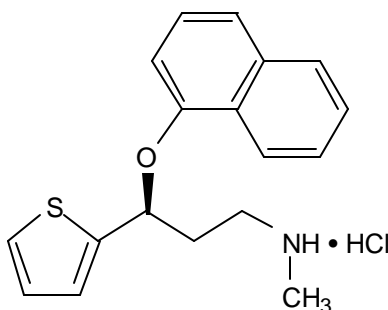


CYMBALTA[®]

(duloxetine hydrochloride) Delayed-release Capsules

DESCRIPTION

Cymbalta[®] (duloxetine hydrochloride) is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) for oral administration. Its chemical designation is (+)-(S)-N-methyl-γ-(1-naphthoxy)-2-thiophenepropylamine hydrochloride. The empirical formula is C₁₈H₁₉NOS•HCl, which



corresponds to a molecular weight of 333.88. The structural formula is:

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

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

CLINICAL PHARMACOLOGY

Pharmacodynamics

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

Pharmacokinetics

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

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

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

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

51 **Special Populations**

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

54 Age — The pharmacokinetics of duloxetine after a single dose of 40 mg were compared in healthy
55 elderly females (65 to 77 years) and healthy middle-age females (32 to 50 years). There was no
56 difference in the C_{max} , but the AUC of duloxetine was somewhat (about 25%) higher and the half-life
57 about 4 hours longer in the elderly females. Population pharmacokinetic analyses suggest that the typical
58 values for clearance decrease by approximately 1% for each year of age between 25 to 75 years of
59 age; but age as a predictive factor only accounts for a small percentage of between-patient variability.
60 Dosage adjustment based on the age of the patient is not necessary (*see* DOSAGE AND
61 ADMINISTRATION).

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

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

65 Renal Insufficiency — Limited data are available on the effects of duloxetine in patients with end-stage
66 renal disease (ESRD). After a single 60-mg dose of duloxetine, C_{max} and AUC values were
67 approximately 100% greater in patients with end-stage renal disease receiving chronic intermittent
68 hemodialysis than in subjects with normal renal function. The elimination half-life, however, was similar in
69 both groups. The AUCs of the major circulating metabolites, 4-hydroxy duloxetine glucuronide and
70 5-hydroxy, 6-methoxy duloxetine sulfate, largely excreted in urine, were approximately 7- to 9-fold
71 higher and would be expected to increase further with multiple dosing. For this reason, Cymbalta is not
72 recommended for patients with end-stage renal disease (requiring dialysis) or severe renal impairment
73 (estimated creatinine clearance [CrCl] <30 mL/min) (*see* DOSAGE AND ADMINISTRATION).
74 Population PK analyses suggest that mild to moderate degrees of renal dysfunction (estimated CrCl
75 30-80 mL/min) have no significant effect on duloxetine apparent clearance.

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

83 Drug-Drug Interactions (also see PRECAUTIONS, Drug Interactions)

84 Potential for Other Drugs to Affect Duloxetine

85 Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

86 Inhibitors of CYP1A2 — When duloxetine was co-administered with fluvoxamine, a potent CYP1A2
87 inhibitor, to male subjects (n=14) the AUC was increased over 5-fold, the C_{max} was increased about
88 2.5-fold, and duloxetine $t_{1/2}$ was increased approximately 3-fold. Other drugs that inhibit CYP1A2
89 metabolism include cimetidine and quinolone antimicrobials such as ciprofloxacin and enoxacin.

90 Inhibitors of CYP2D6 — Because CYP2D6 is involved in duloxetine metabolism, concomitant use of
91 duloxetine with potent inhibitors of CYP2D6 would be expected to, and does, result in higher
92 concentrations of duloxetine (see PRECAUTIONS, Drug Interactions).

93 Studies with Benzodiazepines

94 *Lorazepam* — Under steady-state conditions for duloxetine (60 mg Q 12 hours) and lorazepam
95 (2 mg Q 12 hours), the pharmacokinetics of duloxetine were not affected by co-administration.

96 *Temazepam* — Under steady-state conditions for duloxetine (20 mg qhs) and temazepam
97 (30 mg qhs), the pharmacokinetics of duloxetine were not affected by co-administration.

98 Potential for Duloxetine to Affect Other Drugs

99 Drugs Metabolized by CYP1A2 — *In vitro* drug interaction studies demonstrate that duloxetine does
100 not induce CYP1A2 activity. Therefore, an increase in the metabolism of CYP1A2 substrates
101 (e.g., theophylline, caffeine) resulting from induction is not anticipated, although clinical studies of
102 induction have not been performed. Although duloxetine is an inhibitor of the CYP1A2 isoform in
103 *in vitro* studies, the pharmacokinetics of theophylline, a CYP1A2 substrate, were not significantly
104 affected by co-administration with duloxetine (60 mg BID). Duloxetine is thus unlikely to have a
105 clinically significant effect on the metabolism of CYP1A2 substrates.

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

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

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

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

121 Studies with Benzodiazepines

122 *Lorazepam* — Under steady-state conditions for duloxetine (60 mg Q 12 hours) and lorazepam
123 (2 mg Q 12 hours), the pharmacokinetics of lorazepam were not affected by co-administration.

