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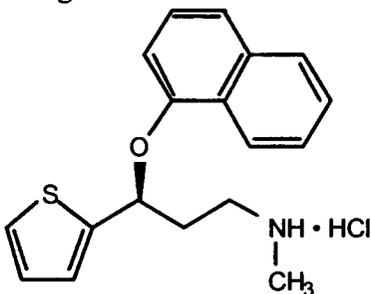
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CYMBALTA[®]

(duloxetine hydrochloride)

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:



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

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

CLINICAL PHARMACOLOGY

18 Pharmacodynamics

19 Although the mechanism of the antidepressant action of duloxetine in humans is unknown, it is
20 believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS.
21 Preclinical studies have shown that duloxetine is a potent inhibitor of neuronal serotonin and
22 norepinephrine reuptake and a less potent inhibitor of dopamine reuptake. Duloxetine has no
23 significant affinity for dopaminergic, adrenergic, cholinergic or histaminergic receptors *in vitro*.
24 Duloxetine does not inhibit monoamine oxidase (MAO). Duloxetine undergoes extensive
25 metabolism, but the major circulating metabolites have not been shown to contribute significantly
26 to the pharmacologic activity of duloxetine.

27 Pharmacokinetics

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

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

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

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

52 **Special Populations**

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

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

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

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

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

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

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

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

87 Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

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

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

96 Studies with Benzodiazepines —

97 Lorazepam — Under steady-state conditions, for duloxetine (60 mg Q 12 hours) and lorazepam
98 (2 mg Q 12 hours) the pharmacokinetics of duloxetine were not affected by co-administration.

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

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

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

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

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

117 Drugs Metabolized by CYP3A — Results of *in vitro* studies demonstrate that duloxetine does
118 not inhibit or induce CYP3A activity. Therefore, an increase or decrease in the metabolism of
119 CYP3A substrates (e.g., oral contraceptives and other steroidal agents) resulting from induction or
120 inhibition is 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 (30 mg
125 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 duloxetine 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
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 9
135 weeks; in the third study, patients were randomized to Cymbalta 20 or 40 mg twice daily (N=86
136 and N=91, respectively) or placebo (N=89) for 8 weeks; in the fourth study, patients were
137 randomized to Cymbalta 40 or 60 mg twice daily (N=95 and N=93, respectively) or placebo
138 (N=93) for 8 weeks. There is no evidence that doses greater than 60 mg/day confer any additional
139 benefit.

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

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

INDICATIONS AND USAGE

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

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

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

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

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

CONTRAINDICATIONS

161 Hypersensitivity

162 Duloxetine is contraindicated in patients with a known hypersensitivity to the product.

163 Monoamine Oxidase Inhibitors

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

166 Uncontrolled Narrow-Angle Glaucoma

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

169 WARNINGS

170 **Clinical Worsening and Suicide Risk** — Patients with major depressive disorder, both adult
171 and pediatric, may experience worsening of their depression and/or the emergence of suicidal
172 ideation and behavior (suicidality), whether or not they are taking antidepressant medications, and
173 this risk may persist until significant remission occurs. Although there has been a long-standing
174 concern that antidepressants may have a role in inducing worsening of depression and the
175 emergence of suicidality in certain patients, a causal role for antidepressants in inducing such
176

177 behaviors has not been established. Nevertheless, patients being treated with antidepressants
178 **should be observed closely for clinical worsening and suicidality, especially at the beginning**
179 **of a course of drug therapy, or at the time of dose changes, either increases or decreases.**
180 Consideration should be given to changing the therapeutic regimen, including possibly
181 discontinuing the medication, in patients whose depression is persistently worse or whose
182 emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting
183 symptoms.

184 Because of the possibility of co-morbidity between major depressive disorder and other
185 psychiatric and nonpsychiatric disorders, the same precautions observed when treating patients
186 with major depressive disorder should be observed when treating patients with other psychiatric
187 and nonpsychiatric disorders.

188 The following symptoms – anxiety, agitation, panic attacks, insomnia, irritability, hostility
189 (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania – have
190 been reported in adult and pediatric patients being treated with antidepressants for major
191 depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although
192 a causal link between the emergence of such symptoms and either the worsening of depression
193 and/or the emergence of suicidal impulses has not been established, consideration should be given
194 to changing the therapeutic regimen, including possibly discontinuing the medication, in patients
195 for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting
196 symptoms.

