

1
2
3

SYMBYAX[®]
(olanzapine and fluoxetine HCl capsules)

4

WARNING

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

20 **Increased Mortality in Elderly Patients with Dementia-Related Psychosis** — Elderly
21 patients with dementia-related psychosis treated with atypical antipsychotic drugs are at
22 an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled
23 trials (modal duration of 10 weeks) in these patients revealed a risk of death in the
24 drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over
25 the course of a typical 10-week controlled trial, the rate of death in drug-treated patients
26 was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the
27 causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g.,
28 heart failure, sudden death) or infections (e.g., pneumonia) in nature. SYMBYAX
29 (olanzapine and fluoxetine HCl) is not approved for the treatment of patients with
30 dementia-related psychosis (see WARNINGS).

31

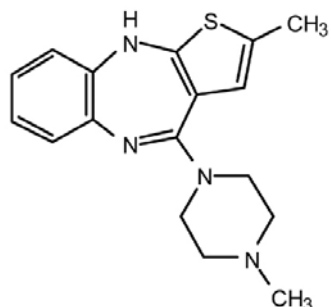
DESCRIPTION

32 SYMBYAX[®] (olanzapine and fluoxetine HCl capsules) combines 2 psychotropic agents,
33 olanzapine (the active ingredient in Zyprexa[®], and Zyprexa Zydis[®]) and fluoxetine hydrochloride
34 (the active ingredient in Prozac[®], Prozac Weekly[™], and Sarafem[®]).

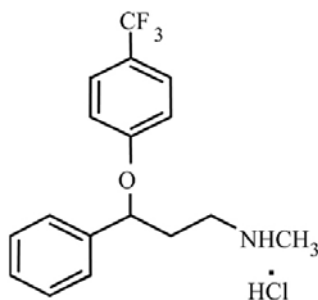
35 Olanzapine belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-
36 4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b] [1,5]benzodiazepine. The molecular formula is
37 C₁₇H₂₀N₄S, which corresponds to a molecular weight of 312.44.

38 Fluoxetine hydrochloride is a selective serotonin reuptake inhibitor (SSRI). The chemical
39 designation is (±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-*p*-tolyl)oxy]propylamine
40 hydrochloride. The molecular formula is C₁₇H₁₈F₃NO•HCl, which corresponds to a molecular
41 weight of 345.79.

42 The chemical structures are:



olanzapine



fluoxetine hydrochloride

43
44
45
46
47
48
49

Olanzapine is a yellow crystalline solid, which is practically insoluble in water.

Fluoxetine hydrochloride is a white to off-white crystalline solid with a solubility of 14 mg/mL in water.

SYMBYAX capsules are available for oral administration in the following strength combinations:

	3 mg/25 mg	6 mg/25 mg	6 mg/50 mg	12 mg/25 mg	12 mg/50 mg
olanzapine equivalent	3	6	6	12	12
fluoxetine base equivalent	25	25	50	25	50

50
51
52
53
54

Each capsule also contains pregelatinized starch, gelatin, dimethicone, titanium dioxide, sodium lauryl sulfate, edible black ink, red iron oxide, yellow iron oxide, and/or black iron oxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

56 Although the exact mechanism of SYMBYAX is unknown, it has been proposed that the
57 activation of 3 monoaminergic neural systems (serotonin, norepinephrine, and dopamine) is
58 responsible for its enhanced antidepressant effect. This is supported by animal studies in which
59 the olanzapine/fluoxetine combination has been shown to produce synergistic increases in
60 norepinephrine and dopamine release in the prefrontal cortex compared with either component
61 alone, as well as increases in serotonin.

62 Olanzapine is a psychotropic agent with high affinity binding to the following receptors:
63 serotonin 5HT_{2A/2C}, 5HT₆, (K_i=4, 11, and 5 nM, respectively), dopamine D₁₋₄ (K_i=11 to 31 nM),
64 histamine H₁ (K_i=7 nM), and adrenergic α₁ receptors (K_i=19 nM). Olanzapine is an antagonist
65 with moderate affinity binding for serotonin 5HT₃ (K_i=57 nM) and muscarinic M₁₋₅ (K_i=73, 96,
66 132, 32, and 48 nM, respectively). Olanzapine binds weakly to GABA_A, BZD, and β-adrenergic
67 receptors (K_i>10 μM). Fluoxetine is an inhibitor of the serotonin transporter and is a weak
68 inhibitor of the norepinephrine and dopamine transporters.

69 Antagonism at receptors other than dopamine and 5HT₂ may explain some of the other
70 therapeutic and side effects of olanzapine. Olanzapine's antagonism of muscarinic M₁₋₅ receptors

71 may explain its anticholinergic-like effects. The antagonism of histamine H₁ receptors by
72 olanzapine may explain the somnolence observed with this drug. The antagonism of
73 α_1 -adrenergic receptors by olanzapine may explain the orthostatic hypotension observed with
74 this drug. Fluoxetine has relatively low affinity for muscarinic, α_1 -adrenergic, and histamine H₁
75 receptors.

76 **Pharmacokinetics**

77 Fluoxetine (administered as a 60-mg single dose or 60 mg daily for 8 days) caused a small
78 increase in the mean maximum concentration of olanzapine (16%) following a 5-mg dose, an
79 increase in the mean area under the curve (17%) and a small decrease in mean apparent clearance
80 of olanzapine (16%). In another study, a similar decrease in apparent clearance of olanzapine of
81 14% was observed following olanzapine doses of 6 or 12 mg with concomitant fluoxetine doses
82 of 25 mg or more. The decrease in clearance reflects an increase in bioavailability. The terminal
83 half-life is not affected, and therefore the time to reach steady state should not be altered. The
84 overall steady-state plasma concentrations of olanzapine and fluoxetine when given as the
85 combination in the therapeutic dose ranges were comparable with those typically attained with
86 each of the monotherapies. The small change in olanzapine clearance, observed in both studies,
87 likely reflects the inhibition of a minor metabolic pathway for olanzapine via CYP2D6 by
88 fluoxetine, a potent CYP2D6 inhibitor, and was not deemed clinically significant. Therefore, the
89 pharmacokinetics of the individual components is expected to reasonably characterize the overall
90 pharmacokinetics of the combination.

91 **Absorption and Bioavailability**

92 **SYMBYAX** — Following a single oral 12-mg/50-mg dose of SYMBYAX, peak plasma
93 concentrations of olanzapine and fluoxetine occur at approximately 4 and 6 hours, respectively.
94 The effect of food on the absorption and bioavailability of SYMBYAX has not been evaluated.
95 The bioavailability of olanzapine given as Zyprexa, and the bioavailability of fluoxetine given as
96 Prozac were not affected by food. It is unlikely that there would be a significant food effect on
97 the bioavailability of SYMBYAX.

98 **Olanzapine** — Olanzapine is well absorbed and reaches peak concentration approximately 6
99 hours following an oral dose. Food does not affect the rate or extent of olanzapine absorption
100 when olanzapine is given as Zyprexa. It is eliminated extensively by first pass metabolism, with
101 approximately 40% of the dose metabolized before reaching the systemic circulation.

102 **Fluoxetine** — Following a single oral 40-mg dose, peak plasma concentrations of fluoxetine
103 from 15 to 55 ng/mL are observed after 6 to 8 hours. Food does not appear to affect the systemic
104 bioavailability of fluoxetine given as Prozac, although it may delay its absorption by 1 to 2
105 hours, which is probably not clinically significant.

106 **Distribution**

107 **SYMBYAX** — The in vitro binding to human plasma proteins of the olanzapine/fluoxetine
108 combination is similar to the binding of the individual components.

109 **Olanzapine** — Olanzapine is extensively distributed throughout the body, with a volume of
110 distribution of approximately 1000 L. It is 93% bound to plasma proteins over the concentration
111 range of 7 to 1100 ng/mL, binding primarily to albumin and α_1 -acid glycoprotein.

112 **Fluoxetine** — Over the concentration range from 200 to 1000 ng/mL, approximately 94.5% of
113 fluoxetine is bound in vitro to human serum proteins, including albumin and α_1 -glycoprotein.
114 The interaction between fluoxetine and other highly protein-bound drugs has not been fully
115 evaluated (*see* PRECAUTIONS, Drugs tightly bound to plasma proteins).

116 **Metabolism and Elimination**

117 **SYMBYAX** — SYMBYAX therapy yielded steady-state concentrations of norfluoxetine
118 similar to those seen with fluoxetine in the therapeutic dose range.

119 **Olanzapine** — Olanzapine displays linear pharmacokinetics over the clinical dosing range. Its
120 half-life ranges from 21 to 54 hours (5th to 95th percentile; mean of 30 hr), and apparent plasma
121 clearance ranges from 12 to 47 L/hr (5th to 95th percentile; mean of 25 L/hr). Administration of
122 olanzapine once daily leads to steady-state concentrations in about 1 week that are approximately
123 twice the concentrations after single doses. Plasma concentrations, half-life, and clearance of
124 olanzapine may vary between individuals on the basis of smoking status, gender, and age (*see*
125 *Special Populations*).

126 Following a single oral dose of ¹⁴C-labeled olanzapine, 7% of the dose of olanzapine was
127 recovered in the urine as unchanged drug, indicating that olanzapine is highly metabolized.
128 Approximately 57% and 30% of the dose was recovered in the urine and feces, respectively. In
129 the plasma, olanzapine accounted for only 12% of the AUC for total radioactivity, indicating
130 significant exposure to metabolites. After multiple dosing, the major circulating metabolites were
131 the 10-N-glucuronide, present at steady state at 44% of the concentration of olanzapine, and
132 4'-N-desmethyl olanzapine, present at steady state at 31% of the concentration of olanzapine.
133 Both metabolites lack pharmacological activity at the concentrations observed.

134 Direct glucuronidation and CYP450-mediated oxidation are the primary metabolic pathways
135 for olanzapine. In vitro studies suggest that CYP1A2, CYP2D6, and the flavin-containing
136 monooxygenase system are involved in olanzapine oxidation. CYP2D6-mediated oxidation
137 appears to be a minor metabolic pathway in vivo, because the clearance of olanzapine is not
138 reduced in subjects who are deficient in this enzyme.

139 **Fluoxetine** — Fluoxetine is a racemic mixture (50/50) of *R*-fluoxetine and *S*-fluoxetine
140 enantiomers. In animal models, both enantiomers are specific and potent serotonin uptake
141 inhibitors with essentially equivalent pharmacologic activity. The *S*-fluoxetine enantiomer is
142 eliminated more slowly and is the predominant enantiomer present in plasma at steady state.

143 Fluoxetine is extensively metabolized in the liver to its only identified active metabolite,
144 norfluoxetine, via the CYP2D6 pathway. A number of unidentified metabolites exist.

145 In animal models, *S*-norfluoxetine is a potent and selective inhibitor of serotonin uptake and
146 has activity essentially equivalent to *R*- or *S*-fluoxetine. *R*-norfluoxetine is significantly less
147 potent than the parent drug in the inhibition of serotonin uptake. The primary route of
148 elimination appears to be hepatic metabolism to inactive metabolites excreted by the kidney.

149 **Clinical Issues Related to Metabolism and Elimination** — The complexity of the
150 metabolism of fluoxetine has several consequences that may potentially affect the clinical use of
151 SYMBYAX.

152 Variability in metabolism — A subset (about 7%) of the population has reduced activity of the
153 drug metabolizing enzyme CYP2D6. Such individuals are referred to as “poor metabolizers” of
154 drugs such as debrisoquin, dextromethorphan, and the tricyclic antidepressants (TCAs). In a
155 study involving labeled and unlabeled enantiomers administered as a racemate, these individuals
156 metabolized *S*-fluoxetine at a slower rate and thus achieved higher concentrations of
157 *S*-fluoxetine. Consequently, concentrations of *S*-norfluoxetine at steady state were lower. The
158 metabolism of *R*-fluoxetine in these poor metabolizers appears normal. When compared with
159 normal metabolizers, the total sum at steady state of the plasma concentrations of the 4
160 enantiomers was not significantly greater among poor metabolizers. Thus, the net
161 pharmacodynamic activities were essentially the same. Alternative nonsaturable pathways

162 (non-CYP2D6) also contribute to the metabolism of fluoxetine. This explains how fluoxetine
163 achieves a steady-state concentration rather than increasing without limit.

164 Because the metabolism of fluoxetine, like that of a number of other compounds including
165 TCAs and other selective serotonin antidepressants, involves the CYP2D6 system, concomitant
166 therapy with drugs also metabolized by this enzyme system (such as the TCAs) may lead to drug
167 interactions (*see* PRECAUTIONS, Drug Interactions).

168 **Accumulation and slow elimination** — The relatively slow elimination of fluoxetine
169 (elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic
170 administration) and its active metabolite, norfluoxetine (elimination half-life of 4 to 16 days after
171 acute and chronic administration), leads to significant accumulation of these active species in
172 chronic use and delayed attainment of steady state, even when a fixed dose is used. After 30 days
173 of dosing at 40 mg/day, plasma concentrations of fluoxetine in the range of 91 to 302 ng/mL and
174 norfluoxetine in the range of 72 to 258 ng/mL have been observed. Plasma concentrations of
175 fluoxetine were higher than those predicted by single-dose studies, because the metabolism of
176 fluoxetine is not proportional to dose. However, norfluoxetine appears to have linear
177 pharmacokinetics. Its mean terminal half-life after a single dose was 8.6 days and after multiple
178 dosing was 9.3 days. Steady-state levels after prolonged dosing are similar to levels seen at 4 to 5
179 weeks.

180 The long elimination half-lives of fluoxetine and norfluoxetine assure that, even when dosing
181 is stopped, active drug substance will persist in the body for weeks (primarily depending on
182 individual patient characteristics, previous dosing regimen, and length of previous therapy at
183 discontinuation). This is of potential consequence when drug discontinuation is required or when
184 drugs are prescribed that might interact with fluoxetine and norfluoxetine following the
185 discontinuation of fluoxetine.

186 **Special Populations**

187 **Geriatric** — Based on the individual pharmacokinetic profiles of olanzapine and fluoxetine,
188 the pharmacokinetics of SYMBYAX may be altered in geriatric patients. Caution should be used
189 in dosing the elderly, especially if there are other factors that might additively influence drug
190 metabolism and/or pharmacodynamic sensitivity.

191 In a study involving 24 healthy subjects, the mean elimination half-life of olanzapine was
192 about 1.5 times greater in elderly subjects (>65 years of age) than in non-elderly subjects (≤65
193 years of age).

194 The disposition of single doses of fluoxetine in healthy elderly subjects (>65 years of age) did
195 not differ significantly from that in younger normal subjects. However, given the long half-life
196 and nonlinear disposition of the drug, a single-dose study is not adequate to rule out the
197 possibility of altered pharmacokinetics in the elderly, particularly if they have systemic illness or
198 are receiving multiple drugs for concomitant diseases. The effects of age upon the metabolism of
199 fluoxetine have been investigated in 260 elderly but otherwise healthy depressed patients (≥60
200 years of age) who received 20 mg fluoxetine for 6 weeks. Combined fluoxetine plus
201 norfluoxetine plasma concentrations were 209.3 ± 85.7 ng/mL at the end of 6 weeks. No unusual
202 age-associated pattern of adverse events was observed in those elderly patients.