124 *Temazepam* — Under steady-state conditions for duloxetine (20 mg qhs) and temazepam
125 (30 mg qhs), the pharmacokinetics of temazepam were not affected by co-administration.

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

129

CLINICAL STUDIES

130 **Major Depressive Disorder**

131 The efficacy of Cymbalta as a treatment for depression was established in 4 randomized,
132 double-blind, placebo-controlled, fixed-dose studies in adult outpatients (18 to 83 years) meeting
133 DSM-IV criteria for major depression. In 2 studies, patients were randomized to Cymbalta 60 mg
134 once daily (N=123 and N=128, respectively) or placebo (N=122 and N=139, respectively) for
135 9 weeks; in the third study, patients were randomized to Cymbalta 20 or 40 mg twice daily (N=86 and
136 N=91, respectively) or placebo (N=89) for 8 weeks; in the fourth study, patients were randomized to
137 Cymbalta 40 or 60 mg twice daily (N=95 and N=93, respectively) or placebo (N=93) for 8 weeks.
138 There is no evidence that doses greater than 60 mg/day confer any additional benefit.

139 In all 4 studies, Cymbalta demonstrated superiority over placebo as measured by improvement in the
140 17-item Hamilton Depression Rating Scale (HAMD-17) total score.

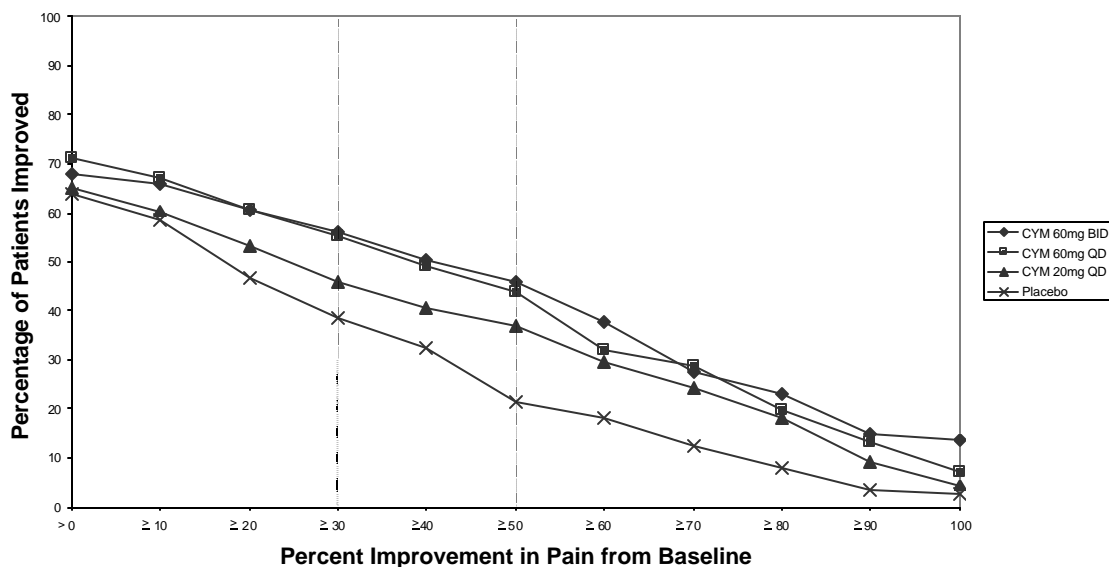
141 Analyses of the relationship between treatment outcome and age, gender, and race did not suggest
142 any differential responsiveness on the basis of these patient characteristics.

143 **Diabetic Peripheral Neuropathic Pain**

144 The efficacy of Cymbalta for the management of neuropathic pain associated with diabetic peripheral
145 neuropathy (DPN) was established in 2 randomized, 12-week, double-blind, placebo-controlled,
146 fixed-dose studies in adult patients having diabetic peripheral neuropathy for at least 6 months. Study 1
147 and 2 enrolled a total of 791 patients of whom 592 (75%) completed the studies. Patients enrolled had
148 Type I or II diabetes mellitus with a diagnosis of painful distal symmetrical sensorimotor polyneuropathy
149 for at least 6 months. The patients had a baseline pain score of ≥ 4 on an 11-point scale ranging from
150 0 (no pain) to 10 (worst possible pain). Patients were permitted up to 4 g of acetaminophen per day as
151 needed for pain, in addition to Cymbalta. Patients recorded their pain daily in a diary.

