECAUTIONS sections. The events were reported by more
907 than one patient, are not common as background events and/or were considered possibly drug
908 related (e.g., because of the drug's pharmacology) or potentially important.

909 It is important to emphasize that, although the events reported occurred during treatment with
 910 Cymbalta, they were not necessarily caused by it. Events are further categorized by body system
 911 and listed in order of decreasing frequency according to the following definitions: frequent
 912 adverse events are those occurring in at least 1/100 patients; infrequent adverse events are those
 913 occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than
 914 1/1000 patients.

915 **Blood and Lymphatic System Disorders** — *Infrequent*: anemia and lymphadenopathy;
 916 *Rare*: leukopenia and thrombocytopenia.

917 **Cardiac Disorders** — *Frequent*: palpitations; *Infrequent*: atrial fibrillation, coronary artery
 918 disease, myocardial infarction, and tachycardia; *Rare*: bundle branch block right, cardiac failure,
 919 and cardiac failure congestive.

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

921 **Eye Disorders** — *Frequent*: vision blurred; *Infrequent*: conjunctivitis, diplopia, and visual
 922 disturbance; *Rare*: glaucoma, macular degeneration, maculopathy, photopsia, and retinal
 923 detachment.

924 **Gastrointestinal Disorders** — *Frequent*: abdominal pain and flatulence;
 925 *Infrequent*: dysphagia, eructation, gastritis, halitosis, irritable bowel syndrome, and stomatitis;
 926 *Rare*: aphthous stomatitis, colitis, esophageal stenosis, gastric ulcer, gingivitis, hematochezia,
 927 impaired gastric emptying, and melena.

928 **General Disorders and Administration Site Conditions** — *Frequent*: chills/rigors;
 929 *Infrequent*: edema, edema peripheral, feeling abnormal, feeling hot and/or cold, influenza-like
 930 illness, malaise, and thirst; *Rare*: face edema and sluggishness.

931 **Hepato-biliary Disorders** — *Rare*: hepatic steatosis.

932 **Infections and Infestations** — *Infrequent*: gastroenteritis and laryngitis; *Rare*: diverticulitis.

933 **Investigations** — *Frequent*: weight decreased and weight increased; *Infrequent*: blood
 934 cholesterol increased; *Rare*: blood creatinine increased, urine output decreased, and white blood
 935 cell count increased.

936 **Metabolism and Nutrition Disorders** — *Infrequent*: dehydration, hypercholesterolemia,
 937 hyperlipidemia, hypoglycemia, and increased appetite; *Rare*: dyslipidemia and
 938 hypertriglyceridemia.

939 **Musculoskeletal and Connective Tissue Disorders** — *Frequent*: musculoskeletal pain;
 940 *Infrequent*: muscle tightness and muscle twitching; *Rare*: muscular weakness.

941 **Nervous System Disorders** — *Frequent*: dysgeusia, lethargy, and parasthesia/hypoesthesia;
 942 *Infrequent*: coordination abnormal, disturbance in attention, dyskinesia, hypersomnia, and
 943 myoclonus; *Rare*: dysarthria.

944 **Psychiatric Disorders** — *Frequent*: agitation, anxiety, libido decreased, nervousness,
 945 nightmare/abnormal dreams, and sleep disorder; *Infrequent*: apathy, bruxism,
 946 disorientation/confusional state, irritability, mood swings, restlessness, suicide attempt, and
 947 tension; *Rare*: completed suicide, mania, and pressure of speech.

948 **Renal and Urinary Disorders** — *Infrequent*: dysuria, micturition urgency, nocturia, urinary
 949 hesitation, urinary incontinence, urinary retention, urine flow decreased, and urine odor
 950 abnormal; *Rare*: nephropathy.

951 **Reproductive System and Breast Disorders** — *Frequent*: anorgasmia/orgasm abnormal,
 952 ejaculation delayed, and ejaculation disorder; *Infrequent*: menopausal symptoms.

953 **Respiratory, Thoracic and Mediastinal Disorders** — *Frequent*: yawning; *Infrequent*: throat
 954 tightness; *Rare*: pharyngeal edema.

955 **Skin and Subcutaneous Tissue Disorders** — *Frequent*: pruritus and rash; *Infrequent*: acne,
956 alopecia, cold sweat, eczema, erythema, increased tendency to bruise, night sweats,
957 photosensitivity reaction, and skin ulcer; *Rare*: dermatitis exfoliative, ecchymosis, and
958 hyperkeratosis.