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

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

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

218 **Monoamine Oxidase Inhibitors (MAOI) — In patients receiving a serotonin reuptake**
219 **inhibitor in combination with a monoamine oxidase inhibitor, there have been reports of**
220 **serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic**
221 **instability with possible rapid fluctuations of vital signs, and mental status changes that**
222 **include extreme agitation progressing to delirium and coma. These reactions have also been**
223 **reported in patients who have recently discontinued serotonin reuptake inhibitors and are**
224 **then started on an MAOI. Some cases presented with features resembling neuroleptic**
225 **malignant syndrome. The effects of combined use of duloxetine and MAOIs have not been**
226 **evaluated in humans or animals. Therefore, because duloxetine is an inhibitor of both**

227 serotonin and norepinephrine reuptake, it is recommended that duloxetine not be used in
228 combination with an MAOI, or within at least 14 days of discontinuing treatment with an
229 MAOI. Based on the half-life of duloxetine, at least 5 days should be allowed after stopping
230 duloxetine before starting an MAOI.

231

PRECAUTIONS

232 General

233 Hepatotoxicity

234 Duloxetine increases the risk of elevation of serum transaminase levels. Liver transaminase
235 elevations resulted in the discontinuation of 0.3% (27/8454) of duloxetine-treated patients. In
236 these patients, the median time to detection of the transaminase elevation was about two months.
237 In controlled trials in MDD, elevations of alanine transaminase (ALT) to > 3 times the upper limit
238 of normal occurred in 0.9% (8/930) of duloxetine-treated patients and in 0.3% (2/652) placebo-
239 treated patients. In the full cohort of placebo controlled trials in any indication, 1% (39/3732) of
240 duloxetine-treated patients had a > 3 times the upper limit of normal elevation of ALT compared to
241 0.2% (6/2568) of placebo-treated patients. In placebo-controlled studies using a fixed dose
242 design, there was evidence of a dose-response relationship for ALT and AST elevation of > 3
243 times the upper limit of normal and > 5 times the upper limit of normal, respectively.

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

252 Effect on Blood Pressure — In clinical trials, duloxetine treatment was associated with mean
253 increases in blood pressure, averaging 2 mm Hg systolic and 0.5 mm Hg diastolic and an increase
254 in the incidence of at least one measurement of systolic blood pressure over 140 mm Hg compared
255 to placebo. Blood pressure should be measured prior to initiating treatment and periodically
256 measured throughout treatment (*see* ADVERSE REACTIONS, Vital Sign Changes).

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

263 Seizures — Duloxetine has not been systematically evaluated in patients with a seizure disorder,
264 and such patients were excluded from clinical studies. In placebo-controlled clinical trials in
265 patients with major depressive disorder, seizures occurred in 0.1% (1/1139) of patients treated
266 with duloxetine and 0% (0/777) of patients treated with placebo. Like other drugs effective in the
267 treatment of major depressive disorder, duloxetine should be prescribed with care in patients with
268 a history of a seizure disorder.

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

272 Discontinuation of Treatment with Cymbalta- Discontinuation symptoms have been
273 systematically evaluated in patients taking Cymbalta. Following abrupt discontinuation in placebo-
274 controlled clinical trials of up to 9-weeks duration, the following symptoms occurred at a rate
275 greater than or equal to 2% and at a significantly higher rate in duloxetine-treated patients

276 compared to those discontinuing from placebo: dizziness; nausea; headache; paresthesia; vomiting;
277 irritability; and nightmare.

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

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

290 Use in Patients with Concomitant Illness — Clinical experience with duloxetine in patients with
291 concomitant systemic illnesses is limited. There is no information on the effect that alterations in
292 gastric motility may have on the stability of duloxetine's enteric coating. As duloxetine is rapidly
293 hydrolyzed in acidic media to naphthol, caution is advised in using duloxetine in patients with
294 conditions that may slow gastric emptying.