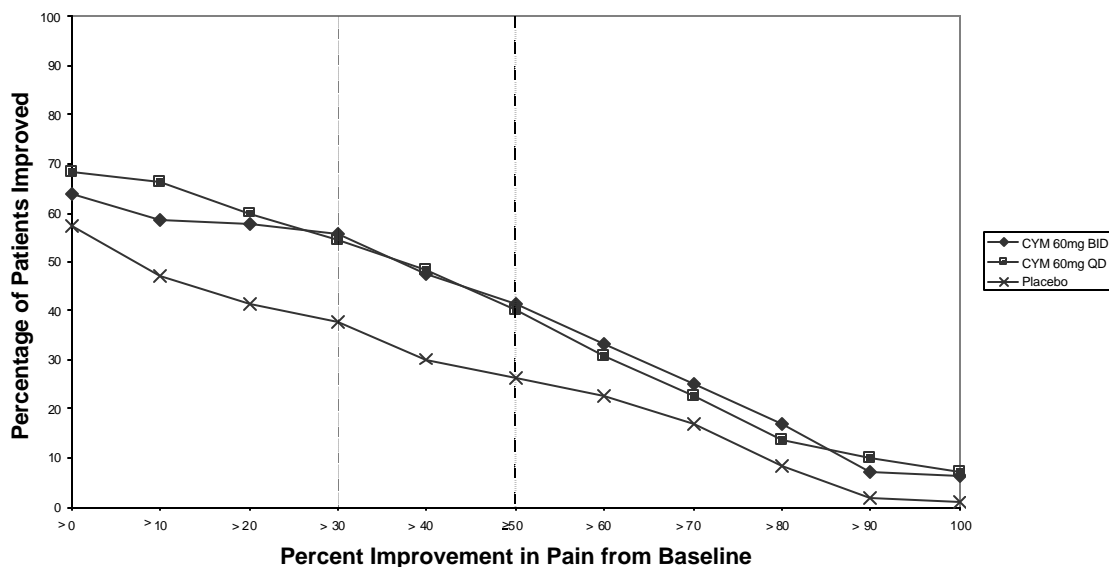
152 Both studies compared Cymbalta 60 mg once daily or 60 mg twice daily with placebo. Study 1
153 additionally compared Cymbalta 20 mg with placebo. A total of 457 patients (342 Cymbalta,
154 115 placebo) were enrolled in Study 1 and a total of 334 patients (226 Cymbalta, 108 placebo) were
155 enrolled in Study 2. Treatment with Cymbalta 60 mg one or two times a day statistically significantly
156 improved the endpoint mean pain scores from baseline and increased the proportion of patients with at
157 least a 50% reduction in pain score from baseline. For various degrees of improvement in pain from
158 baseline to study endpoint, Figures 1 and 2 show the fraction of patients achieving that degree of
159 improvement. The figures are cumulative, so that patients whose change from baseline is, for
160 example, 50%, are also included at every level of improvement below 50%. Patients who did not
161 complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as
162 early as Week 1, which persisted throughout the study.

163



164
165
166

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



167
168
169

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

170

INDICATIONS AND USAGE

171 Major Depressive Disorder

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

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

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

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

184 The effectiveness of Cymbalta in long-term use for major depressive disorder, that is, for more than
185 9 weeks, has not been systematically evaluated in controlled trials. The physician who elects to use
186 Cymbalta for extended periods should periodically evaluate the long-term usefulness of the drug for the
187 individual patient.

188 **Diabetic Peripheral Neuropathic Pain**

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

191 **CONTRAINDICATIONS**

192 **Hypersensitivity**

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

195 **Monoamine Oxidase Inhibitors**

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

198 **Uncontrolled Narrow-Angle Glaucoma**

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

201 **WARNINGS**

202 **Clinical Worsening and Suicide Risk** — Patients with major depressive disorder, both adult and
203 pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and
204 behavior (suicidality), whether or not they are taking antidepressant medications, and this risk may
205 persist until significant remission occurs. Although there has been a long-standing concern that
206 antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in
207 certain patients, a causal role for antidepressants in inducing such behaviors has not been established.
208 **Nevertheless, patients being treated with antidepressants should be observed closely for**
209 **clinical worsening and suicidality, especially at the beginning of a course of drug therapy, or at**
210 **the time of dose changes, either increases or decreases.** Consideration should be given to
211 changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose
212 depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part
213 of the patient's presenting symptoms.

214 Because of the possibility of co-morbidity between major depressive disorder and other psychiatric
215 and nonpsychiatric disorders, the same precautions observed when treating patients with major
216 depressive disorder should be observed when treating patients with other psychiatric and nonpsychiatric
217 disorders.

218 The following symptoms - anxiety, agitation, panic attacks, insomnia, irritability, hostility
219 (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania - have been
220 reported in adult and pediatric patients being treated with antidepressants for major depressive disorder
221 as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the

222 emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal
223 impulses has not been established, consideration should be given to changing the therapeutic regimen,
224 including possibly discontinuing the medication, in patients for whom such symptoms are severe, abrupt
225 in onset, or were not part of the patient's presenting symptoms.

226 **Families and caregivers of patients being treated with antidepressants for major depressive**
227 **disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the**
228 **need to monitor patients for the emergence of agitation, irritability, and the other symptoms**
229 **described above, as well as the emergence of suicidality, and to report such symptoms**
230 **immediately to health care providers.** Prescriptions for Cymbalta should be written for the smallest
231 quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

232 If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is
233 feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (*see*
234 *PRECAUTIONS and DOSAGE AND ADMINISTRATION, Discontinuing Cymbalta*, for a
235 description of the risks of discontinuation of Cymbalta).