203 **Renal Impairment** — The pharmacokinetics of SYMBYAX has not been studied in patients
204 with renal impairment. However, olanzapine and fluoxetine individual pharmacokinetics do not
205 differ significantly in patients with renal impairment. SYMBYAX dosing adjustment based upon
206 renal impairment is not routinely required.

207 Because olanzapine is highly metabolized before excretion and only 7% of the drug is excreted
208 unchanged, renal dysfunction alone is unlikely to have a major impact on the pharmacokinetics
209 of olanzapine. The pharmacokinetic characteristics of olanzapine were similar in patients with
210 severe renal impairment and normal subjects, indicating that dosage adjustment based upon the
211 degree of renal impairment is not required. In addition, olanzapine is not removed by dialysis.
212 The effect of renal impairment on olanzapine metabolite elimination has not been studied.

213 In depressed patients on dialysis (N=12), fluoxetine administered as 20 mg once daily for 2
214 months produced steady-state fluoxetine and norfluoxetine plasma concentrations comparable
215 with those seen in patients with normal renal function. While the possibility exists that renally
216 excreted metabolites of fluoxetine may accumulate to higher levels in patients with severe renal
217 dysfunction, use of a lower or less frequent dose is not routinely necessary in renally impaired
218 patients.

219 **Hepatic Impairment** — Based on the individual pharmacokinetic profiles of olanzapine and
220 fluoxetine, the pharmacokinetics of SYMBYAX may be altered in patients with hepatic
221 impairment. The lowest starting dose should be considered for patients with hepatic impairment
222 (*see* PRECAUTIONS, Use in Patients with Concomitant Illness *and* DOSAGE AND
223 ADMINISTRATION, Special Populations).

224 Although the presence of hepatic impairment may be expected to reduce the clearance of
225 olanzapine, a study of the effect of impaired liver function in subjects (N=6) with clinically
226 significant cirrhosis (Childs-Pugh Classification A and B) revealed little effect on the
227 pharmacokinetics of olanzapine.

228 As might be predicted from its primary site of metabolism, liver impairment can affect the
229 elimination of fluoxetine. The elimination half-life of fluoxetine was prolonged in a study of
230 cirrhotic patients, with a mean of 7.6 days compared with the range of 2 to 3 days seen in
231 subjects without liver disease; norfluoxetine elimination was also delayed, with a mean duration
232 of 12 days for cirrhotic patients compared with the range of 7 to 9 days in normal subjects.

233 **Gender** — Clearance of olanzapine is approximately 30% lower in women than in men. There
234 were, however, no apparent differences between men and women in effectiveness or adverse
235 effects. Dosage modifications based on gender should not be needed.

236 **Smoking Status** — Olanzapine clearance is about 40% higher in smokers than in nonsmokers,
237 although dosage modifications are not routinely required.

238 **Race** — No SYMBYAX pharmacokinetic study was conducted to investigate the effects of
239 race. In vivo studies have shown that exposures to olanzapine are similar among Japanese,
240 Chinese and Caucasians, especially after normalization for body weight differences. Dosage
241 modifications for race, therefore, are not routinely required.

242 **Combined Effects** — The combined effects of age, smoking, and gender could lead to
243 substantial pharmacokinetic differences in populations. The clearance of olanzapine in young
244 smoking males, for example, may be 3 times higher than that in elderly nonsmoking females.
245 SYMBYAX dosing modification may be necessary in patients who exhibit a combination of
246 factors that may result in slower metabolism of the olanzapine component (*see* DOSAGE AND
247 ADMINISTRATION, Special Populations).

248 **CLINICAL STUDIES**

249 The efficacy of SYMBYAX for the treatment of depressive episodes associated with bipolar
250 disorder was established in 2 identically designed, 8-week, randomized, double-blind, controlled
251 studies of patients who met Diagnostic and Statistical Manual 4th edition (DSM-IV) criteria for
252 Bipolar I Disorder, Depressed utilizing flexible dosing of SYMBYAX (6/25, 6/50, or

253 12/50 mg/day), olanzapine (5 to 20 mg/day), and placebo. These studies included patients (≥ 18
 254 years of age) with or without psychotic symptoms and with or without a rapid cycling course.

255 The primary rating instrument used to assess depressive symptoms in these studies was the
 256 Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale with
 257 total scores ranging from 0 to 60. The primary outcome measure of these studies was the change
 258 from baseline to endpoint in the MADRS total score. In both studies, SYMBYAX was
 259 statistically significantly superior to both olanzapine monotherapy and placebo in reduction of
 260 the MADRS total score. The results of the studies are summarized below (Table 1).

261
 262 **Table 1: MADRS Total Score**
 263 **Mean Change from Baseline to Endpoint**

	Treatment Group	Baseline Mean	Change to Endpoint Mean¹
Study 1	SYMBYAX (N=40)	30	-16 ^a
	Olanzapine (N=182)	32	-12
	Placebo (N=181)	31	-10
Study 2	SYMBYAX (N=42)	32	-18 ^a
	Olanzapine (N=169)	33	-14
	Placebo (N=174)	31	-9

264 ¹ Negative number denotes improvement from baseline.

265 ^a Statistically significant compared to both olanzapine and placebo.

266 **INDICATIONS AND USAGE**

267 SYMBYAX is indicated for the treatment of depressive episodes associated with bipolar
 268 disorder. The efficacy of SYMBYAX was established in 2 identically designed, 8-week,
 269 randomized, double-blind clinical studies.

270 Unlike with unipolar depression, there are no established guidelines for the length of time
 271 patients with bipolar disorder experiencing a major depressive episode should be treated with
 272 agents containing antidepressant drugs.

273 The effectiveness of SYMBYAX for maintaining antidepressant response in this patient
 274 population beyond 8 weeks has not been established in controlled clinical studies. Physicians
 275 who elect to use SYMBYAX for extended periods should periodically reevaluate the benefits
 276 and long-term risks of the drug for the individual patient.

277 **CONTRAINDICATIONS**

278 **Hypersensitivity** — SYMBYAX is contraindicated in patients with a known hypersensitivity
 279 to the product or any component of the product.

280 **Monoamine Oxidase Inhibitors (MAOI)** — There have been reports of serious, sometimes
 281 fatal reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible
 282 rapid fluctuations of vital signs, and mental status changes that include extreme agitation
 283 progressing to delirium and coma) in patients receiving fluoxetine in combination with an
 284 MAOI, and in patients who have recently discontinued fluoxetine and are then started on an
 285 MAOI. Some cases presented with features resembling neuroleptic malignant syndrome.

286 Therefore, SYMBYAX should not be used in combination with an MAOI, or within a minimum
 287 of 14 days of discontinuing therapy with an MAOI. Since fluoxetine and its major metabolite
 288 have very long elimination half-lives, at least 5 weeks [perhaps longer, especially if fluoxetine
 289 has been prescribed chronically and/or at higher doses (*see* CLINICAL PHARMACOLOGY,
 290 Accumulation and slow elimination)] should be allowed after stopping SYMBYAX before
 291 starting an MAOI.

292 **Pimozide** — Concomitant use in patients taking pimozide is contraindicated (*see*
 293 PRECAUTIONS).

294 **Thioridazine** — Thioridazine should not be administered with SYMBYAX or administered
 295 within a minimum of 5 weeks after discontinuation of SYMBYAX (*see* WARNINGS,
 296 Thioridazine).

297 WARNINGS

298 **Clinical Worsening and Suicide Risk** — Patients with major depressive disorder (MDD),
 299 both adult and pediatric, may experience worsening of their depression and/or the emergence of
 300 suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they
 301 are taking antidepressant medications, and this risk may persist until significant remission
 302 occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these
 303 disorders themselves are the strongest predictors of suicide. There has been a long-standing
 304 concern, however, that antidepressants may have a role in inducing worsening of depression and
 305 the emergence of suicidality in certain patients during the early phases of treatment. Pooled
 306 analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others)
 307 showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in
 308 children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and
 309 other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality
 310 with antidepressants compared to placebo in adults beyond age 24; there was a reduction with
 311 antidepressants compared to placebo in adults aged 65 and older.

312 The pooled analyses of placebo-controlled trials in children and adolescents with MDD,
 313 obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24
 314 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-
 315 controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-
 316 term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients.
 317 There was considerable variation in risk of suicidality among drugs, but a tendency toward an
 318 increase in the younger patients for almost all drugs studied. There were differences in absolute
 319 risk of suicidality across the different indications, with the highest incidence in MDD. The risk
 320 differences (drug versus placebo), however, were relatively stable within age strata and across
 321 indications. These risk differences (drug-placebo difference in the number of cases of suicidality
 322 per 1000 patients treated) are provided in Table 2.

323
 324 **Table 2**

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo

25-64	1 fewer case
≥65	6 fewer cases

325
326 No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but
327 the number was not sufficient to reach any conclusion about drug effect on suicide.

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

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

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

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

347 If the decision has been made to discontinue treatment, medication should be tapered, as
348 rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with
349 certain symptoms (*see* PRECAUTIONS and DOSAGE AND ADMINISTRATION,
350 Discontinuation of Treatment with SYMBYAX, for a description of the risks of discontinuation
351 of SYMBYAX).

352 **Families and caregivers of patients being treated with antidepressants for major**
353 **depressive disorder or other indications, both psychiatric and nonpsychiatric, should be**
354 **alerted about the need to monitor patients for the emergence of agitation, irritability,**
355 **unusual changes in behavior, and the other symptoms described above, as well as the**
356 **emergence of suicidality, and to report such symptoms immediately to health care**
357 **providers. Such monitoring should include daily observation by families and caregivers.**
358 Prescriptions for SYMBYAX should be written for the smallest quantity of capsules consistent
359 with good patient management, in order to reduce the risk of overdose.

360 It should be noted that SYMBYAX is not approved for use in treating any indications in the
361 pediatric population.

362 **Screening Patients for Bipolar Disorder** — A major depressive episode may be the initial
363 presentation of bipolar disorder. It is generally believed (though not established in controlled
364 trials) that treating such an episode with an antidepressant alone may increase the likelihood of
365 precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the
366 symptoms described above represent such a conversion is unknown. However, prior to initiating
367 treatment with an antidepressant, patients with depressive symptoms should be adequately
368 screened to determine if they are at risk for bipolar disorder; such screening should include a

369 detailed psychiatric history, including a family history of suicide, bipolar disorder, and
370 depression. It should be noted that SYMBYAX is approved for use in treating bipolar
371 depression.

372 **Increased Mortality in Elderly Patients with Dementia-Related Psychosis — Elderly**
373 **patients with dementia-related psychosis treated with atypical antipsychotic drugs are at**
374 **an increased risk of death compared to placebo. SYMBYAX (olanzapine and**
375 **fluoxetine HCl) is not approved for the treatment of patients with dementia-related**
376 **psychosis (see BOX WARNING).**

377 In olanzapine placebo-controlled clinical trials of elderly patients with dementia-related
378 psychosis, the incidence of death in olanzapine-treated patients was significantly greater than
379 placebo-treated patients (3.5% vs 1.5%, respectively).

380 **Cerebrovascular Adverse Events (CVAE), Including Stroke, in Elderly Patients with**
381 **Dementia-Related Psychosis** — Cerebrovascular adverse events (e.g., stroke, transient ischemic
382 attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients
383 with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher
384 incidence of cerebrovascular adverse events in patients treated with olanzapine compared to
385 patients treated with placebo. Olanzapine is not approved for the treatment of patients with
386 dementia-related psychosis.

387 **Hyperglycemia** — Hyperglycemia, in some cases extreme and associated with ketoacidosis or
388 hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics,
389 including olanzapine alone, as well as olanzapine taken concomitantly with fluoxetine.

390 Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is
391 complicated by the possibility of an increased background risk of diabetes mellitus in patients
392 with schizophrenia and the increasing incidence of diabetes mellitus in the general population.
393 Given these confounders, the relationship between atypical antipsychotic use and
394 hyperglycemia-related adverse events is not completely understood. However, epidemiological
395 studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in
396 patients treated with the atypical antipsychotics. While relative risk estimates are inconsistent,
397 the association between atypical antipsychotics and increases in glucose levels appears to fall on
398 a continuum and olanzapine appears to have a greater association than some other atypical
399 antipsychotics.

400 Mean increases in blood glucose have been observed in patients treated (median exposure of
401 9.2 months) with olanzapine in phase 1 of the Clinical Antipsychotic Trials of Intervention
402 Effectiveness (CATIE). The mean increase of serum glucose (fasting and nonfasting samples)
403 from baseline to the average of the two highest serum concentrations was 15.0 mg/dL.

404 In an analysis of 7 controlled clinical studies, 2 of which were placebo-controlled, with
405 treatment duration up to 12 weeks, SYMBYAX was associated with a statistically significantly
406 greater mean change in random glucose compared to placebo (8.65 mg/dL versus -3.86 mg/dL).
407 In patients with baseline normal random glucose levels (<140 mg/dL), 2.3% of those treated with
408 SYMBYAX were found to have high glucose levels (≥ 200 mg/dL) during SYMBYAX treatment
409 and were statistically significantly different compared to 0.3% of those treated with placebo. In
410 patients with baseline borderline random glucose levels (≥ 140 mg/dL and <200 mg/dL), 34.1%
411 of those treated with SYMBYAX were found to have high glucose levels (≥ 200 mg/dL) during
412 SYMBYAX treatment and were statistically significantly different compared to 3.6% of those
413 treated with placebo. The difference in mean changes between SYMBYAX and placebo was
414 greater in patients with evidence of glucose dysregulation at baseline (including those patients

415 diagnosed with diabetes mellitus or related adverse events, patients treated with anti-diabetic
416 agents, patients with a baseline random glucose level ≥ 200 mg/dL, or a baseline fasting glucose
417 level ≥ 126 mg/dL). These patients had a greater mean increase in HbA_{1c}.

418 Controlled fasting glucose data is limited for SYMBYAX; however, in an analysis of 5
419 placebo-controlled olanzapine monotherapy studies with treatment duration up to 12 weeks,
420 olanzapine was associated with a greater mean change in fasting glucose levels compared to
421 placebo (2.76 mg/dL vs 0.17 mg/dL).

422 *Olanzapine Monotherapy in Adolescents* — The safety and efficacy of olanzapine and
423 olanzapine and fluoxetine in combination have not been established in patients under the age of
424 18 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent
425 patients, including those with schizophrenia (6 weeks) or bipolar disorder (manic or mixed
426 episodes) (3 weeks), olanzapine was associated with a statistically significantly greater mean
427 change in fasting glucose levels compared to placebo (2.68 mg/dL versus -2.59 mg/dL). In
428 patients with baseline normal fasting glucose levels (< 100 mg/dL), zero out of 124 (0%) of those
429 treated with olanzapine were found to have high glucose levels (≥ 126 mg/dL) during olanzapine
430 treatment versus 1 out of 53 (1.9%) of those treated with placebo. In patients with baseline
431 borderline fasting glucose levels (≥ 100 mg/dL and < 126 mg/dL), 2 out of 14 (14.3%) of those
432 treated with olanzapine were found to have high glucose levels (≥ 126 mg/dL) during olanzapine
433 treatment versus zero out of 13 (0%) of those treated with placebo.