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

302 Increased plasma concentrations of duloxetine, and especially of its metabolites, occur in
303 patients with ESRD and severe renal impairment (creatinine clearance <30 mL/min). For this
304 reason, duloxetine is not recommended for patients with ESRD (see CLINICAL
305 PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

306 Markedly increased exposure to duloxetine occurs in patients with hepatic insufficiency and
307 duloxetine should not be administered to these patients (see CLINICAL PHARMACOLOGY and
308 DOSAGE AND ADMINISTRATION).

309 **Information for Patients**

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

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

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

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

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

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

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

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

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

335 **Laboratory Tests**

336 No specific laboratory tests are recommended.

337 **Drug Interactions (also see CLINICAL PHARMACOLOGY, Drug-Drug Interactions)** 338 **Potential for Other Drugs to Affect Duloxetine**

339 Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

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

344 Inhibitors of CYP2D6 — Because CYP2D6 is involved in duloxetine metabolism, concomitant
345 use of duloxetine with potent inhibitors of CYP2D6 may result in higher concentrations of
346 duloxetine. Paroxetine (20 mg QD) increased the concentration of duloxetine (40 mg QD) by about
347 60%, and greater degrees of inhibition are expected with higher doses of paroxetine. Similar
348 effects would be expected with other potent CYP2D6 inhibitors (e.g., fluoxetine, quinidine).

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

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

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

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

366

367 **Duloxetine May Have a Clinically Important Interaction with the Following Other Drugs:**

368 Alcohol — When duloxetine and ethanol were administered several hours apart so that peak
369 concentrations of each would coincide, duloxetine did not increase the impairment of mental and
370 motor skills caused by alcohol.

371 In the duloxetine clinical trials database, three duloxetine treated patients had liver injury as
 372 manifested by ALT and total bilirubin elevations, with evidence of obstruction. Substantial
 373 intercurrent ethanol use was present in each of these cases, and this may have contributed to the
 374 abnormalities seen. (see PRECAUTIONS, Hepatotoxicity).

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

378 Potential for Interaction with Drugs that Affect Gastric Acidity — Duloxetine has an enteric
 379 coating that resists dissolution until reaching a segment of the gastrointestinal tract where the pH
 380 exceeds 5.5. In extremely acidic conditions, duloxetine, unprotected by the enteric coating, may
 381 undergo hydrolysis to form naphthol. Drugs that raise the gastrointestinal pH may lead to an earlier
 382 release of duloxetine. However, co-administration of duloxetine with aluminum- and magnesium-
 383 containing antacids (51 mEq) or duloxetine with famotidine, had no significant effect on the rate or
 384 extent of duloxetine absorption after administration of a 40 mg oral dose. It is unknown whether the
 385 concomitant administration of proton pump inhibitors affects duloxetine absorption.

386 Monoamine Oxidase Inhibitors — See CONTRAINDICATIONS and WARNINGS.

387 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

389 In female mice receiving duloxetine at dietary doses of approximately 140 mg/kg/day (11 times
 390 the maximum recommended human dose [MRHD] of 60 mg/day on a mg/m² basis), there was an
 391 increased incidence of hepatocellular adenomas and carcinomas; the no-effect level was
 392 approximately 50 mg/kg (4 times the MRHD on a mg/m² basis). Tumor incidence was not
 393 increased in male mice receiving duloxetine at dietary doses up to approximately 100 mg/kg/day
 394 (8 times the MRHD on a mg/m² basis).

395 In rats, dietary doses of duloxetine up to approximately 27 mg/kg/day in females (4 times the
 396 MRHD on a mg/m² basis) or approximately 36 mg/kg/day in males (6 times the MRHD on a mg/m²
 397 basis) did not increase the incidence of tumors.

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

404 Impairment of Fertility — Duloxetine administered orally to either male or female rats prior to
 405 and throughout mating at daily doses up to 45 mg/kg (7 times the maximum recommended human
 406 dose [MRHD] on a mg/m² basis) did not alter mating or fertility.

407 **Pregnancy**

408 **Pregnancy-Nonteratogenic Effects**

409 Neonates exposed to SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in
 410 the third trimester have developed complications requiring prolonged hospitalization, respiratory
 411 support, and tube feeding. Such complications can arise immediately upon delivery. Reported
 412 clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature
 413 instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia,
 414 tremor, jitteriness, irritability, and constant crying. These features are consistent with either a
 415 direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be
 416 noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see
 417 WARNINGS, Monoamine Oxidase Inhibitors). When treating a pregnant woman with Cymbalta
 418 during the third trimester, the physician should carefully consider the potential risks and benefits of
 419 treatment (see DOSAGE AND ADMINISTRATION).