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

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

257

PRECAUTIONS

258 **General**

259 Hepatotoxicity — Cymbalta increases the risk of elevation of serum transaminase levels. Liver
260 transaminase elevations resulted in the discontinuation of 0.4% (31/8454) of Cymbalta-treated patients.
261 In these patients, the median time to detection of the transaminase elevation was about two months. In
262 controlled trials in MDD, elevations of alanine transaminase (ALT) to >3 times the upper limit of normal
263 occurred in 0.9% (8/930) of Cymbalta-treated patients and in 0.3% (2/652) of placebo-treated
264 patients. In controlled trials in DPN, elevations of ALT to >3 times the upper limit of normal occurred in
265 1.68% (8/477) of Cymbalta-treated patients and in 0% (0/187) of placebo-treated patients. In the full
266 cohort of placebo-controlled trials in any indication, 1% (39/3732) of Cymbalta-treated patients had a
267 >3 times the upper limit of normal elevation of ALT compared to 0.2% (6/2568) of placebo-treated
268 patients. In placebo-controlled studies using a fixed-dose design, there was evidence of a
269 dose-response relationship for ALT and AST elevation of >3 times the upper limit of normal and
270 >5 times the upper limit of normal, respectively.

271 The combination of transaminase elevations and elevated bilirubin, without evidence of obstruction, is
272 generally recognized as an important predictor of severe liver injury. Three Cymbalta patients had
273 elevations of transaminases and bilirubin, but also had elevation of alkaline phosphatase, suggesting an
274 obstructive process; in these patients, there was evidence of heavy alcohol use and this may have
275 contributed to the abnormalities seen. Two placebo-treated patients also had transaminase elevations
276 with elevated bilirubin. Because it is possible that duloxetine and alcohol may interact to cause liver
277 injury, Cymbalta should ordinarily not be prescribed to patients with substantial alcohol use.

278 Effect on Blood Pressure — In MDD clinical trials, Cymbalta treatment was associated with mean
279 increases in blood pressure, averaging 2 mm Hg systolic and 0.5 mm Hg diastolic and an increase in the
280 incidence of at least one measurement of systolic blood pressure over 140 mm Hg compared to
281 placebo.

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

284 Activation of Mania/Hypomania — In placebo-controlled trials in patients with major depressive
285 disorder, activation of mania or hypomania was reported in 0.1% (1/1139) of Cymbalta-treated
286 patients and 0.1% (1/777) of placebo-treated patients. Activation of mania/hypomania has been
287 reported in a small proportion of patients with mood disorders who were treated with other marketed
288 drugs effective in the treatment of major depressive disorder. As with these other agents, Cymbalta
289 should be used cautiously in patients with a history of mania.

290 Seizures — Cymbalta has not been systematically evaluated in patients with a seizure disorder, and
291 such patients were excluded from clinical studies. In placebo-controlled clinical trials in patients with
292 major depressive disorder, seizures occurred in 0.1% (1/1139) of patients treated with Cymbalta and
293 0% (0/777) of patients treated with placebo. In placebo-controlled clinical trials in patients with diabetic
294 peripheral neuropathy, seizures did not occur in any patients treated with either Cymbalta or placebo.
295 Cymbalta should be prescribed with care in patients with a history of a seizure disorder.

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

299 Discontinuation of Treatment with Cymbalta — Discontinuation symptoms have been systematically
300 evaluated in patients taking Cymbalta. Following abrupt discontinuation in MDD placebo-controlled
301 clinical trials of up to 9-weeks duration, the following symptoms occurred at a rate greater than or equal
302 to 2% and at a significantly higher rate in Cymbalta-treated patients compared to those discontinuing
303 from placebo: dizziness; nausea; headache; paresthesia; vomiting; irritability; and nightmare.

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

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

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

320 Cymbalta has not been systematically evaluated in patients with a recent history of myocardial
321 infarction or unstable coronary artery disease. Patients with these diagnoses were generally excluded
322 from clinical studies during the product's premarketing testing. However, the electrocardiograms of
323 321 patients who received Cymbalta in MDD placebo-controlled clinical trials and had qualitatively
324 normal ECGs at baseline were evaluated; Cymbalta was not associated with the development of
325 clinically significant ECG abnormalities (*see* ADVERSE REACTIONS, Electrocardiogram Changes).

326 In DPN placebo-controlled clinical trials, Cymbalta-treated patients did not develop abnormal ECGs
327 at a rate different from that in placebo-treated patients (*see* ADVERSE REACTIONS,
328 Electrocardiogram Changes).

329 In clinical trials of Cymbalta for the management of neuropathic pain associated with diabetic
330 peripheral neuropathy, the mean duration of diabetes was approximately 11 years, the mean baseline
331 fasting blood glucose was 163 mg/dL, and the mean baseline hemoglobin A_{1c} (HbA_{1c}) was 7.8%. In
332 these studies, small increases in fasting blood glucose were observed in Cymbalta-treated patients
333 compared to placebo at 12 weeks and routine care at 52 weeks. The increase was similar at both time
334 points. Overall diabetic control did not worsen as evidenced by stable HbA_{1c} values and by no
335 differences in incidence of serious and non-serious diabetes-related adverse events relative to placebo
336 or routine care.