434 Physicians should consider the risks and benefits when prescribing SYMBYAX to patients
435 with an established diagnosis of diabetes mellitus, or having borderline increased blood glucose
436 level (fasting 100-126 mg/dL, nonfasting 140-200 mg/dL). Patients taking SYMBYAX should
437 be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes
438 mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical
439 antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and
440 periodically during treatment. Any patient treated with atypical antipsychotics should be
441 monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and
442 weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical
443 antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has
444 resolved when the atypical antipsychotic was discontinued; however, some patients required
445 continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

446 **Hyperlipidemia** — Undesirable alterations in lipids have been observed with SYMBYAX use.
447 Clinical monitoring, including baseline and follow-up lipid evaluations in patients using
448 SYMBYAX, is advised.

449 Significant, and sometimes very high (> 500 mg/dL), elevations in triglyceride levels have been
450 observed with SYMBYAX use. Significant increases in total cholesterol have also been seen
451 with SYMBYAX use.

452 Controlled fasting lipid data is limited for SYMBYAX.

453 In an analysis of 7 controlled clinical studies, 2 of which were placebo-controlled, with
454 treatment duration up to 12 weeks, SYMBYAX-treated patients had an increase from baseline in
455 mean random total cholesterol of 12.1 mg/dL compared to a statistically significantly different
456 increase from baseline in mean random total cholesterol of 4.8 mg/dL for olanzapine-treated
457 patients and a decrease in mean random total cholesterol of 5.5 mg/dL for placebo-treated
458 patients. Table 3 shows categorical changes in nonfasting lipid values.

459
460
461**Table 3: Changes in Nonfasting Lipids Values from Controlled Clinical Studies with Treatment Duration up to 12 Weeks**

Laboratory Analyte	Category Change from Baseline	Treatment Arm	N	Patients
Nonfasting Triglycerides	Increase by ≥ 50 mg/dL	OFC	174	67.8%
		Olanzapine	172	72.7%
	Normal to High (<150 mg/dL to ≥ 500 mg/dL)	OFC	57	0%
		Olanzapine	58	0%
	Borderline to High (≥ 150 mg/dL and <500 mg/dL to ≥ 500 mg/dL)	OFC	106	15.1%
		Olanzapine	103	8.7%
Nonfasting Total Cholesterol	Increase by ≥ 40 mg/dL	OFC	685	35% ^{a,b}
		Olanzapine	749	22.7%
		Placebo	390	9%
	Normal to High (<200 mg/dL to ≥ 240 mg/dL)	OFC	256	8.2% ^{a,b}
		Olanzapine	279	2.9%
		Placebo	175	1.7%
	Borderline to High (≥ 200 mg/dL and <240 mg/dL to ≥ 240 mg/dL)	OFC	213	36.2% ^{a,b}
		Olanzapine	261	27.6%
		Placebo	111	9.9%

462 ^a Statistically significant compared to olanzapine.463 ^b Statistically significant compared to placebo.

464

465 Controlled fasting lipid data is limited for SYMBYAX; however, in an analysis of 5
466 placebo-controlled olanzapine monotherapy studies with treatment duration up to 12 weeks,
467 olanzapine-treated patients had statistically significant increases from baseline in mean fasting
468 total cholesterol, LDL cholesterol, and triglycerides of 5.3 mg/dL, 3.0 mg/dL, and 20.8 mg/dL
469 respectively compared to decreases from baseline in mean fasting total cholesterol, LDL
470 cholesterol, and triglycerides of 6.1 mg/dL, 4.3 mg/dL, and 10.7 mg/dL for placebo-treated
471 patients. For fasting HDL cholesterol, no statistically significant differences were observed
472 between olanzapine-treated patients and placebo-treated patients. Mean increases in fasting lipid
473 values (total cholesterol, LDL cholesterol, and triglycerides) were greater in patients without
474 evidence of lipid dysregulation at baseline, where lipid dysregulation was defined as patients
475 diagnosed with dyslipidemia or related adverse events, patients treated with lipid lowering
476 agents, patients with high baseline lipid levels. Table 4 shows categorical changes in fasting lipid
477 values.

478

Table 4: Changes in Fasting Lipids Values from Adult Placebo-Controlled Olanzapine Monotherapy Studies with Treatment Duration up to 12 Weeks

479

480

Laboratory Analyte	Category Change from Baseline	Treatment Arm	N	Patients
Fasting Triglycerides	Increase by ≥ 50 mg/dL	Olanzapine	745	39.6% ^a
		Placebo	402	26.1%
	Normal to High	Olanzapine	457	9.2% ^a

	(<150 mg/dL to \geq 200 mg/dL)	Placebo	251	4.4%
	Borderline to High (\geq 150 mg/dL and <200 mg/dL to \geq 200 mg/dL)	Olanzapine	135	39.3% ^a
		Placebo	65	20.0%
Fasting Total Cholesterol	Increase by \geq 40 mg/dL	Olanzapine	745	21.6% ^a
		Placebo	402	9.5%
	Normal to High (<200 mg/dL to \geq 240 mg/dL)	Olanzapine	392	2.8%
		Placebo	207	2.4%
	Borderline to High (\geq 200 mg/dL and <240 mg/dL to \geq 240 mg/dL)	Olanzapine	222	23.0% ^a
		Placebo	112	12.5%
Fasting LDL Cholesterol	Increase by \geq 30 mg/dL	Olanzapine	536	23.7% ^a
		Placebo	304	14.1%
	Normal to High (<100 mg/dL to \geq 160 mg/dL)	Olanzapine	154	0%
		Placebo	82	1.2%
	Borderline to High (\geq 100 mg/dL and <160 mg/dL to \geq 160 mg/dL)	Olanzapine	302	10.6%
		Placebo	173	8.1%

^a Statistically significant compared to placebo.

481
482
483
484
485
486
487
488
489
490
491
492
493
494
495

In phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), over a median exposure of 9.2 months, the mean increase in triglycerides in patients taking olanzapine was 40.5 mg/dL. In phase 1 of CATIE, the median increase in total cholesterol was 9.4 mg/dL.

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine and olanzapine and fluoxetine in combination have not been established in patients under the age of 18 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, including those with schizophrenia (6 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), for fasting HDL cholesterol, no statistically significant differences were observed between olanzapine-treated patients and placebo-treated patients. Table 5 shows categorical changes in fasting lipid values in adolescent patients.

Table 5: Changes in Fasting Lipids Values from Adolescent Placebo-Controlled Olanzapine Monotherapy Studies

Laboratory Analyte	Category Change from Baseline	Treatment Arm	N	Patients
Fasting Triglycerides	Increase by \geq 50 mg/dL	Olanzapine	138	37% ^a
		Placebo	66	15.2%
	Normal to High (<90 mg/dL to \geq 130 mg/dL)	Olanzapine	67	26.9%
		Placebo	28	10.7%
	Borderline to High (\geq 90 mg/dL and <130 mg/dL to \geq 130 mg/dL)	Olanzapine	37	59.5%
		Placebo	17	35.3%

Fasting Total Cholesterol	Increase by ≥ 40 mg/dL	Olanzapine	138	14.5% ^a
		Placebo	66	4.5%
	Normal to High (< 170 mg/dL to ≥ 200 mg/dL)	Olanzapine	87	6.9%
		Placebo	43	2.3%
	Borderline to High (≥ 170 mg/dL and < 200 mg/dL to ≥ 200 mg/dL)	Olanzapine	36	38.9% ^a
		Placebo	13	7.7%
Fasting LDL Cholesterol	Increase by ≥ 30 mg/dL	Olanzapine	137	17.5%
		Placebo	63	11.1%
	Normal to High (< 110 mg/dL to ≥ 130 mg/dL)	Olanzapine	98	5.1%
		Placebo	44	4.5%
	Borderline to High (≥ 110 mg/dL and < 130 mg/dL to ≥ 130 mg/dL)	Olanzapine	29	48.3% ^a
		Placebo	9	0%

^a Statistically significant compared to placebo.

496
497
498
499
500
501
502
503
504
505
506
507
508
509
510
511
512
513
514

Weight Gain — Potential consequences of weight gain should be considered prior to starting SYMBYAX. Patients receiving SYMBYAX should receive regular monitoring of weight.

In an analysis of 7 controlled clinical studies, 2 of which were placebo-controlled, the mean weight increase for SYMBYAX-treated patients was statistically significantly greater than placebo-treated patients (4 kg vs -0.3 kg). Twenty-two percent of SYMBYAX-treated patients gained at least 7% of their baseline weight, with a median exposure of 6 weeks. This was statistically significantly greater than in placebo-treated patients (1.8%). Approximately three percent of SYMBYAX-treated patients gained at least 15% of their baseline weight, with a median exposure of 8 weeks. This was statistically significantly greater than in placebo-treated patients (0%). Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories. Discontinuation due to weight gain occurred in 2.5% of SYMBYAX-treated patients and zero placebo-treated patients.

Table 6 includes data on weight gain with olanzapine pooled from 68 clinical trials. The data in each column represent data for those patients who completed treatment periods of the durations specified.

Table 6: Weight Gain with Olanzapine Use

Amount Gained kg (lb)	6 Weeks (N=2976) (%)	6 Months (N=1536) (%)	12 Months (N=778) (%)	24 Months (N=422) (%)
≤ 0	27	21	20	22
0-5 (0-11 lb)	57	34	25	22
5-10 (11-22 lb)	15	26	25	22
10-15 (22-33 lb)	2	12	16	18
> 15 (> 33 lb)	0	6	14	16

515

516 During long-term continuation therapy with olanzapine monotherapy (238 median days of
517 exposure), 56% of olanzapine patients met the criterion for having gained greater than 7% of
518 their baseline weight. Average weight gain during long-term therapy was 5.4 kg.

519 *Olanzapine Monotherapy in Adolescents* — The safety and efficacy of olanzapine and
520 olanzapine and fluoxetine in combination have not been established in patients under the age of
521 18 years. In an analysis of 4 placebo-controlled olanzapine monotherapy studies of adolescent
522 patients (ages 13 to 17 years), including those with schizophrenia (6 weeks) or bipolar disorder
523 (manic or mixed episodes) (3 weeks), olanzapine-treated patients gained an average of 4.6 kg,
524 which was statistically significantly different compared to an average of 0.3 kg in
525 placebo-treated patients, with a median exposure of 3 weeks; 40.6% of olanzapine-treated
526 patients gained at least 7% of their baseline body weight, which was statistically significantly
527 different compared to 9.8% of placebo-treated patients, with a median exposure of 4 weeks;
528 7.1% of olanzapine-treated patients gained at least 15% of their baseline weight, compared to
529 2.7% of placebo-treated patients, with a median exposure of 19 weeks. Clinically significant
530 weight gain was observed across all baseline Body Mass Index (BMI) categories, but mean
531 changes in weight were greater in adolescents with BMI categories above normal at baseline.
532 Discontinuation due to weight gain occurred in 1% of olanzapine-treated patients, compared to
533 zero placebo-treated patients.

534 During long-term continuation therapy with olanzapine, 65% of olanzapine-treated patients
535 met the criterion for having gained greater than 7% of their baseline weight. Average weight gain
536 during long-term therapy was 7.4 kg.

537 **Orthostatic Hypotension** — SYMBYAX may induce orthostatic hypotension associated with
538 dizziness, tachycardia, bradycardia, and in some patients, syncope, especially during the initial
539 dose-titration period.

540 In the bipolar depression studies, statistically significantly more orthostatic changes occurred
541 with the SYMBYAX group compared to placebo and olanzapine groups. Orthostatic systolic
542 blood pressure decrease of at least 30 mm Hg occurred in 7.3% (6/82), 1.4% (5/346), and 1.4%
543 (5/352) of the SYMBYAX, olanzapine and placebo groups, respectively. Among the group of
544 controlled clinical studies with SYMBYAX, an orthostatic systolic blood pressure decrease of
545 ≥ 30 mm Hg occurred in 4% (21/512) of SYMBYAX-treated patients, 5% (10/204) of
546 fluoxetine-treated patients, 2% (16/644) of olanzapine-treated patients, and 2% (8/445) of
547 placebo-treated patients. In this group of studies, the incidence of syncope in SYMBYAX-treated
548 patients was 0.4% (2/571) compared to placebo 0.2% (1/477).

549 In a clinical pharmacology study of SYMBYAX, three healthy subjects were discontinued
550 from the trial after experiencing severe, but self-limited, hypotension and bradycardia that
551 occurred 2 to 9 hours following a single 12-mg/50-mg dose of SYMBYAX. Reactions consisting
552 of this combination of hypotension and bradycardia (and also accompanied by sinus pause) have
553 been observed in at least three other healthy subjects treated with various formulations of
554 olanzapine (one oral, two intramuscular). In controlled clinical studies, the incidence of patients
555 with a ≥ 20 bpm decrease in orthostatic pulse concomitantly with a ≥ 20 mm Hg decrease in
556 orthostatic systolic blood pressure was 0.4% (2/549) in the SYMBYAX group, 0.2% (1/455) in
557 the placebo group, 0.8% (5/659) in the olanzapine group, and 0% (0/241) in the fluoxetine group.

558 SYMBYAX should be used with particular caution in patients with known cardiovascular
559 disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities),
560 cerebrovascular disease, or conditions that would predispose patients to hypotension
561 (dehydration, hypovolemia, and treatment with antihypertensive medications).

562 **Allergic Events and Rash** — In SYMBYAX premarketing controlled clinical studies, the
563 overall incidence of rash or allergic events in SYMBYAX-treated patients [4.6% (26/571)] was
564 similar to that of placebo [5.2% (25/477)]. The majority of the cases of rash and/or urticaria were
565 mild; however, three patients discontinued (one due to rash, which was moderate in severity, and
566 two due to allergic events, one of which included face edema).

567 In fluoxetine US clinical studies, 7% of 10,782 fluoxetine-treated patients developed various
568 types of rashes and/or urticaria. Among the cases of rash and/or urticaria reported in
569 premarketing clinical studies, almost a third were withdrawn from treatment because of the rash
570 and/or systemic signs or symptoms associated with the rash. Clinical findings reported in
571 association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome,
572 respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most
573 patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with
574 antihistamines or steroids, and all patients experiencing these events were reported to recover
575 completely.

576 In fluoxetine premarketing clinical studies, 2 patients are known to have developed a serious
577 cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but 1 was
578 considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome
579 that was considered variously to be a vasculitis or erythema multiforme. Other patients have had
580 systemic syndromes suggestive of serum sickness.

581 Since the introduction of fluoxetine, systemic events, possibly related to vasculitis, have
582 developed in patients with rash. Although these events are rare, they may be serious, involving
583 the lung, kidney, or liver. Death has been reported to occur in association with these systemic
584 events.