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

422 When duloxetine was administered orally to pregnant rats and rabbits during the period of
423 organogenesis, there was no evidence of teratogenicity at doses up to 45 mg/kg/day (7 and 15
424 times the maximum recommended human dose [MRHD] on a mg/m² basis, in rats and rabbits,
425 respectively). However, fetal weights were decreased at this dose, with a no-effect level of 10
426 mg/kg (2 and 3 times the MRHD on a mg/m² basis, in rats and rabbits, respectively).

427 When duloxetine was administered orally to pregnant rats throughout gestation and lactation, the
428 survival of pups to 1 day postpartum and pup body weights at birth and during the lactation period
429 were decreased following maternal exposure to 30 mg/kg/day (5 times the MRHD on a mg/m²
430 basis), with a no-effect level of 10 mg/kg. Furthermore, behaviors consistent with increased
431 reactivity, such as increased startle response to noise and decreased habituation of locomotor
432 activity, were observed in pups following maternal exposure to 30 mg/kg/day. Post-weaning
433 growth and reproductive performance of the progeny were not affected adversely by maternal
434 duloxetine treatment.

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

437 **Labor and Delivery**

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

440 **Nursing Mothers**

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

444 **Pediatric Use**

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

447 **Geriatric Use**

448 Of the 2418 patients in clinical studies of duloxetine, 5.9% (143) were 65 years of age or over.
449 No overall differences in safety or effectiveness were observed between these subjects and
450 younger subjects, and other reported clinical experience has not identified differences in responses
451 between the elderly and younger patients, but greater sensitivity of some older individuals cannot
452 be ruled out.

453 **ADVERSE REACTIONS**

454 Duloxetine has been evaluated for safety in 2418 patients diagnosed with major depressive
455 disorder who participated in multiple-dose premarketing trials, representing 1099 patient-years of
456 exposure. Among these 2418 duloxetine-treated patients, 1139 patients participated in eight 8- or
457 9-week, placebo-controlled trials at doses ranging from 40 to 120 mg/day, while the remaining
458 1279 patients were followed for up to 1 year in an open-label safety study using flexible doses
459 from 80 to 120 mg/day. Two placebo-controlled studies with doses of 80 and 120 mg/day had 6-
460 month maintenance extensions. Of these 2418 patients, 993 duloxetine-treated patients were
461 exposed for at least 180 days and 445 duloxetine-treated patients were exposed for at least 1 year.
462 Adverse reactions were assessed by collecting adverse events, results of physical examinations,
463 vital signs, weights, laboratory analyses, and ECGs.

464 Clinical investigators recorded adverse events using descriptive terminology of their own
465 choosing. To provide a meaningful estimate of the proportion of individuals experiencing adverse
466 events, grouping similar types of events into a smaller number of standardized event categories is

467 necessary. In the tables and tabulations that follow, MedDRA terminology has been used to
468 classify reported adverse events.

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

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

481 **Adverse Events Reported as Reasons for Discontinuation of Treatment in** 482 **Placebo-Controlled Trials**

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

489 **Adverse Events Occurring at an Incidence of 2% or More Among Duloxetine-** 490 **Treated Patients in Placebo-Controlled Trials**

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

497

**Table 1: Treatment-Emergent Adverse Events Incidence
 in Placebo-Controlled Trials¹**

System Organ Class / Adverse Event	Percentage of Patients Reporting Event	
	Duloxetine (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

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

502 ²Term includes anorexia.

503 ³Term includes middle insomnia.

504 ⁴Term includes anorgasmia.

505 ⁵Male patients only.

506 ⁶Term includes ejaculation disorder and ejaculation failure.

507

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

512

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

514 Although changes in sexual desire, sexual performance and sexual satisfaction often occur as
 515 manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic
 516 treatment. Reliable estimates of the incidence and severity of untoward experiences involving
 517 sexual desire, performance and satisfaction are difficult to obtain, however, in part because
 518 patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence
 519 of untoward sexual experience and performance cited in product labeling are likely to
 520 underestimate their actual incidence. Table 2 displays the incidence of sexual side effects
 521 spontaneously reported by at least 2% of either male or female patients taking duloxetine in
 522 placebo-controlled trials.