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

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

344 **Information for Patients**

345 Physicians are advised to discuss the following issues with patients for whom they prescribe
346 Cymbalta.

347 Patients and their families should be encouraged to be alert to the emergence of anxiety, agitation,
348 panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, mania, worsening of
349 depression, and suicidal ideation, especially early during antidepressant treatment. Such symptoms
350 should be reported to the patient's physician, especially if they are severe, abrupt in onset, or were not
351 part of the patient's presenting symptoms.

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

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

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

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

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

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

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

369 **Laboratory Tests**

370 No specific laboratory tests are recommended.

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

372 **Potential for Other Drugs to Affect Cymbalta**

373 Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

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

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

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

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

387 Drugs Metabolized by CYP2D6 — Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine
388 was administered (at a dose of 60 mg BID) in conjunction with a single 50-mg dose of desipramine, a
389 CYP2D6 substrate, the AUC of desipramine increased 3-fold. Therefore, co-administration of
390 Cymbalta with other drugs that are extensively metabolized by this isozyme and which have a narrow
391 therapeutic index, including certain antidepressants (tricyclic antidepressants [TCAs], such as
392 nortriptyline, amitriptyline, and imipramine), phenothiazines and Type 1C antiarrhythmics
393 (e.g., propafenone, flecainide), should be approached with caution. Plasma TCA concentrations may
394 need to be monitored and the dose of the TCA may need to be reduced if a TCA is co-administered
395 with Cymbalta. Because of the risk of serious ventricular arrhythmias and sudden death potentially
396 associated with elevated plasma levels of thioridazine, Cymbalta and thioridazine should not be
397 co-administered.

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

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

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

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

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

411 Potential for Interaction with Drugs that Affect Gastric Acidity — Cymbalta has an enteric coating that
412 resists dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. In

413 extremely acidic conditions, Cymbalta, unprotected by the enteric coating, may undergo hydrolysis to
414 form naphthol. Caution is advised in using Cymbalta in patients with conditions that may slow gastric
415 emptying (e.g., some diabetics). Drugs that raise the gastrointestinal pH may lead to an earlier release of
416 duloxetine. However, co-administration of Cymbalta with aluminum- and magnesium-containing
417 antacids (51 mEq) or Cymbalta with famotidine, had no significant effect on the rate or extent of
418 duloxetine absorption after administration of a 40-mg oral dose. It is unknown whether the concomitant
419 administration of proton pump inhibitors affects duloxetine absorption.

420 Monoamine Oxidase Inhibitors — See CONTRAINDICATIONS and WARNINGS.

421 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

423 In female mice receiving duloxetine at 140 mg/kg/day (11 times the maximum recommended human
424 dose [MRHD, 60 mg/day] and 6 times the human dose of 120 mg/day on a mg/m² basis), there was an
425 increased incidence of hepatocellular adenomas and carcinomas. The no-effect dose was 50 mg/kg/day
426 (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m² basis). Tumor incidence
427 was not increased in male mice receiving duloxetine at doses up to 100 mg/kg/day (8 times the MRHD
428 and 4 times the human dose of 120 mg/day on a mg/m² basis).

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

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

437 Impairment of Fertility — Duloxetine administered orally to either male or female rats prior to and
438 throughout mating at doses up to 45 mg/kg/day (7 times the maximum recommended human dose of
439 60 mg/day and 4 times the human dose of 120 mg/day on a mg/m² basis) did not alter mating or fertility.

440 **Pregnancy**

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

443 When duloxetine was administered orally to pregnant rats and rabbits during the period of
444 organogenesis, there was no evidence of teratogenicity at doses up to 45 mg/kg/day (7 times the
445 maximum recommended human dose [MRHD, 60 mg/day] and 4 times the human dose of 120 mg/day
446 on a mg/m² basis, in rat; 15 times the MRHD and 7 times the human dose of 120 mg/day on a mg/m²
447 basis in rabbit). However, fetal weights were decreased at this dose, with a no-effect dose of
448 10 mg/kg/day (2 times the MRHD and ≈1 times the human dose of 120 mg/day on a mg/m² basis in rat;
449 3 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m² basis in rabbits).

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

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

459 **Nonteratogenic Effects** — Neonates exposed to SSRIs or serotonin and norepinephrine reuptake
460 inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged
461 hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon
462 delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures,
463 temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia,
464 tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic
465 effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in
466 some cases, the clinical picture is consistent with serotonin syndrome (*see* WARNINGS, Monoamine
467 Oxidase Inhibitors). When treating a pregnant woman with Cymbalta during the third trimester, the
468 physician should carefully consider the potential risks and benefits of treatment (*see* DOSAGE AND
469 ADMINISTRATION).

470 **Labor and Delivery**

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

473 **Nursing Mothers**

474 Duloxetine and/or its metabolites are excreted into the milk of lactating rats. It is unknown whether or
475 not duloxetine and/or its metabolites are excreted into human milk, but nursing while on Cymbalta is not
476 recommended.