585 Anaphylactoid events, including bronchospasm, angioedema, and urticaria alone and in
586 combination, have been reported.

587 Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis,
588 have been reported rarely. These events have occurred with dyspnea as the only preceding
589 symptom.

590 Whether these systemic events and rash have a common underlying cause or are due to
591 different etiologies or pathogenic processes is not known. Furthermore, a specific underlying
592 immunologic basis for these events has not been identified. Upon the appearance of rash or of
593 other possible allergic phenomena for which an alternative etiology cannot be identified,
594 SYMBYAX should be discontinued.

595 **Serotonin Syndrome** — The development of a potentially life-threatening serotonin syndrome
596 may occur with SNRIs and SSRIs, including SYMBYAX treatment, particularly with
597 concomitant use of serotonergic drugs (including triptans) and with drugs which impair
598 metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental
599 status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia,
600 labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia,
601 incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

602 The concomitant use of SYMBYAX with MAOIs intended to treat depression is
603 contraindicated (*see* CONTRAINDICATIONS, Monoamine Oxidase Inhibitors (MAOI) *and*
604 PRECAUTIONS, Drug Interactions).

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

608 The concomitant use of SYMBYAX with serotonin precursors (such as tryptophan) is not
609 recommended (*see* PRECAUTIONS, Drug Interactions).

610 **Neuroleptic Malignant Syndrome (NMS)** — A potentially fatal symptom complex
611 sometimes referred to as NMS has been reported in association with administration of
612 antipsychotic drugs, including olanzapine. Clinical manifestations of NMS are hyperpyrexia,
613 muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or
614 blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include
615 elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

616 The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a
617 diagnosis, it is important to exclude cases where the clinical presentation includes both serious
618 medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated
619 extrapyramidal signs and symptoms (EPS). Other important considerations in the differential
620 diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central
621 nervous system pathology.

622 The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs
623 and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and
624 medical monitoring, and 3) treatment of any concomitant serious medical problems for which
625 specific treatments are available. There is no general agreement about specific pharmacological
626 treatment regimens for NMS.

627 If after recovering from NMS, a patient requires treatment with an antipsychotic, the patient
628 should be carefully monitored, since recurrences of NMS have been reported.

629 **Tardive Dyskinesia** — A syndrome of potentially irreversible, involuntary, dyskinetic
630 movements may develop in patients treated with antipsychotic drugs. Although the prevalence of
631 the syndrome appears to be highest among the elderly, especially elderly women, it is impossible
632 to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which
633 patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their
634 potential to cause tardive dyskinesia is unknown.

635 The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are
636 believed to increase as the duration of treatment and the total cumulative dose of antipsychotic
637 drugs administered to the patient increase. However, the syndrome can develop, although much
638 less commonly, after relatively brief treatment periods at low doses or may even arise after
639 discontinuation of treatment.

640 There is no known treatment for established cases of tardive dyskinesia, although the syndrome
641 may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic
642 treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the
643 syndrome and thereby may possibly mask the underlying process. The effect that symptomatic
644 suppression has upon the long-term course of the syndrome is unknown.

645 The incidence of dyskinetic movement in SYMBYAX-treated patients was infrequent. The
646 mean score on the Abnormal Involuntary Movement Scale (AIMS) across clinical studies
647 involving SYMBYAX-treated patients decreased from baseline. Nonetheless, SYMBYAX
648 should be prescribed in a manner that is most likely to minimize the risk of tardive dyskinesia. If
649 signs and symptoms of tardive dyskinesia appear in a patient on SYMBYAX, drug
650 discontinuation should be considered. However, some patients may require treatment with
651 SYMBYAX despite the presence of the syndrome. The need for continued treatment should be
652 reassessed periodically.

653 **Thioridazine** — In a study of 19 healthy male subjects, which included 6 slow and 13 rapid
 654 hydroxylators of debrisoquin, a single 25-mg oral dose of thioridazine produced a 2.4-fold higher
 655 C_{max} and a 4.5-fold higher AUC for thioridazine in the slow hydroxylators compared with the
 656 rapid hydroxylators. The rate of debrisoquin hydroxylation is felt to depend on the level of
 657 CYP2D6 isozyme activity. Thus, this study suggests that drugs that inhibit CYP2D6, such as
 658 certain SSRIs, including fluoxetine, will produce elevated plasma levels of thioridazine (*see*
 659 PRECAUTIONS).

660 Thioridazine administration produces a dose-related prolongation of the QT_c interval, which is
 661 associated with serious ventricular arrhythmias, such as torsades de pointes-type arrhythmias and
 662 sudden death. This risk is expected to increase with fluoxetine-induced inhibition of thioridazine
 663 metabolism (*see* CONTRAINDICATIONS, Thioridazine).

664

PRECAUTIONS

665 General

666 **Concomitant Use of Olanzapine and Fluoxetine Products** — SYMBYAX contains the same
 667 active ingredients that are in Zyprexa and Zyprexa Zydis (olanzapine) and in Prozac, Prozac
 668 Weekly, and Sarafem (fluoxetine HCl). Caution should be exercised when prescribing these
 669 medications concomitantly with SYMBYAX.

670 **Abnormal Bleeding** — SSRIs and SNRIs, including fluoxetine, may increase the risk of
 671 bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and
 672 other anti-coagulants may add to this risk. Case reports and epidemiological studies (case-control
 673 and cohort design) have demonstrated an association between use of drugs that interfere with
 674 serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to
 675 SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to
 676 life-threatening hemorrhages.

677 Patients should be cautioned about the risk of bleeding associated with the concomitant use of
 678 SYMBYAX and NSAIDs, aspirin, or other drugs that affect coagulation (*see* DRUG
 679 INTERACTIONS).

680 **Mania/Hypomania** — In the two controlled bipolar depression studies there was no
 681 statistically significant difference in the incidence of manic events (manic reaction or manic
 682 depressive reaction) between SYMBYAX- and placebo-treated patients. In one of the studies, the
 683 incidence of manic events was (7% [3/43]) in SYMBYAX-treated patients compared to (3%
 684 [5/184]) in placebo-treated patients. In the other study, the incidence of manic events was (2%
 685 [1/43]) in SYMBYAX-treated patients compared to (8% [15/193]) in placebo-treated patients.
 686 This limited controlled trial experience of SYMBYAX in the treatment of bipolar depression
 687 makes it difficult to interpret these findings until additional data is obtained. Because of this and
 688 the cyclical nature of bipolar disorder, patients should be monitored closely for the development
 689 of symptoms of mania/hypomania during treatment with SYMBYAX.

690 **Body Temperature Regulation** — Disruption of the body's ability to reduce core body
 691 temperature has been attributed to antipsychotic drugs. Appropriate care is advised when
 692 prescribing SYMBYAX for patients who will be experiencing conditions which may contribute
 693 to an elevation in core body temperature (e.g., exercising strenuously, exposure to extreme heat,
 694 receiving concomitant medication with anticholinergic activity, or being subject to dehydration).

695 **Cognitive and Motor Impairment** — Somnolence was a commonly reported adverse event
 696 associated with SYMBYAX treatment, occurring at an incidence of 22% in SYMBYAX patients
 697 compared with 11% in placebo patients. Somnolence led to discontinuation in 2% (10/571) of
 698 patients in the premarketing controlled clinical studies.

Formatted: Not Highlight

Formatted: Not Highlight

699 As with any CNS-active drug, SYMBYAX has the potential to impair judgment, thinking, or
 700 motor skills. Patients should be cautioned about operating hazardous machinery, including
 701 automobiles, until they are reasonably certain that SYMBYAX therapy does not affect them
 702 adversely.

703 **Discontinuation of Treatment with SYMBYAX**

704 During marketing of fluoxetine, a component of SYMBYAX, and other SSRIs and SNRIs
 705 (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of
 706 adverse events occurring upon discontinuation of these drugs, particularly when abrupt,
 707 including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances
 708 (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy,
 709 emotional lability, insomnia, and hypomania. While these events are generally self-limiting,
 710 there have been reports of serious discontinuation symptoms. Patients should be monitored for
 711 these symptoms when discontinuing treatment with fluoxetine. A gradual reduction in the dose
 712 rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur
 713 following a decrease in the dose or upon discontinuation of treatment, then resuming the
 714 previously prescribed dose may be considered. Subsequently, the physician may continue
 715 decreasing the dose but at a more gradual rate. Plasma fluoxetine and norfluoxetine
 716 concentration decrease gradually at the conclusion of therapy, which may minimize the risk of
 717 discontinuation symptoms with this drug (*see* DOSAGE AND ADMINISTRATION).

718 **Dysphagia** — Esophageal dysmotility and aspiration have been associated with antipsychotic
 719 drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with
 720 advanced Alzheimer's disease. Olanzapine and other antipsychotic drugs should be used
 721 cautiously in patients at risk for aspiration pneumonia.

722 **Half-Life** — Because of the long elimination half-lives of fluoxetine and its major active
 723 metabolite, changes in dose will not be fully reflected in plasma for several weeks, affecting both
 724 strategies for titration to final dose and withdrawal from treatment (*see* CLINICAL
 725 PHARMACOLOGY, Accumulation and slow elimination).

726 **Hyperprolactinemia** — As with other drugs that antagonize dopamine D₂ receptors,
 727 SYMBYAX elevates prolactin levels, and a modest elevation persists during administration;
 728 however, possibly associated clinical manifestations (e.g., galactorrhea and breast enlargement)
 729 were infrequently observed.

730 Tissue culture experiments indicate that approximately one-third of human breast cancers are
 731 prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is
 732 contemplated in a patient with previously detected breast cancer of this type. Although
 733 disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported
 734 with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels
 735 is unknown for most patients. As is common with compounds that increase prolactin release, an
 736 increase in mammary gland neoplasia was observed in the olanzapine carcinogenicity studies
 737 conducted in mice and rats (*see* Carcinogenesis). However, neither clinical studies nor
 738 epidemiologic studies have shown an association between chronic administration of this class of
 739 drugs and tumorigenesis in humans; the available evidence is considered too limited to be
 740 conclusive.

741 **Hyponatremia** — Hyponatremia may occur as a result of treatment with SSRIs and SNRIs,
 742 including SYMBYAX. In many cases, this hyponatremia appears to be the result of the
 743 syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium
 744 lower than 110 mmol/L have been reported and appeared to be reversible when SYMBYAX was

Formatted: Not Highlight

Formatted: No underline, Font
color: Auto, Not Highlight

Formatted: No underline, Font
color: Auto, Not Highlight

Formatted: Not Highlight

745 discontinued. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and
746 SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater
747 risk (*see* Geriatric Use). Discontinuation of SYMBYAX should be considered in patients with
748 symptomatic hyponatremia and appropriate medical intervention should be instituted.

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

753 **Seizures** — Seizures occurred in 0.2% (4/2066) of SYMBYAX-treated patients during
754 open-label premarketing clinical studies. No seizures occurred in the premarketing controlled
755 SYMBYAX studies. Seizures have also been reported with both olanzapine and fluoxetine
756 monotherapy. Therefore, SYMBYAX should be used cautiously in patients with a history of
757 seizures or with conditions that potentially lower the seizure threshold. Conditions that lower the
758 seizure threshold may be more prevalent in a population of ≥ 65 years of age.

759 **Transaminase Elevations** — As with olanzapine, asymptomatic elevations of hepatic
760 transaminases [ALT (SGPT), AST (SGOT), and GGT] and alkaline phosphatase have been
761 observed with SYMBYAX. In the SYMBYAX-controlled database, ALT (SGPT) elevations (≥ 3
762 times the upper limit of the normal range) were observed in 6.3% (31/495) of patients exposed to
763 SYMBYAX compared with 0.5% (2/384) of the placebo patients and 4.5% (25/560) of
764 olanzapine-treated patients. The difference between SYMBYAX and placebo was statistically
765 significant. None of these 31 SYMBYAX-treated patients experienced jaundice and three had
766 transient elevations >200 IU/L.

767 In olanzapine placebo-controlled studies, clinically significant ALT (SGPT) elevations (≥ 3
768 times the upper limit of the normal range) were observed in 2% (6/243) of patients exposed to
769 olanzapine compared with 0% (0/115) of the placebo patients. None of these patients
770 experienced jaundice. In 2 of these patients, liver enzymes decreased toward normal despite
771 continued treatment, and in 2 others, enzymes decreased upon discontinuation of olanzapine. In
772 the remaining 2 patients, 1, seropositive for hepatitis C, had persistent enzyme elevations for 4
773 months after discontinuation, and the other had insufficient follow-up to determine if enzymes
774 normalized.

775 Within the larger olanzapine premarketing database of about 2400 patients with baseline SGPT
776 ≤ 90 IU/L, the incidence of SGPT elevation to >200 IU/L was 2% (50/2381). Again, none of
777 these patients experienced jaundice or other symptoms attributable to liver impairment and most
778 had transient changes that tended to normalize while olanzapine treatment was continued.
779 Among all 2500 patients in olanzapine clinical studies, approximately 1% (23/2500)
780 discontinued treatment due to transaminase increases.

781 Rare postmarketing reports of hepatitis have been received. Very rare cases of cholestatic or
782 mixed liver injury have also been reported in the postmarketing period.

783 Caution should be exercised in patients with signs and symptoms of hepatic impairment, in
784 patients with pre-existing conditions associated with limited hepatic functional reserve, and in
785 patients who are being treated with potentially hepatotoxic drugs. Periodic assessment of
786 transaminases is recommended in patients with significant hepatic disease (*see* Laboratory
787 Tests).

Formatted: No underline, Font
color: Auto, Not Highlight

Formatted: Not Highlight

788 Use in Patients with Concomitant Illness

789 Clinical experience with SYMBYAX in patients with concomitant systemic illnesses is limited
790 (*see* CLINICAL PHARMACOLOGY, Renal Impairment *and* Hepatic Impairment). The
791 following precautions for the individual components may be applicable to SYMBYAX.

792 Olanzapine exhibits *in vitro* muscarinic receptor affinity. In premarketing clinical studies,
793 SYMBYAX was associated with constipation, dry mouth, and tachycardia, all adverse events
794 possibly related to cholinergic antagonism. Such adverse events were not often the basis for
795 study discontinuations; SYMBYAX should be used with caution in patients with clinically
796 significant prostatic hypertrophy, narrow angle glaucoma, a history of paralytic ileus, or related
797 conditions.

798 In five placebo-controlled studies of olanzapine in elderly patients with dementia-related
799 psychosis (n=1184), the following treatment-emergent adverse events were reported in
800 olanzapine-treated patients at an incidence of at least 2% and significantly greater than
801 placebo-treated patients: falls, somnolence, peripheral edema, abnormal gait, urinary
802 incontinence, lethargy, increased weight, asthenia, pyrexia, pneumonia, dry mouth and visual
803 hallucinations. The rate of discontinuation due to adverse events was significantly greater with
804 olanzapine than placebo (13% vs 7%). Elderly patients with dementia-related psychosis treated
805 with olanzapine are at an increased risk of death compared to placebo. Olanzapine is not
806 approved for the treatment of patients with dementia-related psychosis. If the prescriber elects to
807 treat elderly patients with dementia-related psychosis, vigilance should be exercised (*see* BOX
808 WARNING *and* WARNINGS).