959 **Vascular Disorders** — *Frequent*: hot flush; *Infrequent*: flushing, orthostatic hypotension, and
960 peripheral coldness; *Rare*: hypertensive crisis and phlebitis.

961 **Postmarketing Spontaneous Reports**

962 Adverse events reported since market introduction that were temporally related to duloxetine
963 therapy and not mentioned elsewhere in labeling include: anaphylactic reaction, angioneurotic
964 edema, erythema multiforme, extrapyramidal disorder, glaucoma, hallucinations, hyperglycemia,
965 hypersensitivity, hypertensive crisis, rash, Stevens-Johnson Syndrome, supraventricular
966 arrhythmia, trismus, and urticaria.

967 **DRUG ABUSE AND DEPENDENCE**

968 **Controlled Substance Class**

969 Duloxetine is not a controlled substance.

970 **Physical and Psychological Dependence**

971 In animal studies, duloxetine did not demonstrate barbiturate-like (depressant) abuse potential.
972 In drug dependence studies, duloxetine did not demonstrate dependence-producing potential in
973 rats.

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

981 **OVERDOSAGE**

982 There is limited clinical experience with duloxetine overdose in humans. In clinical trials,
983 cases of acute ingestions up to 3000 mg, alone or in combination with other drugs, were reported
984 with none being fatal. However, in postmarketing experience, fatal outcomes have been reported
985 for acute overdoses, primarily with mixed overdoses, but also with duloxetine only, at doses as
986 low as approximately 1000 mg. Signs and symptoms of overdose (mostly with mixed drugs)
987 included serotonin syndrome, somnolence, vomiting, and seizures.

988 **Management of Overdose**

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

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

997 Activated charcoal may be useful in limiting absorption of duloxetine from the gastrointestinal
998 tract. Administration of activated charcoal has been shown to decrease AUC and C_{max} by an

999 average of one-third, although some subjects had a limited effect of activated charcoal. Due to
1000 the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and
1001 exchange transfusion are unlikely to be beneficial.

1002 In managing overdose, the possibility of multiple drug involvement should be considered. A
1003 specific caution involves patients who are taking or have recently taken Cymbalta and might
1004 ingest excessive quantities of a TCA. In such a case, decreased clearance of the parent tricyclic
1005 and/or its active metabolite may increase the possibility of clinically significant sequelae and
1006 extend the time needed for close medical observation (*see* PRECAUTIONS, Drug Interactions).
1007 The physician should consider contacting a poison control center for additional information on
1008 the treatment of any overdose. Telephone numbers for certified poison control centers are listed
1009 in the *Physicians' Desk Reference* (PDR).

1010 **DOSAGE AND ADMINISTRATION**

1011 **Initial Treatment**

1012 **Major Depressive Disorder**

1013 Cymbalta should be administered at a total dose of 40 mg/day (given as 20 mg BID) to
1014 60 mg/day (given either once a day or as 30 mg BID) without regard to meals.

1015 There is no evidence that doses greater than 60 mg/day confer any additional benefits.

1016 **Diabetic Peripheral Neuropathic Pain**

1017 Cymbalta should be administered at a total dose of 60 mg/day given once a day, without regard
1018 to meals.

1019 While a 120 mg/day dose was shown to be safe and effective, there is no evidence that doses
1020 higher than 60 mg confer additional significant benefit, and the higher dose is clearly less well
1021 tolerated. For patients for whom tolerability is a concern, a lower starting dose may be
1022 considered. Since diabetes is frequently complicated by renal disease, a lower starting dose and
1023 gradual increase in dose should be considered for patients with renal impairment (*see*
1024 CLINICAL PHARMACOLOGY, Special Populations *and* below).

1025 **Generalized Anxiety Disorder**

1026 For most patients, the recommended starting dose for Cymbalta is 60 mg administered
1027 once daily without regard to meals. For some patients, it may be desirable to start at 30 mg
1028 once daily for 1 week, to allow patients to adjust to the medication before increasing to 60 mg
1029 once daily. While a 120 mg once daily dose was shown to be effective, there is no evidence that
1030 doses greater than 60 mg once daily confer additional benefit. Nevertheless, if a decision is made
1031 to increase the dose beyond 60 mg once daily, dose increases should be in increments of 30 mg
1032 once daily. The safety of doses above 120 mg once daily has not been adequately evaluated.