477 **Pediatric Use**

478 Safety and efficacy in pediatric patients have not been established (*see* WARNINGS, Clinical
479 Worsening and Suicide Risk).

480 **Geriatric Use**

481 Of the 2418 patients in clinical studies of Cymbalta for MDD, 5.9% (143) were 65 years of age or
482 over. Of the 1074 patients in the DPN studies, 33% (357) were 65 years of age or over. No overall
483 differences in safety or effectiveness were observed between these subjects and younger subjects, and
484 other reported clinical experience has not identified differences in responses between the elderly and
485 younger patients, but greater sensitivity of some older individuals cannot be ruled out.

486 **ADVERSE REACTIONS**

487 Cymbalta has been evaluated for safety in 2418 patients diagnosed with major depressive disorder
488 who participated in multiple-dose premarketing trials, representing 1099 patient-years of exposure.
489 Among these 2418 Cymbalta-treated patients, 1139 patients participated in eight 8- or 9-week,
490 placebo-controlled trials at doses ranging from 40 to 120 mg/day, while the remaining 1279 patients
491 were followed for up to 1 year in an open-label safety study using flexible doses from 80 to
492 120 mg/day. Two placebo-controlled studies with doses of 80 and 120 mg/day had 6-month
493 maintenance extensions. Of these 2418 patients, 993 Cymbalta-treated patients were exposed for at
494 least 180 days and 445 Cymbalta-treated patients were exposed for at least 1 year.

495 Cymbalta has also been evaluated for safety in 1074 patients with diabetic peripheral neuropathy
496 representing 472 patient-years of exposure. Among these 1074 Cymbalta-treated patients, 568 patients
497 participated in two 12- to 13-week, placebo-controlled trials at doses ranging from 20 to 120 mg/day.
498 An additional 449 patients were enrolled in an open-label safety study using 120 mg/day for a duration
499 of 6 months. Another 57 patients, originally treated with placebo, were exposed to Cymbalta for up to
500 12 months at 60 mg twice daily in an extension phase. Among these 1074 patients, 484 had 6 months
501 of exposure to Cymbalta, and 220 had 12 months of exposure.

502 For both MDD and DPN clinical trials, adverse reactions were assessed by collecting adverse events,
503 results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

504 Clinical investigators recorded adverse events using descriptive terminology of their own choosing. To
505 provide a meaningful estimate of the proportion of individuals experiencing adverse events, grouping

506 similar types of events into a smaller number of standardized event categories is necessary. In the tables
507 and tabulations that follow, MedDRA terminology has been used to classify reported adverse events.

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

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

520 **Adverse Events Reported as Reasons for Discontinuation of Treatment in** 521 **Placebo-Controlled Trials**

522 **Major Depressive Disorder**

523 Approximately 10% of the 1139 patients who received Cymbalta in the MDD placebo-controlled
524 trials discontinued treatment due to an adverse event, compared with 4% of the 777 patients receiving
525 placebo. Nausea (Cymbalta 1.4%, placebo 0.1%) was the only common adverse event reported as
526 reason for discontinuation and considered to be drug-related (i.e., discontinuation occurring in at least
527 1% of the Cymbalta-treated patients and at a rate of at least twice that of placebo).

528 **Diabetic Peripheral Neuropathic Pain**

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

536 **Adverse Events Occurring at an Incidence of 2% or More Among Cymbalta-** 537 **Treated Patients in Placebo-Controlled Trials**

538 **Major Depressive Disorder**

539 Table 1 gives the incidence of treatment-emergent adverse events that occurred in 2% or more of
540 patients treated with Cymbalta in the acute phase of MDD placebo-controlled trials and with an
541 incidence greater than placebo. The most commonly observed adverse events in Cymbalta-treated
542 MDD patients (incidence of 5% or greater and at least twice the incidence in placebo patients)
543 were: nausea; dry mouth; constipation; decreased appetite; fatigue; somnolence; and increased sweating
544 (*see* Table 1).

545

**Table 1: Treatment-Emergent Adverse Events Incidence
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

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

550 ² Term includes anorexia.

551 ³ Term includes middle insomnia.

552 ⁴ Term includes anorgasmia.

553 ⁵ Male patients only.

554 ⁶ Term includes ejaculation disorder and ejaculation failure.
555

556 **Diabetic Peripheral Neuropathic Pain**

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

563

**Table 2: 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

564 ¹ Events reported by at least 2% of patients treated with Cymbalta and more often than placebo. The following
565 events were reported by at least 2% of patients treated with Cymbalta for DPN and had an incidence equal to or
566 less than placebo: edema peripheral, influenza, upper respiratory tract infection, back pain, arthralgia, pain in
567 extremity, and pruritus.

568 ² Male patients only.

569

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

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

575 Although changes in sexual desire, sexual performance and sexual satisfaction often occur as
576 manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment.
577 Reliable estimates of the incidence and severity of untoward experiences involving sexual desire,
578 performance and satisfaction are difficult to obtain, however, in part because patients and physicians
579 may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience
580 and performance cited in product labeling are likely to underestimate their actual incidence. Table 3
581 displays the incidence of sexual side effects spontaneously reported by at least 2% of either male or
582 female patients taking Cymbalta in MDD placebo-controlled trials.