809 As with other CNS-active drugs, SYMBYAX should be used with caution in elderly patients
810 with dementia. Olanzapine is not approved for the treatment of patients with dementia-related
811 psychosis. If the prescriber elects to treat elderly patients with dementia-related psychosis,
812 vigilance should be exercised (*see* BOX WARNING *and* WARNINGS).

813 SYMBYAX has not been evaluated or used to any appreciable extent in patients with a recent
814 history of myocardial infarction or unstable heart disease. Patients with these diagnoses were
815 excluded from clinical studies during the premarket testing.

816 Caution is advised when using SYMBYAX in cardiac patients and in patients with diseases or
817 conditions that could affect hemodynamic responses (*see* WARNINGS, Orthostatic
818 Hypotension).

819 In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite,
820 norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A
821 lower dose of the fluoxetine-component of SYMBYAX should be used in patients with cirrhosis.
822 Caution is advised when using SYMBYAX in patients with diseases or conditions that could
823 affect its metabolism (*see* CLINICAL PHARMACOLOGY, Hepatic Impairment *and* DOSING
824 AND ADMINISTRATION, Special Populations).

825 Olanzapine and fluoxetine individual pharmacokinetics do not differ significantly in patients
826 with renal impairment. SYMBYAX dosing adjustment based upon renal impairment is not
827 routinely required (*see* CLINICAL PHARMACOLOGY, Renal Impairment).

828 Information for Patients

829 Prescribers or other health professionals should inform patients, their families, and their
830 caregivers about the benefits and risks associated with treatment with SYMBYAX and should
831 counsel them in its appropriate use. A patient Medication Guide about “Antidepressant
832 Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions” is
833 available for SYMBYAX. The prescriber or health professional should instruct patients, their

834 families, and their caregivers to read the Medication Guide and should assist them in
835 understanding its contents. Patients should be given the opportunity to discuss the contents of the
836 Medication Guide and to obtain answers to any questions they may have. The complete text of
837 the Medication Guide is reprinted at the end of this document.

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

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

851 **Hyperglycemia** — Patients should be advised of the potential risk of hyperglycemia-related
852 adverse events. Patients should be monitored regularly for worsening of glucose control.

853 **Weight Gain** — Patients should be counseled that SYMBYAX is associated with weight gain.
854 Patients should have their weight monitored regularly.

855 **Serotonin Syndrome** — Patients should be cautioned about the risk of serotonin syndrome
856 with the concomitant use of SYMBYAX and triptans, tramadol or other serotonergic agents.

857 **Abnormal Bleeding** — Patients should be cautioned about the concomitant use of
858 SYMBYAX and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since the
859 combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has
860 been associated with an increased risk of bleeding (*see* PRECAUTIONS, Abnormal Bleeding).

861 **Alcohol** — Patients should be advised to avoid alcohol while taking SYMBYAX.

862 **Cognitive and Motor Impairment** — As with any CNS-active drug, SYMBYAX has the
863 potential to impair judgment, thinking, or motor skills. Patients should be cautioned about
864 operating hazardous machinery, including automobiles, until they are reasonably certain that
865 SYMBYAX therapy does not affect them adversely.

866 **Concomitant Medication** — Patients should be advised to inform their physician if they are
867 taking Prozac[®], Prozac Weekly[™], Sarafem[®], fluoxetine, Zyprexa[®], or Zyprexa Zydis[®]. Patients
868 should also be advised to inform their physicians if they are taking or plan to take any
869 prescription or over-the-counter drugs, including herbal supplements, since there is a potential
870 for interactions.

871 **Heat Exposure and Dehydration** — Patients should be advised regarding appropriate care in
872 avoiding overheating and dehydration.

873 **Nursing** — Patients, if taking SYMBYAX, should be advised not to breast-feed.

874 **Orthostatic Hypotension** — Patients should be advised of the risk of orthostatic hypotension,
875 especially during the period of initial dose titration and in association with the use of
876 concomitant drugs that may potentiate the orthostatic effect of olanzapine, e.g., diazepam or
877 alcohol (*see* WARNINGS and Drug Interactions).

878 **Pregnancy** — Patients should be advised to notify their physician if they become pregnant or
879 intend to become pregnant during SYMBYAX therapy.

880 **Rash** — Patients should be advised to notify their physician if they develop a rash or hives
881 while taking SYMBYAX.

882 **Treatment Adherence** — Patients should be advised to take SYMBYAX exactly as
883 prescribed, and to continue taking SYMBYAX as prescribed even after their mood symptoms
884 improve. Patients should be advised that they should not alter their dosing regimen, or stop
885 taking SYMBYAX, without consulting their physician.

886 Patient information is printed at the end of this insert. Physicians should discuss this
887 information with their patients and instruct them to read the Medication Guide before starting
888 therapy with SYMBYAX and each time their prescription is refilled.

889 **Laboratory Tests**

890 Periodic assessment of transaminases is recommended in patients with significant hepatic
891 disease (*see* Transaminase Elevations).

892 **Drug Interactions**

893 The risks of using SYMBYAX in combination with other drugs have not been extensively
894 evaluated in systematic studies. The drug-drug interactions of the individual components are
895 applicable to SYMBYAX. As with all drugs, the potential for interaction by a variety of
896 mechanisms (e.g., pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc.) is a
897 possibility. Caution is advised if the concomitant administration of SYMBYAX and other
898 CNS-active drugs is required. In evaluating individual cases, consideration should be given to
899 using lower initial doses of the concomitantly administered drugs, using conservative titration
900 schedules, and monitoring of clinical status (*see* CLINICAL PHARMACOLOGY, Accumulation
901 and slow elimination).

902 Antihypertensive agents — Because of the potential for olanzapine to induce hypotension,
903 SYMBYAX may enhance the effects of certain antihypertensive agents (*see* WARNINGS,
904 Orthostatic Hypotension).

905 Anti-Parkinsonian — The olanzapine component of SYMBYAX may antagonize the effects of
906 levodopa and dopamine agonists.

907 Benzodiazepines — Multiple doses of olanzapine did not influence the pharmacokinetics of
908 diazepam and its active metabolite N-desmethyldiazepam. However, the coadministration of
909 diazepam with olanzapine potentiated the orthostatic hypotension observed with olanzapine.

910 When concurrently administered with fluoxetine, the half-life of diazepam may be prolonged
911 in some patients (*see* CLINICAL PHARMACOLOGY, Accumulation and slow elimination).
912 Coadministration of alprazolam and fluoxetine has resulted in increased alprazolam plasma
913 concentrations and in further psychomotor performance decrement due to increased alprazolam
914 levels.

915 Biperiden — Multiple doses of olanzapine did not influence the pharmacokinetics of biperiden.

916 Carbamazepine — Carbamazepine therapy (200 mg BID) causes an approximate 50% increase
917 in the clearance of olanzapine. This increase is likely due to the fact that carbamazepine is a
918 potent inducer of CYP1A2 activity. Higher daily doses of carbamazepine may cause an even
919 greater increase in olanzapine clearance.

920 Patients on stable doses of carbamazepine have developed elevated plasma anticonvulsant
921 concentrations and clinical anticonvulsant toxicity following initiation of concomitant fluoxetine
922 treatment.

923 Clozapine — Elevation of blood levels of clozapine has been observed in patients receiving
924 concomitant fluoxetine.

925 Electroconvulsive therapy (ECT) — There are no clinical studies establishing the benefit of the
926 combined use of ECT and fluoxetine. There have been rare reports of prolonged seizures in
927 patients on fluoxetine receiving ECT treatment (*see Seizures*).

928 Ethanol — Ethanol (45 mg/70 kg single dose) did not have an effect on olanzapine
929 pharmacokinetics. The coadministration of ethanol with SYMBYAX may potentiate sedation
930 and orthostatic hypotension.

931 Fluvoxamine — Fluvoxamine, a CYP1A2 inhibitor, decreases the clearance of olanzapine.
932 This results in a mean increase in olanzapine C_{max} following fluvoxamine administration of 54%
933 in female nonsmokers and 77% in male smokers. The mean increase in olanzapine AUC is 52%
934 and 108%, respectively. Lower doses of the olanzapine component of SYMBYAX should be
935 considered in patients receiving concomitant treatment with fluvoxamine.

936 Haloperidol — Elevation of blood levels of haloperidol has been observed in patients receiving
937 concomitant fluoxetine.

938 Lithium — Multiple doses of olanzapine did not influence the pharmacokinetics of lithium.
939 There have been reports of both increased and decreased lithium levels when lithium was used
940 concomitantly with fluoxetine. Cases of lithium toxicity and increased serotonergic effects have
941 been reported. Lithium levels should be monitored in patients taking SYMBYAX concomitantly
942 with lithium.

943 Monoamine oxidase inhibitors — *See CONTRAINDICATIONS*.

944 Phenytoin — Patients on stable doses of phenytoin have developed elevated plasma levels of
945 phenytoin with clinical phenytoin toxicity following initiation of concomitant fluoxetine.

946 Pimozide — Clinical studies of pimozide with other antidepressants demonstrate an increase in
947 drug interaction or QT_c prolongation. While a specific study with pimozide and fluoxetine has
948 not been conducted, the potential for drug interactions or QT_c prolongation warrants restricting
949 the concurrent use of pimozide and fluoxetine. Concomitant use of fluoxetine and pimozide is
950 contraindicated (*see CONTRAINDICATIONS*).

951 Serotonergic drugs — Based on the mechanism of action of SNRIs and SSRIs, including
952 SYMBYAX, and the potential for serotonin syndrome, caution is advised when SYMBYAX is
953 coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such
954 as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol,
955 or St. John's Wort (*see WARNINGS, Serotonin Syndrome*). The concomitant use of
956 SYMBYAX with other SSRIs, SNRIs or tryptophan is not recommended (*see Tryptophan*).

957 Theophylline — Multiple doses of olanzapine did not affect the pharmacokinetics of
958 theophylline or its metabolites.

959 Thioridazine — *See CONTRAINDICATIONS and WARNINGS, Thioridazine*.

960 Tricyclic antidepressants (TCAs) — Single doses of olanzapine did not affect the
961 pharmacokinetics of imipramine or its active metabolite desipramine.

962 In two fluoxetine studies, previously stable plasma levels of imipramine and desipramine have
963 increased >2- to 10-fold when fluoxetine has been administered in combination. This influence
964 may persist for three weeks or longer after fluoxetine is discontinued. Thus, the dose of TCA
965 may need to be reduced and plasma TCA concentrations may need to be monitored temporarily
966 when SYMBYAX is coadministered or has been recently discontinued (*see Drugs metabolized*
967 *by CYP2D6 and CLINICAL PHARMACOLOGY, Accumulation and slow elimination*).

968 Triptans — There have been rare postmarketing reports of serotonin syndrome with use of an
969 SSRI and a triptan. If concomitant treatment of SYMBYAX with a triptan is clinically

970 warranted, careful observation of the patient is advised, particularly during treatment initiation
 971 and dose increases (*see* WARNINGS, Serotonin Syndrome).

972 Tryptophan — Five patients receiving fluoxetine in combination with tryptophan experienced
 973 adverse reactions, including agitation, restlessness, and gastrointestinal distress.

974 Valproate — In vitro studies using human liver microsomes determined that olanzapine has
 975 little potential to inhibit the major metabolic pathway, glucuronidation, of valproate. Further,
 976 valproate has little effect on the metabolism of olanzapine in vitro. Thus, a clinically significant
 977 pharmacokinetic interaction between olanzapine and valproate is unlikely.

978 Warfarin — Warfarin (20-mg single dose) did not affect olanzapine pharmacokinetics. Single
 979 doses of olanzapine did not affect the pharmacokinetics of warfarin.

980 Drugs that interfere with hemostasis (e.g., NSAIDs, Aspirin, Warfarin) — Serotonin release by
 981 platelets plays an important role in hemostasis. Epidemiological studies of the case-control and
 982 cohort design that have demonstrated an association between use of psychotropic drugs that
 983 interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also
 984 shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding (*see*
 985 PRECAUTIONS, Abnormal Bleeding). Altered anticoagulant effects, including increased
 986 bleeding, have been reported when SSRIs or SNRIs are coadministered with warfarin (*see*
 987 PRECAUTIONS, Abnormal Bleeding). Patients receiving warfarin therapy should be carefully
 988 monitored when SYMBYAX is initiated or discontinued.

989 Drugs metabolized by CYP2D6 — In vitro studies utilizing human liver microsomes suggest
 990 that olanzapine has little potential to inhibit CYP2D6. Thus, olanzapine is unlikely to cause
 991 clinically important drug interactions mediated by this enzyme.

992 Fluoxetine inhibits the activity of CYP2D6, and may make individuals with normal CYP2D6
 993 metabolic activity resemble a poor metabolizer. Coadministration of fluoxetine with other drugs
 994 that are metabolized by CYP2D6, including certain antidepressants (e.g., TCAs), antipsychotics
 995 (e.g., phenothiazines and most atypicals), and antiarrhythmics (e.g., propafenone, flecainide, and
 996 others) should be approached with caution. Therapy with medications that are predominantly
 997 metabolized by the CYP2D6 system and that have a relatively narrow therapeutic index should
 998 be initiated at the low end of the dose range if a patient is receiving fluoxetine concurrently or
 999 has taken it in the previous five weeks. If fluoxetine is added to the treatment regimen of a
 1000 patient already receiving a drug metabolized by CYP2D6, the need for a decreased dose of the
 1001 original medication should be considered. Drugs with a narrow therapeutic index represent the
 1002 greatest concern (including but not limited to, flecainide, propafenone, vinblastine, and TCAs).
 1003 Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with
 1004 elevated thioridazine plasma levels, thioridazine should not be administered with fluoxetine or
 1005 within a minimum of five weeks after fluoxetine has been discontinued (*see*
 1006 CONTRAINDICATIONS, Monoamine Oxidase Inhibitors (MAOI) *and* WARNINGS,
 1007 Thioridazine).

1008 Drugs metabolized by CYP3A — In vitro studies utilizing human liver microsomes suggest
 1009 that olanzapine has little potential to inhibit CYP3A. Thus, olanzapine is unlikely to cause
 1010 clinically important drug interactions mediated by these enzymes.

1011 In an in vivo interaction study involving the coadministration of fluoxetine with single doses of
 1012 terfenadine (a CYP3A substrate), no increase in plasma terfenadine concentrations occurred with
 1013 concomitant fluoxetine. In addition, in vitro studies have shown ketoconazole, a potent inhibitor
 1014 of CYP3A activity, to be at least 100 times more potent than fluoxetine or norfluoxetine as an
 1015 inhibitor of the metabolism of several substrates for this enzyme, including astemizole, cisapride,

Formatted: Not Highlight

Formatted: Not Highlight

1016 and midazolam. These data indicate that fluoxetine's extent of inhibition of CYP3A activity is
1017 not likely to be of clinical significance.