523

**Table 2: Treatment-Emergent Sexual Dysfunction-Related Adverse Events Incidence
 in Placebo-Controlled Trials¹**

Adverse Event	Percentage of Patients Reporting Event			
	% Male Patients		% Female Patients	
	Duloxetine (N=378)	Placebo (N=247)	Duloxetine (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

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

525 ²Term includes anorgasmia.

526 ³Term includes ejaculation disorder and ejaculation failure.

527 NA= Not applicable.

528

529 Because adverse sexual events are presumed to be voluntarily underreported, the Arizona Sexual
 530 Experience Scale (ASEX), a validated measure designed to identify sexual side effects, was used
 531 prospectively in 4 placebo-controlled trials. In these trials, as shown in Table 3 below, patients
 532 treated with duloxetine experienced significantly more sexual dysfunction, as measured by the total
 533 score on the ASEX, than did patients treated with placebo. Gender analysis showed that this
 534 difference occurred only in males. Males treated with duloxetine experienced more difficulty with
 535 ability to reach orgasm (ASEX Item 4) than males treated with placebo. Females did not
 536 experience more sexual dysfunction on duloxetine than on placebo as measured by ASEX total

537 score. These studies did not, however, include an active control drug with known effects on female
 538 sexual dysfunction, so that there is no evidence that its effects differ from other antidepressants.
 539 Negative numbers signify an improvement from a baseline level of dysfunction, which is
 540 commonly seen in depressed patients. Physicians should routinely inquire about possible sexual
 541 side effects.
 542

**Table 3: Mean Change in ASEX Scores by Gender
 in Placebo-Controlled Trials**

	Male Patients		Female Patients	
	Duloxetine (n=175)	Placebo (n=83)	Duloxetine (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

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

544 *p=0.013 versus placebo.

545 **p<0.001 versus placebo.

546

547 **Urinary Hesitation**

548 Duloxetine is in a class of drugs known to affect urethral resistance. If symptoms of urinary
 549 hesitation develop during treatment with duloxetine, consideration should be given to the
 550 possibility that they might be drug-related.

551 **Laboratory Changes**

552 Duloxetine treatment, for up to 9-weeks in placebo-controlled clinical trials, was associated
 553 with small mean increases from baseline to endpoint in ALT, AST, CPK, and alkaline
 554 phosphatase; infrequent, modest, transient, abnormal values were observed for these analytes in
 555 duloxetine-treated patients when compared with placebo-treated patients (*see* PRECAUTIONS).

556 **Vital Sign Changes**

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

561 Duloxetine treatment, for up to 9-weeks in placebo-controlled clinical trials caused a small
 562 increase in heart rate compared to placebo of about 2 beats per minute.

563 **Weight Changes**

564 In placebo-controlled clinical trials, patients treated with duloxetine for up to 9-weeks
 565 experienced a mean weight loss of approximately 0.5 kg, compared with a mean weight gain of
 566 approximately 0.2 kg in placebo-treated patients.

567 **Electrocardiogram Changes**

568 Electrocardiograms were obtained from 321 duloxetine-treated patients with major depressive
 569 disorder and 169 placebo-treated patients in clinical trials lasting up to 8-weeks. The rate-
 570 corrected QT (QTc) interval in duloxetine-treated patients did not differ from that seen in placebo-

571 treated patients. No clinically significant differences were observed for QT, PR, and QRS
572 intervals between duloxetine-treated and placebo-treated patients.

573

574 **Other Adverse Events Observed During the Premarketing Evaluation of Duloxetine**

575

576 Following is a list of modified MedDRA terms that reflect treatment-emergent adverse events as
577 defined in the introduction to the ADVERSE REACTIONS section reported by patients treated
578 with duloxetine at multiple doses throughout the dose range studied during any phase of a trial
579 within the premarketing database. The events included are those not already listed elsewhere in
580 ADVERSE REACTIONS and not considered in the WARNINGS and PRECAUTIONS sections,
581 that were reported with an incidence of greater than or equal to 0.05%, are not common as
582 background events and were considered possibly drug related (e.g., because of the drug's
583 pharmacology) or potentially important.