583

Table 3: Treatment-Emergent Sexual Dysfunction-Related Adverse Events Incidence in MDD Placebo-Controlled Trials¹

Adverse Event	Percentage of Patients Reporting Event			
	% 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

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

585 ² Term includes anorgasmia.

586 ³ Term includes ejaculation disorder and ejaculation failure.

587 NA=Not applicable.

588

589 Because adverse sexual events are presumed to be voluntarily underreported, the Arizona Sexual
590 Experience Scale (ASEX), a validated measure designed to identify sexual side effects, was used
591 prospectively in 4 MDD placebo-controlled trials. In these trials, as shown in Table 4 below, patients
592 treated with Cymbalta experienced significantly more sexual dysfunction, as measured by the total score
593 on the ASEX, than did patients treated with placebo. Gender analysis showed that this difference

594 occurred only in males. Males treated with Cymbalta experienced more difficulty with ability to reach
 595 orgasm (ASEX Item 4) than males treated with placebo. Females did not experience more sexual
 596 dysfunction on Cymbalta than on placebo as measured by ASEX total score. These studies did not,
 597 however, include an active control drug with known effects on female sexual dysfunction, so that there is
 598 no evidence that its effects differ from other antidepressants. Negative numbers signify an improvement
 599 from a baseline level of dysfunction, which is commonly seen in depressed patients. Physicians should
 600 routinely inquire about possible sexual side effects.

601

**Table 4: 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

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

603 *p=0.013 versus placebo.

604 **p<0.001 versus placebo.

605

606 Urinary Hesitation

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

610 Laboratory Changes

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

615 Vital Sign Changes

616 Cymbalta treatment, for up to 9-weeks in MDD placebo-controlled clinical trials of 40 to 120 mg
 617 daily doses caused increases in blood pressure, averaging 2 mm Hg systolic and 0.5 mm Hg diastolic
 618 compared to placebo and an increase in the incidence of at least one measurement of systolic blood
 619 pressure over 140 mm Hg (*see* PRECAUTIONS).

620 Cymbalta treatment, for up to 9-weeks in MDD placebo-controlled clinical trials and for up to 13-
 621 weeks in DPN placebo-controlled trials caused a small increase in heart rate compared to placebo of
 622 about 2 beats per minute.

623 Weight Changes

624 In MDD placebo-controlled clinical trials, patients treated with Cymbalta for up to 9-weeks
 625 experienced a mean weight loss of approximately 0.5 kg, compared with a mean weight gain of
 626 approximately 0.2 kg in placebo-treated patients.

627 In DPN placebo-controlled clinical trials, patients treated with Cymbalta for up to 13-weeks
 628 experienced a mean weight loss of approximately 1.1 kg, compared with a mean weight gain of
 629 approximately 0.2 kg in placebo-treated patients.

630 **Electrocardiogram Changes**

631 Electrocardiograms were obtained from 321 Cymbalta-treated patients with major depressive
 632 disorder and 169 placebo-treated patients in clinical trials lasting up to 8-weeks. The rate-corrected
 633 QT (QTc) interval in Cymbalta-treated patients did not differ from that seen in placebo-treated patients.
 634 No clinically significant differences were observed for QT, PR, and QRS intervals between
 635 Cymbalta-treated and placebo-treated patients.

636 Electrocardiograms were obtained from 528 Cymbalta-treated patients with DPN and 205 placebo-
 637 treated patients in clinical trials lasting up to 13-weeks. The rate-corrected QT (QTc) interval in
 638 Cymbalta-treated patients did not differ from that seen in placebo-treated patients. No clinically
 639 significant differences were observed for QT, PR, QRS, or QTc measurements between Cymbalta-
 640 treated and placebo-treated patients.

641 **Other Adverse Events Observed During the Premarketing Evaluation of Cymbalta 642 for MDD and the Pain of DPN**

643 Following is a list of modified MedDRA terms that reflect treatment-emergent adverse events as
 644 defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with
 645 Cymbalta at multiple doses throughout the dose range studied during any phase of a trial within the
 646 premarketing database. The events included are those not already listed elsewhere in ADVERSE
 647 REACTIONS and not considered in the WARNINGS and PRECAUTIONS sections, that were
 648 reported with an incidence of greater than or equal to 0.05% and by more than one patient, are not
 649 common as background events and were considered possibly drug related (e.g., because of the drug's
 650 pharmacology) or potentially important.

651 It is important to emphasize that, although the events reported occurred during treatment with
 652 Cymbalta, they were not necessarily caused by it. Events are further categorized by body system and
 653 listed in order of decreasing frequency according to the following definitions: frequent adverse events are
 654 those occurring in at least 1/100 patients (only those not already listed in the tabulated results from
 655 placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to
 656 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

657 **Blood and Lymphatic System Disorders** — *Infrequent*: anemia, leukopenia, increased white
 658 blood cell count, lymphadenopathy, and thrombocytopenia.

659 **Cardiac Disorders** — *Infrequent*: atrial fibrillation, bundle branch block right, cardiac failure,
 660 cardiac failure congestive, coronary artery disease, and myocardial infarction.