1018 Effect of olanzapine on drugs metabolized by other CYP enzymes — In vitro studies utilizing
1019 human liver microsomes suggest that olanzapine has little potential to inhibit CYP1A2,
1020 CYP2C9, and CYP2C19. Thus, olanzapine is unlikely to cause clinically important drug
1021 interactions mediated by these enzymes.

1022 The effect of other drugs on olanzapine — Fluoxetine, an inhibitor of CYP2D6, decreases
1023 olanzapine clearance a small amount (*see* CLINICAL PHARMACOLOGY, Pharmacokinetics).
1024 Agents that induce CYP1A2 or glucuronyl transferase enzymes, such as omeprazole and
1025 rifampin, may cause an increase in olanzapine clearance. Fluvoxamine, an inhibitor of CYP1A2,
1026 decreases olanzapine clearance (*see* Drug Interactions, Fluvoxamine). The effect of CYP1A2
1027 inhibitors, such as fluvoxamine and some fluoroquinolone antibiotics, on SYMBYAX has not
1028 been evaluated. Although olanzapine is metabolized by multiple enzyme systems, induction or
1029 inhibition of a single enzyme may appreciably alter olanzapine clearance. Therefore, a dosage
1030 increase (for induction) or a dosage decrease (for inhibition) may need to be considered with
1031 specific drugs.

1032 Drugs tightly bound to plasma proteins — The in vitro binding of SYMBYAX to human
1033 plasma proteins is similar to the individual components. The interaction between SYMBYAX
1034 and other highly protein-bound drugs has not been fully evaluated. Because fluoxetine is tightly
1035 bound to plasma protein, the administration of fluoxetine to a patient taking another drug that is
1036 tightly bound to protein (e.g., Coumadin, digitoxin) may cause a shift in plasma concentrations
1037 potentially resulting in an adverse effect. Conversely, adverse effects may result from
1038 displacement of protein-bound fluoxetine by other tightly bound drugs (*see* CLINICAL
1039 PHARMACOLOGY, Distribution *and* PRECAUTIONS, Drug Interactions).

1040 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

1041 No carcinogenicity, mutagenicity, or fertility studies were conducted with SYMBYAX. The
1042 following data are based on findings in studies performed with the individual components.

1043 **Carcinogenesis**

1044 Olanzapine — Oral carcinogenicity studies were conducted in mice and rats. Olanzapine was
1045 administered to mice in two 78-week studies at doses of 3, 10, and 30/20 mg/kg/day [equivalent
1046 to 0.8 to 5 times the maximum recommended human daily dose (MRHD) on a mg/m² basis] and
1047 0.25, 2, and 8 mg/kg/day (equivalent to 0.06 to 2 times the MRHD on a mg/m² basis). Rats were
1048 dosed for 2 years at doses of 0.25, 1, 2.5, and 4 mg/kg/day (males) and 0.25, 1, 4, and
1049 8 mg/kg/day (females) (equivalent to 0.1 to 2 and 0.1 to 4 times the MRHD on a mg/m² basis,
1050 respectively). The incidence of liver hemangiomas and hemangiosarcomas was significantly
1051 increased in one mouse study in females dosed at 8 mg/kg/day (2 times the MRHD on a mg/m²
1052 basis). These tumors were not increased in another mouse study in females dosed at 10 or
1053 30/20 mg/kg/day (2 to 5 times the MRHD on a mg/m² basis); in this study, there was a high
1054 incidence of early mortalities in males of the 30/20 mg/kg/day group. The incidence of
1055 mammary gland adenomas and adenocarcinomas was significantly increased in female mice
1056 dosed at ≥2 mg/kg/day and in female rats dosed at ≥4 mg/kg/day (0.5 and 2 times the MRHD on
1057 a mg/m² basis, respectively). Antipsychotic drugs have been shown to chronically elevate
1058 prolactin levels in rodents. Serum prolactin levels were not measured during the olanzapine
1059 carcinogenicity studies; however, measurements during subchronic toxicity studies showed that
1060 olanzapine elevated serum prolactin levels up to 4-fold in rats at the same doses used in the
1061 carcinogenicity study. An increase in mammary gland neoplasms has been found in rodents after

1062 chronic administration of other antipsychotic drugs and is considered to be prolactin-mediated.
1063 The relevance for human risk of the finding of prolactin-mediated endocrine tumors in rodents is
1064 unknown (*see* PRECAUTIONS, Hyperprolactinemia).

1065 Fluoxetine — The dietary administration of fluoxetine to rats and mice for two years at doses
1066 of up to 10 and 12 mg/kg/day, respectively (approximately 1.2 and 0.7 times, respectively, the
1067 MRHD on a mg/m² basis), produced no evidence of carcinogenicity.

1068 Mutagenesis

1069 Olanzapine — No evidence of mutagenic potential for olanzapine was found in the Ames
1070 reverse mutation test, in vivo micronucleus test in mice, the chromosomal aberration test in
1071 Chinese hamster ovary cells, unscheduled DNA synthesis test in rat hepatocytes, induction of
1072 forward mutation test in mouse lymphoma cells, or in vivo sister chromatid exchange test in
1073 bone marrow of Chinese hamsters.

1074 Fluoxetine — Fluoxetine and norfluoxetine have been shown to have no genotoxic effects
1075 based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat
1076 hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese
1077 hamster bone marrow cells.

1078 Impairment of Fertility

1079 SYMBYAX — Fertility studies were not conducted with SYMBYAX. However, in a
1080 repeat-dose rat toxicology study of three months duration, ovary weight was decreased in
1081 females treated with the low-dose [2 and 4 mg/kg/day (1 and 0.5 times the MRHD on a mg/m²
1082 basis), respectively] and high-dose [4 and 8 mg/kg/day (2 and 1 times the MRHD on a mg/m²
1083 basis), respectively] combinations of olanzapine and fluoxetine. Decreased ovary weight, and
1084 corpora luteal depletion and uterine atrophy were observed to a greater extent in the females
1085 receiving the high-dose combination than in females receiving either olanzapine or fluoxetine
1086 alone. In a 3-month repeat-dose dog toxicology study, reduced epididymal sperm and reduced
1087 testicular and prostate weights were observed with the high-dose combination of olanzapine and
1088 fluoxetine [5 and 5 mg/kg/day (9 and 2 times the MRHD on a mg/m² basis), respectively] and
1089 with olanzapine alone (5 mg/kg/day or 9 times the MRHD on a mg/m² basis).

1090 Olanzapine — In a fertility and reproductive performance study in rats, male mating
1091 performance, but not fertility, was impaired at a dose of 22.4 mg/kg/day and female fertility was
1092 decreased at a dose of 3 mg/kg/day (11 and 1.5 times the MRHD on a mg/m² basis, respectively).
1093 Discontinuance of olanzapine treatment reversed the effects on male-mating performance. In
1094 female rats, the precoital period was increased and the mating index reduced at 5 mg/kg/day (2.5
1095 times the MRHD on a mg/m² basis). Diestrus was prolonged and estrus was delayed at
1096 1.1 mg/kg/day (0.6 times the MRHD on a mg/m² basis); therefore, olanzapine may produce a
1097 delay in ovulation.

1098 Fluoxetine — Two fertility studies conducted in adult rats at doses of up to 7.5 and
1099 12.5 mg/kg/day (approximately 0.9 and 1.5 times the MRHD on a mg/m² basis) indicated that
1100 fluoxetine had no adverse effects on fertility (*see* Pediatric Use).

1101 **Pregnancy — Pregnancy Category C**

1102 SYMBYAX

1103 Embryo fetal development studies were conducted in rats and rabbits with olanzapine and
1104 fluoxetine in low-dose and high-dose combinations. In rats, the doses were: 2 and 4 mg/kg/day
1105 (low-dose) [1 and 0.5 times the MRHD on a mg/m² basis, respectively], and 4 and 8 mg/kg/day
1106 (high-dose) [2 and 1 times the MRHD on a mg/m² basis, respectively]. In rabbits, the doses were

1107 4 and 4 mg/kg/day (low-dose) [4 and 1 times the MRHD on a mg/m² basis, respectively], and 8
1108 and 8 mg/kg/day (high-dose) [9 and 2 times the MRHD on a mg/m² basis, respectively]. In these
1109 studies, olanzapine and fluoxetine were also administered alone at the high-doses (4 and
1110 8 mg/kg/day, respectively, in the rat; 8 and 8 mg/kg/day, respectively, in the rabbit). In the
1111 rabbit, there was no evidence of teratogenicity; however, the high-dose combination produced
1112 decreases in fetal weight and retarded skeletal ossification in conjunction with maternal toxicity.
1113 Similarly, in the rat there was no evidence of teratogenicity; however, a decrease in fetal weight
1114 was observed with the high-dose combination.

1115 In a pre- and postnatal study conducted in rats, olanzapine and fluoxetine were administered
1116 during pregnancy and throughout lactation in combination (low-dose: 2 and 4 mg/kg/day [1 and
1117 0.5 times the MRHD on a mg/m² basis], respectively, high-dose: 4 and 8 mg/kg/day [2 and 1
1118 times the MRHD on a mg/m² basis], respectively, and alone: 4 and 8 mg/kg/day [2 and 1 times
1119 the MRHD on a mg/m² basis], respectively). Administration of the high-dose combination
1120 resulted in a marked elevation in offspring mortality and growth retardation in comparison to the
1121 same doses of olanzapine and fluoxetine administered alone. These effects were not observed
1122 with the low-dose combination; however, there were a few cases of testicular degeneration and
1123 atrophy, depletion of epididymal sperm and infertility in the male progeny. The effects of the
1124 high-dose combination on postnatal endpoints could not be assessed due to high progeny
1125 mortality.

1126 There are no adequate and well-controlled studies with SYMBYAX in pregnant women.

1127 SYMBYAX should be used during pregnancy only if the potential benefit justifies the
1128 potential risk to the fetus.

1129 Olanzapine

1130 In reproduction studies in rats at doses up to 18 mg/kg/day and in rabbits at doses up to
1131 30 mg/kg/day (9 and 30 times the MRHD on a mg/m² basis, respectively), no evidence of
1132 teratogenicity was observed. In a rat teratology study, early resorptions and increased numbers of
1133 nonviable fetuses were observed at a dose of 18 mg/kg/day (9 times the MRHD on a mg/m²
1134 basis). Gestation was prolonged at 10 mg/kg/day (5 times the MRHD on a mg/m² basis). In a
1135 rabbit teratology study, fetal toxicity (manifested as increased resorptions and decreased fetal
1136 weight) occurred at a maternally toxic dose of 30 mg/kg/day (30 times the MRHD on a mg/m²
1137 basis).

1138 Placental transfer of olanzapine occurs in rat pups.

1139 There are no adequate and well-controlled clinical studies with olanzapine in pregnant women.
1140 Seven pregnancies were observed during premarketing clinical studies with olanzapine,
1141 including two resulting in normal births, one resulting in neonatal death due to a cardiovascular
1142 defect, three therapeutic abortions, and one spontaneous abortion.

1143 Fluoxetine

1144 In embryo fetal development studies in rats and rabbits, there was no evidence of teratogenicity
1145 following administration of up to 12.5 and 15 mg/kg/day, respectively (1.5 and 3.6 times the
1146 MRHD on a mg/m² basis, respectively) throughout organogenesis. However, in rat reproduction
1147 studies, an increase in stillborn pups, a decrease in pup weight, and an increase in pup deaths
1148 during the first 7 days postpartum occurred following maternal exposure to 12 mg/kg/day (1.5
1149 times the MRHD on a mg/m² basis) during gestation or 7.5 mg/kg/day (0.9 times the MRHD on
1150 a mg/m² basis) during gestation and lactation. There was no evidence of developmental
1151 neurotoxicity in the surviving offspring of rats treated with 12 mg/kg/day during gestation. The
1152 no-effect dose for rat pup mortality was 5 mg/kg/day (0.6 times the MRHD on a mg/m² basis).

1153 **Nonteratogenic Effects** — Neonates exposed to fluoxetine and other SSRIs or serotonin and
1154 norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed
1155 complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such
1156 complications can arise immediately upon delivery. Reported clinical findings have included
1157 respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty,
1158 vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and
1159 constant crying. These features are consistent with either a direct toxic effect of SSRIs and
1160 SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the
1161 clinical picture is consistent with serotonin syndrome (*see* CONTRAINDICATIONS,
1162 Monoamine Oxidase Inhibitors).

1163 Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent
1164 pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1-2 per 1000 live births in the
1165 general population and is associated with substantial neonatal morbidity and mortality. In a
1166 retrospective case-control study of 377 women whose infants were born with PPHN and 836
1167 women whose infants were born healthy, the risk for developing PPHN was approximately
1168 six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants
1169 who had not been exposed to antidepressants during pregnancy. There is currently no
1170 corroborative evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy;
1171 this is the first study that has investigated the potential risk. The study did not include enough
1172 cases with exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN
1173 risk.

1174 When treating a pregnant woman with fluoxetine during the third trimester, the physician
1175 should carefully consider both the potential risks and benefits of treatment (*see* DOSAGE AND
1176 ADMINISTRATION). Physicians should note that in a prospective longitudinal study of 201
1177 women with a history of major depression who were euthymic at the beginning of pregnancy,
1178 women who discontinued antidepressant medication during pregnancy were more likely to
1179 experience a relapse of major depression than women who continued antidepressant medication.

1180 **Labor and Delivery**

1181 **SYMBYAX**

1182 The effect of SYMBYAX on labor and delivery in humans is unknown. Parturition in rats was
1183 not affected by SYMBYAX. SYMBYAX should be used during labor and delivery only if the
1184 potential benefit justifies the potential risk.

1185 **Olanzapine**

1186 Parturition in rats was not affected by olanzapine. The effect of olanzapine on labor and
1187 delivery in humans is unknown.

1188 **Fluoxetine**

1189 The effect of fluoxetine on labor and delivery in humans is unknown. Fluoxetine crosses the
1190 placenta; therefore, there is a possibility that fluoxetine may have adverse effects on the
1191 newborn.

1192 **Nursing Mothers**

1193 **SYMBYAX**

1194 There are no adequate and well-controlled studies with SYMBYAX in nursing mothers or
1195 infants. No studies have been conducted to examine the excretion of olanzapine or fluoxetine in

1196 breast milk following SYMBYAX treatment. It is recommended that women not breast-feed
1197 when receiving SYMBYAX.

1198 Olanzapine

1199 In a study in lactating, healthy women, olanzapine was excreted in breast milk. Mean infant
1200 dose at steady state was estimated to be 1.8% of the maternal olanzapine dose.

1201 Fluoxetine

1202 Fluoxetine is excreted in human breast milk. In one breast milk sample, the concentration of
1203 fluoxetine plus norfluoxetine was 70.4 ng/mL. The concentration in the mother's plasma was
1204 295.0 ng/mL. No adverse effects on the infant were reported. In another case, an infant nursed by
1205 a mother on fluoxetine developed crying, sleep disturbance, vomiting, and watery stools. The
1206 infant's plasma drug levels were 340 ng/mL of fluoxetine and 208 ng/mL of norfluoxetine on the
1207 2nd day of feeding.