1033 **Maintenance/Continuation/Extended Treatment**

1034 **Major Depressive Disorder**

1035 It is generally agreed that acute episodes of major depression require several months or longer
1036 of sustained pharmacologic therapy. There is insufficient evidence available to answer the
1037 question of how long a patient should continue to be treated with Cymbalta. Patients should be
1038 periodically reassessed to determine the need for maintenance treatment and the appropriate dose
1039 for such treatment.

1040 **Diabetic Peripheral Neuropathic Pain**

1041 As the progression of diabetic peripheral neuropathy is highly variable and management of
1042 pain is empirical, the effectiveness of Cymbalta must be assessed individually. Efficacy beyond

1043 12 weeks has not been systematically studied in placebo-controlled trials, but a one-year
1044 open-label safety study was conducted.

1045 **Generalized Anxiety Disorder**

1046 Generalized anxiety disorder is generally recognized as a chronic condition. The effectiveness
1047 of Cymbalta in long-term use for GAD, that is, for more than 10 weeks, has not been
1048 systematically evaluated in controlled trials. The physician who elects to use Cymbalta for
1049 extended periods should periodically evaluate the long-term usefulness of the drug for the
1050 individual patient.

1051 **Special Populations**

1052 Dosage for Renally Impaired Patients — Cymbalta is not recommended for patients with
1053 end-stage renal disease (requiring dialysis) or in severe renal impairment (estimated creatinine
1054 clearance <30 mL/min) (*see* CLINICAL PHARMACOLOGY).

1055 Dosage for Hepatically Impaired Patients — It is recommended that Cymbalta not be
1056 administered to patients with any hepatic insufficiency (*see* CLINICAL PHARMACOLOGY
1057 *and* PRECAUTIONS).

1058 Dosage for Elderly Patients — No dose adjustment is recommended for elderly patients on the
1059 basis of age. As with any drug, caution should be exercised in treating the elderly. When
1060 individualizing the dosage in elderly patients, extra care should be taken when increasing the
1061 dose.

1062 Treatment of Pregnant Women During the Third Trimester — Neonates exposed to SSRIs or
1063 SNRIs, late in the third trimester have developed complications requiring prolonged
1064 hospitalization, respiratory support, and tube feeding (*see* PRECAUTIONS). When treating
1065 pregnant women with Cymbalta during the third trimester, the physician should carefully
1066 consider the potential risks and benefits of treatment. The physician may consider tapering
1067 Cymbalta in the third trimester.

1068 Dosage for Nursing Mothers — Because the safety of duloxetine in infants is not known,
1069 nursing while on Cymbalta is not recommended (*see* CLINICAL PHARMACOLOGY).

1070 **Discontinuing Cymbalta**

1071 Symptoms associated with discontinuation of Cymbalta and other SSRIs and SNRIs have been
1072 reported (*see* PRECAUTIONS). Patients should be monitored for these symptoms when
1073 discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is
1074 recommended whenever possible. If intolerable symptoms occur following a decrease in the dose
1075 or upon discontinuation of treatment, then resuming the previously prescribed dose may be
1076 considered. Subsequently, the physician may continue decreasing the dose but at a more gradual
1077 rate.

1078 **Switching Patients to or from a Monoamine Oxidase Inhibitor**

1079 At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy
1080 with Cymbalta. In addition, at least 5 days should be allowed after stopping Cymbalta before
1081 starting an MAOI (*see* CONTRAINDICATIONS *and* WARNINGS).