661 **Eye Disorders** — *Infrequent*: diplopia, glaucoma, keratoconjunctivitis sicca, macular degeneration,
 662 maculopathy, photopsia, and retinal detachment.

663 **Gastrointestinal Disorders** — *Frequent*: gastritis; *Infrequent*: aphthous stomatitis, blood in stool,
 664 colitis, diverticulitis, dysphagia, esophageal stenosis acquired, gastric irritation, gastric ulcer, gingivitis,
 665 impaired gastric emptying, irritable bowel syndrome, lower abdominal pain, and melena.

666 **General Disorders and Administration Site Conditions** — *Frequent*: rigors;
 667 *Infrequent*: edema, feeling jittery, influenza-like illness, and thirst.

668 **Hepato-biliary Disorders** — *Infrequent*: hepatic steatosis.

669 **Investigations** — *Frequent*: weight increased; *Infrequent*: blood cholesterol increased, blood
 670 creatinine increased, and urine output decreased.

671 **Metabolism and Nutrition Disorders** — *Frequent*: hypoglycemia and increased appetite;
 672 *Infrequent*: dehydration, dyslipidemia, hypercholesterolemia, hyperlipidemia, and hypertriglyceridemia.

673 **Musculoskeletal and Connective Tissue Disorders** — *Infrequent*: muscular weakness.

- 674 **Nervous System Disorders** — *Frequent*: hypoesthesia; *Infrequent*: ataxia and dysarthria.
- 675 **Psychiatric Disorders** — *Frequent*: initial insomnia, irritability, lethargy, nervousness, nightmare,
676 restlessness, and sleep disorder; *Infrequent*: completed suicide, mania, mood swings, pressure of
677 speech, sluggishness, and suicide attempt.
- 678 **Renal and Urinary Disorders** — *Frequent*: dysuria; *Infrequent*: micturition urgency, nephropathy,
679 urinary hesitation, urinary incontinence, urinary retention, and urine flow decreased.
- 680 **Respiratory, Thoracic and Mediastinal Disorders** — *Infrequent*: oropharyngeal swelling.
- 681 **Skin and Subcutaneous Tissue Disorders** — *Frequent*: night sweats, pruritus, rash, and skin
682 ulcer; *Infrequent*: acne, alopecia, cold sweat, exfoliative dermatitis, ecchymosis, eczema, erythema,
683 face edema, hyperkeratosis, increased tendency to bruise, photosensitivity reaction, erythematous rash,
684 and pruritic rash.
- 685 **Vascular Disorders** — *Infrequent*: hypertensive crisis, peripheral edema, and phlebitis.

686 **DRUG ABUSE AND DEPENDENCE**

687 **Controlled Substance Class**

688 Duloxetine is not a controlled substance.

689 **Physical and Psychological Dependence**

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

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

698 **OVERDOSAGE**

699 There is limited clinical experience with Cymbalta overdose in humans. In premarketing clinical trials,
700 as of October 2003, no cases of fatal acute overdose of Cymbalta have been reported. Four non-fatal
701 acute ingestions of Cymbalta (300 to 1400 mg), alone or in combination with other drugs, have been
702 reported.

703 **Management of Overdose**

704 There is no specific antidote to Cymbalta. In case of acute overdose, treatment should consist of
705 those general measures employed in the management of overdose with any drug.

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

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

715 In managing overdose, the possibility of multiple drug involvement should be considered. A specific
716 caution involves patients who are taking or have recently taken Cymbalta and might ingest excessive
717 quantities of a TCA. In such a case, decreased clearance of the parent tricyclic and/or its active
718 metabolite may increase the possibility of clinically significant sequelae and extend the time needed for
719 close medical observation (*see* PRECAUTIONS, Drug Interactions). The physician should consider

720 contacting a poison control center for additional information on the treatment of any overdose.
721 Telephone numbers for certified poison control centers are listed in the *Physicians' Desk*
722 *Reference* (PDR).

723 **DOSAGE AND ADMINISTRATION**

724 **Initial Treatment**

725 **Major Depressive Disorder**

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

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

729 **Diabetic Peripheral Neuropathic Pain**

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

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

738 **Maintenance/Continuation/Extended Treatment**

739 **Major Depressive Disorder**

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

744 **Diabetic Peripheral Neuropathic Pain**

745 As the progression of diabetic peripheral neuropathy is highly variable and management of pain is
746 empirical, the effectiveness of Cymbalta must be assessed individually. Efficacy beyond 12 weeks has
747 not been systematically studied in placebo-controlled trials, but a one-year open-label safety study was
748 conducted.

749 **Special Populations**

750 Dosage for Renally Impaired Patients — Cymbalta is not recommended for patients with end-stage
751 renal disease (requiring dialysis) or in severe renal impairment (estimated creatinine clearance
752 <30 mL/min) (*see* CLINICAL PHARMACOLOGY).

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

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

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

763 **Discontinuing Cymbalta**

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

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

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

774 **HOW SUPPLIED**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

793

794 *equivalent to duloxetine base.

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

796

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

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