1208 Pediatric Use

1209 Safety and effectiveness in the pediatric population have not been established (*see* BOX
1210 WARNING and WARNINGS, Clinical Worsening and Suicide Risk). Anyone considering the
1211 use of SYMBYAX in a child or adolescent must balance the potential risks with the clinical
1212 need.

1213 Fluoxetine

1214 Significant toxicity, including myotoxicity, long-term neurobehavioral and reproductive
1215 toxicity, and impaired bone development, has been observed following exposure of juvenile
1216 animals to fluoxetine. Some of these effects occurred at clinically relevant exposures.

1217 In a study in which fluoxetine (3, 10, or 30 mg/kg) was orally administered to young rats from
1218 weaning (Postnatal Day 21) through adulthood (Day 90), male and female sexual development
1219 was delayed at all doses, and growth (body weight gain, femur length) was decreased during the
1220 dosing period in animals receiving the highest dose. At the end of the treatment period, serum
1221 levels of creatine kinase (marker of muscle damage) were increased at the intermediate and high
1222 doses, and abnormal muscle and reproductive organ histopathology (skeletal muscle
1223 degeneration and necrosis, testicular degeneration and necrosis, epididymal vacuolation and
1224 hypospermia) was observed at the high dose. When animals were evaluated after a recovery
1225 period (up to 11 weeks after cessation of dosing), neurobehavioral abnormalities (decreased
1226 reactivity at all doses and learning deficit at the high dose) and reproductive functional
1227 impairment (decreased mating at all doses and impaired fertility at the high dose) were seen; in
1228 addition, testicular and epididymal microscopic lesions and decreased sperm concentrations were
1229 found in the high dose group, indicating that the reproductive organ effects seen at the end of
1230 treatment were irreversible. The reversibility of fluoxetine-induced muscle damage was not
1231 assessed. Adverse effects similar to those observed in rats treated with fluoxetine during the
1232 juvenile period have not been reported after administration of fluoxetine to adult animals. Plasma
1233 exposures (AUC) to fluoxetine in juvenile rats receiving the low, intermediate, and high dose in
1234 this study were approximately 0.1-0.2, 1-2, and 5-10 times, respectively, the average exposure in
1235 pediatric patients receiving the maximum recommended dose (MRD) of 20 mg/day. Rat
1236 exposures to the major metabolite, norfluoxetine, were approximately 0.3-0.8, 1-8, and 3-20
1237 times, respectively, pediatric exposure at the MRD.

1238 A specific effect of fluoxetine on bone development has been reported in mice treated with
1239 fluoxetine during the juvenile period. When mice were treated with fluoxetine (5 or 20 mg/kg,
1240 intraperitoneal) for 4 weeks starting at 4 weeks of age, bone formation was reduced resulting in

1241 decreased bone mineral content and density. These doses did not affect overall growth (body
 1242 weight gain or femoral length). The doses administered to juvenile mice in this study are
 1243 approximately 0.5 and 2 times the MRD for pediatric patients on a body surface area (mg/m^2)
 1244 basis.

1245 In another mouse study, administration of fluoxetine (10 mg/kg intraperitoneal) during early
 1246 postnatal development (Postnatal Days 4 to 21) produced abnormal emotional behaviors
 1247 (decreased exploratory behavior in elevated plus-maze, increased shock avoidance latency) in
 1248 adulthood (12 weeks of age). The dose used in this study is approximately equal to the pediatric
 1249 MRD on a mg/m^2 basis. Because of the early dosing period in this study, the significance of
 1250 these findings to the approved pediatric use in humans is uncertain.

1251 Geriatric Use

1252 SYMBYAX

1253 Clinical studies of SYMBYAX did not include sufficient numbers of patients ≥ 65 years of age
 1254 to determine whether they respond differently from younger patients. Other reported clinical
 1255 experience has not identified differences in responses between the elderly and younger patients.
 1256 In general, dose selection for an elderly patient should be cautious, usually starting at the low end
 1257 of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac
 1258 function, and of concomitant disease or other drug therapy (*see* DOSAGE AND
 1259 ADMINISTRATION).

1260 Olanzapine

1261 Of the 2500 patients in premarketing clinical studies with olanzapine, 11% (263 patients) were
 1262 ≥ 65 years of age. In patients with schizophrenia, there was no indication of any different
 1263 tolerability of olanzapine in the elderly compared with younger patients. Studies in patients with
 1264 dementia-related psychosis have suggested that there may be a different tolerability profile in
 1265 this population compared with younger patients with schizophrenia. In placebo-controlled
 1266 studies of olanzapine in elderly patients with dementia-related psychosis, there was a
 1267 significantly higher incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic
 1268 attack) in patients treated with olanzapine compared to patients treated with placebo. Olanzapine
 1269 is not approved for the treatment of patients with dementia-related psychosis. If the prescriber
 1270 elects to treat elderly patients with dementia-related psychosis, vigilance should be exercised
 1271 (*see* BOX WARNING, WARNINGS, PRECAUTIONS, Use in Patients with Concomitant
 1272 Illness *and* DOSAGE AND ADMINISTRATION, Special Populations).

1273 As with other CNS-active drugs, olanzapine should be used with caution in elderly patients
 1274 with dementia. Also, the presence of factors that might decrease pharmacokinetic clearance or
 1275 increase the pharmacodynamic response to olanzapine should lead to consideration of a lower
 1276 starting dose for any geriatric patient.

1277 Fluoxetine

1278 US fluoxetine clinical studies included 687 patients ≥ 65 years of age and 93 patients ≥ 75 years
 1279 of age. No overall differences in safety or effectiveness were observed between these subjects
 1280 and younger subjects, and other reported clinical experience has not identified differences in
 1281 responses between the elderly and younger patients, but greater sensitivity of some older
 1282 individuals cannot be ruled out. SSRIs and SNRIs, including SYMBYAX, have been associated
 1283 with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk
 1284 for this adverse event (*see* PRECAUTIONS, Hyponatremia).

ADVERSE REACTIONS

The information below is derived from a premarketing clinical study database for SYMBYAX consisting of 2066 patients with various diagnoses with approximately 1061 patient-years of exposure. The conditions and duration of treatment with SYMBYAX varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or long-term exposure.

Adverse events were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a limited (i.e., reduced) number of standardized event categories.

In the tables and tabulations that follow, COSTART Dictionary terminology has been used to classify reported adverse events. The data in the tables represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. It is possible that events reported during therapy were not necessarily related to drug exposure.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing clinician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

Incidence in Controlled Clinical Studies

The following findings are based on the short-term, controlled premarketing studies in various diagnoses including bipolar depression.

Adverse events associated with discontinuation of treatment — Overall, 10% of the patients in the SYMBYAX group discontinued due to adverse events compared with 4.6% for placebo. Table 7 enumerates the adverse events leading to discontinuation associated with the use of SYMBYAX (incidence of at least 1% for SYMBYAX and greater than that for placebo). The bipolar depression column shows the incidence of adverse events with SYMBYAX in the bipolar depression studies and the “SYMBYAX-Controlled” column shows the incidence in the controlled SYMBYAX studies; the placebo column shows the incidence in the pooled controlled studies that included a placebo arm.

Table 7: Adverse Events Associated with Discontinuation*

Adverse Event	Percentage of Patients Reporting Event		
	SYMBYAX		Placebo (N=477)
	Bipolar Depression (N=86)	SYMBYAX-Controlled (N=571)	
Asthenia	0	1	0
Somnolence	0	2	0
Weight gain	0	2	0
Chest pain	1	0	0

* Table includes events associated with discontinuation of at least 1% and greater than placebo

1323 Commonly observed adverse events in controlled clinical studies — The most commonly
 1324 observed adverse events associated with the use of SYMBYAX (incidence of $\geq 5\%$ and at least
 1325 twice that for placebo in the SYMBYAX-controlled database) were: asthenia, edema, increased
 1326 appetite, peripheral edema, pharyngitis, somnolence, thinking abnormal, tremor, and weight
 1327 gain.

1328 Adverse events occurring at an incidence of 2% or more in controlled clinical studies —
 1329 Table 8 enumerates the treatment-emergent adverse events associated with the use of
 1330 SYMBYAX (incidence of at least 2% for SYMBYAX and twice or more that for placebo).

1331
 1332
 1333

**Table 8: Treatment-Emergent Adverse Events:
 Incidence in Controlled Clinical Studies**

Body System/Adverse Event ¹	Percentage of Patients Reporting Event		
	SYMBYAX		Placebo
	Bipolar Depression (N=86)	SYMBYAX-Controlled (N=571)	(N=477)
Body as a Whole			
Asthenia	13	15	3
Accidental injury	5	3	2
Fever	4	3	1
Cardiovascular System			
Hypertension	2	2	1
Tachycardia	2	2	0
Digestive System			
Diarrhea	19	8	7
Dry mouth	16	11	6
Increased appetite	13	16	4
Tooth disorder	1	2	1
Metabolic and Nutritional Disorders			
Weight gain	17	21	3
Peripheral edema	4	8	1
Edema	0	5	0
Musculoskeletal System			
Joint disorder	1	2	1
Twitching	6	2	1
Arthralgia	5	3	1
Nervous System			
Somnolence	21	22	11
Tremor	9	8	3
Thinking abnormal	6	6	3
Libido decreased	4	2	1
Hyperkinesia	2	1	1
Personality disorder	2	1	1
Sleep disorder	2	1	1
Amnesia	1	3	0

Respiratory System			
Pharyngitis	4	6	3
Dyspnea	1	2	1
Special Senses			
Amblyopia	5	4	2
Ear pain	2	1	1
Otitis media	2	0	0
Speech disorder	0	2	0
Urogenital System			
Abnormal ejaculation ²	7	2	1
Impotence ²	4	2	1
Anorgasmia	3	1	0

1334 ¹ Included are events reported by at least 2% of patients taking SYMBYAX except the following events, which
1335 had an incidence on placebo \geq SYMBYAX: abdominal pain, abnormal dreams, agitation, akathisia, anorexia,
1336 anxiety, apathy, back pain, chest pain, constipation, cough increased, depression, dizziness, dysmenorrhea
1337 (adjusted for gender), dyspepsia, flatulence, flu syndrome, headache, hypertonia, insomnia, manic reaction,
1338 myalgia, nausea, nervousness, pain, palpitation, paresthesia, rash, rhinitis, sinusitis, sweating, vomiting.

1339 ² Adjusted for gender.

1340 **Additional Findings Observed in Clinical Studies**

1341 The following findings are based on clinical studies.

1342 Effect on cardiac repolarization — The mean increase in QT_c interval for SYMBYAX-treated
1343 patients (4.9 msec) in clinical studies was significantly greater than that for placebo-treated
1344 (-0.9 msec) and olanzapine-treated (0.6 msec) patients, but was not significantly different from
1345 fluoxetine-treated (3.7 msec) patients. There were no differences between patients treated with
1346 SYMBYAX, placebo, olanzapine, or fluoxetine in the incidence of QT_c outliers (>500 msec).

1347 Laboratory changes — In SYMBYAX clinical studies, SYMBYAX was associated with
1348 asymptomatic mean increases in alkaline phosphatase, cholesterol, GGT, and uric acid compared
1349 with placebo (*see* PRECAUTIONS, Transaminase Elevations).

1350 SYMBYAX was associated with a slight decrease in hemoglobin that was statistically
1351 significantly greater than that seen with placebo, olanzapine, and fluoxetine.

1352 An elevation in serum prolactin was observed with SYMBYAX. This elevation was not
1353 statistically different than that seen with olanzapine (*see* PRECAUTIONS, Hyperprolactinemia).

1354 Sexual dysfunction — In the pool of controlled SYMBYAX studies, there were higher rates of
1355 the treatment-emergent adverse events decreased libido, anorgasmia, impotence and abnormal
1356 ejaculation in the SYMBYAX group than in the placebo group. One case of decreased libido led
1357 to discontinuation in the SYMBYAX group. In the controlled studies that contained a fluoxetine
1358 arm, the rates of decreased libido and abnormal ejaculation in the SYMBYAX group were less
1359 than the rates in the fluoxetine group. None of the differences were statistically significant.

1360 Sexual dysfunction, including priapism, has been reported with all SSRIs. While it is difficult
1361 to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians
1362 should routinely inquire about such possible side effects.

1363 Vital signs — Tachycardia, bradycardia, and orthostatic hypotension have occurred in
1364 SYMBYAX-treated patients (*see* WARNINGS, Orthostatic Hypotension). The mean pulse of
1365 SYMBYAX-treated patients was reduced by 1.6 beats/min.

1366 Additional findings — In a single 8-week randomized, double-blind, fixed-dose, study
1367 comparing 10 (N=199), 20 (N=200) and 40 (N=200) mg/day of olanzapine in patients with
1368 schizophrenia or schizoaffective disorder, statistically significant differences among 3 dose

1369 groups were observed for the following safety outcomes: weight gain, prolactin elevation, fatigue
 1370 and dizziness. Mean baseline to endpoint increase in weight (10 mg/day: 1.9 kg; 20 mg/day:
 1371 2.3 kg; 40 mg/day: 3 kg) was observed with significant differences between 10 vs 40 mg/day.
 1372 Incidence of treatment-emergent prolactin elevation >24.2 ng/mL (female) or >18.77 ng/mL
 1373 (male) at any time during the trial (10 mg/day: 31.2%; 20 mg/day: 42.7%; 40 mg/day: 61.1%)
 1374 with significant differences between 10 vs 40 mg/day and 20 vs 40 mg/day; fatigue (10 mg/day:
 1375 1.5%; 20 mg/day: 2.1%; 40 mg/day: 6.6%) with significant differences between 10 vs 40 and
 1376 20 vs 40 mg/day; and dizziness (10 mg/day: 2.6%; 20 mg/day: 1.6%; 40 mg/day: 6.6%) with
 1377 significant differences between 20 vs 40 mg, was observed.

1378 **Other Events Observed in Clinical Studies**

1379 Following is a list of all treatment-emergent adverse events reported at anytime by individuals
 1380 taking SYMBYAX in clinical studies except (1) those listed in the body or footnotes of Tables 7
 1381 and 8 above or elsewhere in labeling, (2) those for which the COSTART terms were
 1382 uninformative or misleading, (3) those events for which a causal relationship to SYMBYAX use
 1383 was considered remote, and (4) events occurring in only 1 patient treated with SYMBYAX and
 1384 which did not have a substantial probability of being acutely life-threatening.

1385 Events are classified within body system categories using the following definitions: frequent
 1386 adverse events are defined as those occurring on 1 or more occasions in at least 1/100 patients,
 1387 infrequent adverse events are those occurring in 1/100 to 1/1000 patients, and rare events are
 1388 those occurring in <1/1000 patients.

1389 **Body as a Whole** — *Frequent*: chills, infection, neck pain, neck rigidity, photosensitivity
 1390 reaction; *Infrequent*: cellulitis, cyst, hernia, intentional injury, intentional overdose, malaise,
 1391 moniliasis, overdose, pelvic pain, suicide attempt; *Rare*: death, tolerance decreased.