1082 **HOW SUPPLIED**

1083 Cymbalta[®] (duloxetine hydrochloride) Delayed-release Capsules are available in 20, 30, and
60 mg strengths.

The 20 mg* capsule has an opaque green body and cap, and is imprinted with “20 mg” on the
body and “LILLY 3235” on the cap:

NDC 0002-3235-60 (PU3235) — Bottles of 60

NDC 0002-3235-33 (PU3235) — (ID†100) Blisters

The 30 mg* capsule has an opaque white body and opaque blue cap, and is imprinted with “30 mg” on the body and “LILLY 3240” on the cap:

NDC 0002-3240-30 (PU3240) — Bottles of 30

NDC 0002-3240-90 (PU3240) — Bottles of 90

NDC 0002-3240-04 (PU3240) — Bottles of 1000

NDC 0002-3240-33 (PU3240) — (ID†100) Blisters

The 60 mg* capsule has an opaque green body and opaque blue cap, and is imprinted with “60 mg” on the body and “LILLY 3237” on the cap:

NDC 0002-3237-30 (PU3237) — Bottles of 30

NDC 0002-3237-90 (PU3237) — Bottles of 90

NDC 0002-3237-04 (PU3237) — Bottles of 1000

NDC 0002-3237-33 (PU3237) — (ID†100) Blisters

1084 * equivalent to duloxetine base.

1085 †Identi-Dose® (unit dose medication, Lilly).

1086

1087 Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room
1088 Temperature].

1089 Literature revised June 28, 2007

**Eli Lilly and Company
Indianapolis, IN 46285, USA**

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Medication Guide

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

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1098 Read the Medication Guide that comes with your or your family member’s antidepressant
1099 medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with
1100 antidepressant medicines. **Talk to your, or your family member’s, healthcare provider**
1101 **about:**

- 1102 • all risks and benefits of treatment with antidepressant medicines
- 1103 • all treatment choices for depression or other serious mental illness

1104 **What is the most important information I should know about antidepressant**
1105 **medicines, depression and other serious mental illnesses, and suicidal thoughts**
1106 **or actions?**

- 1107 **1. Antidepressant medicines may increase suicidal thoughts or actions in some**
1108 **children, teenagers, and young adults within the first few months of treatment.**

1109 **2. Depression and other serious mental illnesses are the most important causes of**
 1110 **suicidal thoughts and actions. Some people may have a particularly high risk of**
 1111 **having suicidal thoughts or actions.** These include people who have (or have a family
 1112 history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or
 1113 actions.

1114 **3. How can I watch for and try to prevent suicidal thoughts and actions in myself or a**
 1115 **family member?**

1116 • Pay close attention to any changes, especially sudden changes, in mood, behaviors,
 1117 thoughts, or feelings. This is very important when an antidepressant medicine is
 1118 started or when the dose is changed.

1119 • Call the healthcare provider right away to report new or sudden changes in mood,
 1120 behavior, thoughts, or feelings.

1121 • Keep all follow-up visits with the healthcare provider as scheduled. Call the
 1122 healthcare provider between visits as needed, especially if you have concerns about
 1123 symptoms.

1124 **Call a healthcare provider right away if you or your family member has any of the**
 1125 **following symptoms, especially if they are new, worse, or worry you:**

1126 • thoughts about suicide or dying

1127 • attempts to commit suicide

1128 • new or worse depression

1129 • new or worse anxiety

1130 • feeling very agitated or restless

1131 • panic attacks

1132 • trouble sleeping (insomnia)

1133 • new or worse irritability

1134 • acting aggressive, being angry, or violent

1135 • acting on dangerous impulses

1136 • an extreme increase in activity and talking (mania)

1137 • other unusual changes in behavior or mood

1138 **What else do I need to know about antidepressant medicines?**

1139 • **Never stop an antidepressant medicine without first talking to a healthcare provider.**
 1140 Stopping an antidepressant medicine suddenly can cause other symptoms.

1141 • **Antidepressants are medicines used to treat depression and other illnesses.** It is
 1142 important to discuss all the risks of treating depression and also the risks of not treating it.
 1143 Patients and their families or other caregivers should discuss all treatment choices with the
 1144 healthcare provider, not just the use of antidepressants.

- 1145 • **Antidepressant medicines have other side effects.** Talk to the healthcare provider about
1146 the side effects of the medicine prescribed for you or your family member.
- 1147 • **Antidepressant medicines can interact with other medicines.** Know all of the medicines
1148 that you or your family member takes. Keep a list of all medicines to show the healthcare
1149 provider. Do not start new medicines without first checking with your healthcare provider.
- 1150 • **Not all antidepressant medicines prescribed for children are FDA approved for use in**
1151 **children.** Talk to your child's healthcare provider for more information.
- 1152 *This Medication Guide has been approved by the US Food and Drug Administration for*
1153 *all antidepressants.*
- 1154 Patient Information revised June 21, 2007

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