584

585 It is important to emphasize that, although the events reported occurred during treatment with
586 duloxetine, they were not necessarily caused by it. Events are further categorized by body system
587 and listed in order of decreasing frequency according to the following definitions: frequent
588 adverse events are those occurring in at least 1/100 patients (only those not already listed in the
589 tabulated results from placebo controlled trials appear in this listing); infrequent adverse events
590 are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than
591 1/1000 patients.

592

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

595 **Gastrointestinal Disorders** — *Frequent*: gastritis; *Infrequent*: blood in stool, colitis, dysphagia,
596 esophageal stenosis acquired, gastric ulcer, gingivitis, irritable bowel syndrome, and lower
597 abdominal pain.

598 **Psychiatric Disorders** — *Frequent*: initial insomnia; irritability, lethargy, nervousness,
599 nightmare, restlessness, and sleep disorder; *Infrequent*: completed suicide, mania, mood swings,
600 pressure of speech, sluggishness, and suicide attempt.

601 **Renal and Urinary Disorders** — *Frequent*: dysuria; *Infrequent*: micturition urgency, -urinary
602 hesitation, urinary incontinence, urinary retention, and urine flow decreased.

603 **Skin and Subcutaneous Tissue Disorders** — *Frequent*: night sweats, pruritus, and rash;
604 *Infrequent*: acne, alopecia, cold sweat, ecchymosis, eczema, erythema, face edema, increased
605 tendency to bruise, and photosensitivity reaction.

606 **Vascular Disorders** — *Infrequent*: -peripheral edema and phlebitis.

607

608

DRUG ABUSE AND DEPENDENCE

609 **Controlled Substance Class**

610 Duloxetine is not a controlled substance.

611 **Physical and Psychological Dependence**

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

615 While duloxetine has not been systematically studied in humans for its potential for abuse, there
616 was no indication of drug-seeking behavior in the clinical trials. However, it is not possible to

617 predict on the basis of premarketing experience the extent to which a CNS active drug will be
618 misused, diverted, and/or abused once marketed. Consequently, physicians should carefully
619 evaluate patients for a history of drug abuse and follow such patients closely, observing them for
620 signs of misuse or abuse of duloxetine (e.g., development of tolerance, incrementation of dose,
621 drug-seeking behavior).

622 OVERDOSAGE

623 There is limited clinical experience with duloxetine overdose in humans. In premarketing
624 clinical trials, as of November 2002, no cases of fatal acute overdose of duloxetine have been
625 reported. Four non-fatal acute ingestions of duloxetine (300 to 1400 mg), alone or in combination
626 with other drugs, have been reported.

627 Management of Overdose

628 There is no specific antidote to duloxetine. In case of acute overdose, treatment should consist of
629 those general measures employed in the management of overdose with any drug effective in the
630 treatment of major depressive disorder.

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

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

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

648

649 DOSAGE AND ADMINISTRATION

650 Initial Treatment

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

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

654 Maintenance/Continuation/Extended Treatment

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

660 Special Populations

661 Dosage for Renally Impaired Patients —Cymbalta is not recommended for patients with end
662 stage renal disease (ESRD) (*see* CLINICAL PHARMACOLOGY).

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

666 Dosage for Elderly Patients — No dose adjustment is recommended for elderly patients on the
667 basis of age. As with any drugs effective in the treatment of major depressive disorder, however,
668 caution should be exercised in treating the elderly. When individualizing the dosage, extra care
669 should be taken when increasing the dose.

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

675 **Discontinuing Cymbalta (duloxetine hydrochloride)**

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

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

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

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HOW SUPPLIED

Cymbalta® (duloxetine hydrochloride) 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 0002-3235-30 (PU3235) – Bottles of 30
- NDC 0002-3235-60 (PU3235) – Bottles of 60
- NDC 0002-3235-90 (PU3235) – Bottles of 90
- NDC 0002-3235-71 (PU3235) – Bottles of 180
- NDC 0002-3235-04 (PU3235) – Bottles of 1000
- 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

*equivalent to duloxetine base

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

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

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