1392 **Cardiovascular System** — *Frequent*: migraine, vasodilatation; *Infrequent*: arrhythmia,
 1393 bradycardia, cerebral ischemia, electrocardiogram abnormal, hypotension, QT-interval
 1394 prolonged; *Rare*: angina pectoris, atrial arrhythmia, atrial fibrillation, bundle branch block,
 1395 congestive heart failure, myocardial infarct, peripheral vascular disorder, T-wave inverted.

1396 **Digestive System** — *Frequent*: increased salivation, thirst; *Infrequent*: cholelithiasis, colitis,
 1397 eructation, esophagitis, gastritis, gastroenteritis, gingivitis, hepatomegaly, nausea and vomiting,
 1398 peptic ulcer, periodontal abscess, stomatitis, tooth caries; *Rare*: aphthous stomatitis, fecal
 1399 incontinence, gastrointestinal hemorrhage, gum hemorrhage, intestinal obstruction, liver fatty
 1400 deposit, pancreatitis.

1401 **Endocrine System** — *Infrequent*: hypothyroidism.

1402 **Hemic and Lymphatic System** — *Frequent*: ecchymosis; *Infrequent*: anemia, leukocytosis,
 1403 lymphadenopathy; *Rare*: coagulation disorder, leukopenia, purpura, thrombocytopenia.

1404 **Metabolic and Nutritional** — *Frequent*: generalized edema, weight loss; *Infrequent*: alcohol
 1405 intolerance, dehydration, glycosuria, hyperlipemia, hypoglycemia, hypokalemia, obesity; *Rare*:
 1406 acidosis, bilirubinemia, creatinine increased, gout, hyperkalemia, hypoglycemic reaction.

1407 **Musculoskeletal System** — *Infrequent*: arthritis, bone disorder, generalized spasm, leg
 1408 cramps, tendinous contracture, tenosynovitis; *Rare*: arthrosis, bursitis, myasthenia, myopathy,
 1409 osteoporosis, rheumatoid arthritis.

1410 **Nervous System** — *Infrequent*: abnormal gait, ataxia, buccoglossal syndrome, cogwheel
 1411 rigidity, coma, confusion, depersonalization, dysarthria, emotional lability, euphoria,
 1412 extrapyramidal syndrome, hostility, hypesthesia, hypokinesia, incoordination, movement
 1413 disorder, myoclonus, neuralgia, neurosis, vertigo; *Rare*: acute brain syndrome, aphasia, dystonia,
 1414 libido increased, subarachnoid hemorrhage, withdrawal syndrome.

1415 **Respiratory System** — *Frequent*: bronchitis, lung disorder; *Infrequent*: apnea, asthma,
 1416 epistaxis, hiccup, hyperventilation, laryngitis, pneumonia, voice alteration, yawn; *Rare*:
 1417 emphysema, hemoptysis, laryngismus.

1418 **Skin and Appendages** — *Infrequent*: acne, alopecia, contact dermatitis, dry skin, eczema,
 1419 pruritis, psoriasis, skin discoloration, vesiculobullous rash; *Rare*: exfoliative dermatitis,
 1420 maculopapular rash, seborrhea, skin ulcer.

1421 **Special Senses** — *Frequent*: abnormal vision, taste perversion, tinnitus; *Infrequent*:
 1422 abnormality of accommodation, conjunctivitis, deafness, diplopia, dry eyes, eye pain, miosis;
 1423 *Rare*: eye hemorrhage.

1424 **Urogenital System** — *Frequent*: breast pain, menorrhagia¹, urinary frequency, urinary
 1425 incontinence, urinary tract infection; *Infrequent*: amenorrhea¹, breast enlargement, breast
 1426 neoplasm, cystitis, dysuria, female lactation¹, fibrocystic breast¹, hematuria, hypomenorrhea¹,
 1427 leukorrhea¹, menopause¹, metrorrhagia¹, oliguria, ovarian disorder¹, polyuria, urinary retention,
 1428 urinary urgency, urination impaired, vaginal hemorrhage¹, vaginal moniliasis¹, vaginitis¹; *Rare*:
 1429 breast carcinoma, breast engorgement, endometrial disorder¹, gynecomastia¹, kidney calculus,
 1430 uterine fibroids enlarged¹.

1431 ¹ Adjusted for gender.

1432 **Other Events Observed with Olanzapine or Fluoxetine Monotherapy**

1433 The following adverse events were not observed in SYMBYAX-treated patients during
 1434 premarketing clinical studies but have been reported with olanzapine or fluoxetine monotherapy:
 1435 aplastic anemia, cholestatic jaundice, diabetic coma, dyskinesia, eosinophilic pneumonia,
 1436 erythema multiforme, hepatitis, idiosyncratic hepatitis, jaundice, neutropenia, priapism,
 1437 pulmonary embolism, rhabdomyolysis, serotonin syndrome, serum sickness-like reaction, sudden
 1438 unexpected death, suicidal ideation, vasculitis, venous thromboembolic events (including
 1439 pulmonary embolism and deep venous thrombosis), violent behaviors. Random cholesterol levels
 1440 of ≥ 240 mg/dL and random triglyceride levels of ≥ 1000 mg/dL have been reported.

1441 **DRUG ABUSE AND DEPENDENCE**

1442 **Controlled Substance Class** — SYMBYAX is not a controlled substance.

1443 **Physical and Psychological Dependence** — SYMBYAX, as with fluoxetine and olanzapine,
 1444 has not been systematically studied in humans for its potential for abuse, tolerance, or physical
 1445 dependence. While the clinical studies did not reveal any tendency for any drug-seeking
 1446 behavior, these observations were not systematic, and it is not possible to predict on the basis of
 1447 this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or
 1448 abused once marketed. Consequently, physicians should carefully evaluate patients for history of
 1449 drug abuse and follow such patients closely, observing them for signs of misuse or abuse of
 1450 SYMBYAX (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

1451 In studies in rats and rhesus monkeys designed to assess abuse and dependence potential,
 1452 olanzapine alone was shown to have acute depressive CNS effects but little or no potential of
 1453 abuse or physical dependence at oral doses up to 15 (rat) and 8 (monkey) times the MRHD
 1454 (20 mg) on a mg/m² basis.

1455 **OVERDOSAGE**

1456 **SYMBYAX**

1457 During premarketing clinical studies of the olanzapine/fluoxetine combination, overdose of
 1458 both fluoxetine and olanzapine were reported in five study subjects. Four of the five subjects
 1459 experienced loss of consciousness (3) or coma (1). No fatalities occurred.

1460 Since the market introduction of olanzapine in October 1996, adverse event cases involving
1461 combination use of fluoxetine and olanzapine have been reported to Eli Lilly and Company. An
1462 overdose of combination therapy is defined as confirmed or suspected ingestion of a dose of
1463 olanzapine 20 mg or greater in combination with a dose of fluoxetine 80 mg or greater. As of
1464 1 February 2002, 12 cases of combination therapy overdose were reported, most of which
1465 involved additional substances. Adverse events associated with these reports included
1466 somnolence; impaired consciousness (coma, lethargy); impaired neurologic function (ataxia,
1467 confusion, convulsions, dysarthria); arrhythmias; and fatality. Fatalities have been confounded
1468 by exposure to additional substances including alcohol, thioridazine, oxycodone, and
1469 propoxyphene.

1470 **Olanzapine**

1471 In postmarketing reports of overdose with olanzapine alone, symptoms have been reported in
1472 the majority of cases. In symptomatic patients, symptoms with $\geq 10\%$ incidence included
1473 agitation/aggressiveness, dysarthria, tachycardia, various extrapyramidal symptoms, and reduced
1474 level of consciousness ranging from sedation to coma. Among less commonly reported
1475 symptoms were the following potentially medically serious events: aspiration, cardiopulmonary
1476 arrest, cardiac arrhythmias (such as supraventricular tachycardia as well as a patient that
1477 experienced sinus pause with spontaneous resumption of normal rhythm), delirium, possible
1478 neuroleptic malignant syndrome, respiratory depression/arrest, convulsion, hypertension, and
1479 hypotension. Eli Lilly and Company has received reports of fatality in association with overdose
1480 of olanzapine alone. In 1 case of death, the amount of acutely ingested olanzapine was reported
1481 to be possibly as low as 450 mg; however, in another case, a patient was reported to survive an
1482 acute olanzapine ingestion of 1500 mg.

1483 **Fluoxetine**

1484 Worldwide exposure to fluoxetine is estimated to be over 38 million patients (circa 1999). Of
1485 the 1578 cases of overdose involving fluoxetine, alone or with other drugs, reported from this
1486 population, there were 195 deaths.

1487 Among 633 adult patients who overdosed on fluoxetine alone, 34 resulted in a fatal outcome,
1488 378 completely recovered, and 15 patients experienced sequelae after overdose, including
1489 abnormal accommodation, abnormal gait, confusion, unresponsiveness, nervousness, pulmonary
1490 dysfunction, vertigo, tremor, elevated blood pressure, impotence, movement disorder, and
1491 hypomania. The remaining 206 patients had an unknown outcome. The most common signs and
1492 symptoms associated with non-fatal overdose were seizures, somnolence, nausea, tachycardia,
1493 and vomiting. The largest known ingestion of fluoxetine in adult patients was 8 grams in a
1494 patient who took fluoxetine alone and who subsequently recovered. However, in an adult patient
1495 who took fluoxetine alone, an ingestion as low as 520 mg has been associated with lethal
1496 outcome, but causality has not been established.

1497 Among pediatric patients (ages 3 months to 17 years), there were 156 cases of overdose
1498 involving fluoxetine alone or in combination with other drugs. Six patients died, 127 patients
1499 completely recovered, 1 patient experienced renal failure, and 22 patients had an unknown
1500 outcome. One of the 6 fatalities was a 9-year-old boy who had a history of OCD, Tourette's
1501 Syndrome with tics, attention deficit disorder, and fetal alcohol syndrome. He had been receiving
1502 100 mg of fluoxetine daily for 6 months in addition to clonidine, methylphenidate, and
1503 promethazine. Mixed-drug ingestion or other methods of suicide complicated all 6 overdoses in
1504 children that resulted in fatalities. The largest ingestion in pediatric patients was 3 grams, which
1505 was non-lethal.

1506 Other important adverse events reported with fluoxetine overdose (single or multiple drugs)
 1507 included coma, delirium, ECG abnormalities (such as QT-interval prolongation and ventricular
 1508 tachycardia, including torsades de pointes-type arrhythmias), hypotension, mania, neuroleptic
 1509 malignant syndrome-like events, pyrexia, stupor, and syncope.

1510 **Management of Overdose** — In managing overdose, the possibility of multiple drug
 1511 involvement should be considered. In case of acute overdose, establish and maintain an airway
 1512 and ensure adequate ventilation, which may include intubation. Induction of emesis is not
 1513 recommended as the possibility of obtundation, seizures, or dystonic reactions of the head and
 1514 neck following overdose may create a risk for aspiration. Gastric lavage (after intubation, if
 1515 patient is unconscious) and administration of activated charcoal together with a laxative should
 1516 be considered. Cardiovascular monitoring should commence immediately and should include
 1517 continuous electrocardiographic monitoring to detect possible arrhythmias.

1518 A specific precaution involves patients who are taking or have recently taken SYMBYAX and
 1519 may have ingested excessive quantities of a TCA (tricyclic antidepressant). In such cases,
 1520 accumulation of the parent TCA and/or an active metabolite may increase the possibility of
 1521 serious sequelae and extend the time needed for close medical observation.

1522 Due to the large volume of distribution of olanzapine and fluoxetine, forced diuresis, dialysis,
 1523 hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidote for
 1524 either fluoxetine or olanzapine overdose is known. Hypotension and circulatory collapse should
 1525 be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents.
 1526 Do not use epinephrine, dopamine, or other sympathomimetics with β -agonist activity, since beta
 1527 stimulation may worsen hypotension in the setting of olanzapine-induced alpha blockade.

1528 The physician should consider contacting a poison control center for additional information on
 1529 the treatment of any overdose. Telephone numbers for certified poison control centers are listed
 1530 in the *Physicians' Desk Reference (PDR)*.

1531 **DOSAGE AND ADMINISTRATION**

1532 SYMBYAX should be administered once daily in the evening, generally beginning with the
 1533 6-mg/25-mg capsule. While food has no appreciable effect on the absorption of olanzapine and
 1534 fluoxetine given individually, the effect of food on the absorption of SYMBYAX has not been
 1535 studied. Dosage adjustments, if indicated, can be made according to efficacy and tolerability.
 1536 Antidepressant efficacy was demonstrated with SYMBYAX in a dose range of olanzapine 6 to
 1537 12 mg and fluoxetine 25 to 50 mg (*see CLINICAL STUDIES*).

1538 The safety of doses above 18 mg/75 mg has not been evaluated in clinical studies.

1539 **Special Populations**

1540 The starting dose of SYMBYAX 3 mg/25 mg - 6 mg/25 mg should be used for patients with a
 1541 predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit
 1542 a combination of factors that may slow the metabolism of SYMBYAX (female gender, geriatric
 1543 age, nonsmoking status) or those patients who may be pharmacodynamically sensitive to
 1544 olanzapine. When indicated, dose escalation should be performed with caution in these patients.
 1545 SYMBYAX has not been systematically studied in patients over 65 years of age or in patients
 1546 <18 years of age (*see WARNINGS, Orthostatic Hypotension, PRECAUTIONS, Pediatric Use,*
 1547 *and Geriatric Use, and CLINICAL PHARMACOLOGY, Pharmacokinetics*).

1548 **Treatment of Pregnant Women During the Third Trimester**

1549 Neonates exposed to fluoxetine, a component of SYMBYAX, and other SSRIs or SNRIs, late
 1550 in the third trimester have developed complications requiring prolonged hospitalization,

1551 respiratory support, and tube feeding (*see* PRECAUTIONS). When treating pregnant women
 1552 with fluoxetine during the third trimester, the physician should carefully consider the potential
 1553 risks and benefits of treatment. The physician may consider tapering fluoxetine in the third
 1554 trimester.

1555 **Discontinuation of Treatment with SYMBYAX**

1556 Symptoms associated with discontinuation of fluoxetine, a component of SYMBYAX, and
 1557 other SSRIs and SNRIs, have been reported (*see* PRECAUTIONS). Patients should be monitored
 1558 for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than
 1559 abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a
 1560 decrease in the dose or upon discontinuation of treatment, then resuming the previously
 1561 prescribed dose may be considered. Subsequently, the physician may continue decreasing the
 1562 dose but at a more gradual rate. Plasma fluoxetine and norfluoxetine concentration decrease
 1563 gradually at the conclusion of therapy which may minimize the risk of discontinuation symptoms
 1564 with this drug.

1565 **HOW SUPPLIED**

1566 SYMBYAX capsules are supplied in 3/25-, 6/25-, 6/50-, 12/25-, and 12/50-mg (mg equivalent
 1567 olanzapine/mg equivalent fluoxetine^a) strengths.
 1568

SYMBYAX	CAPSULE STRENGTH				
	3 mg/25 mg	6 mg/25 mg	6 mg/50 mg	12 mg/25 mg	12 mg/50 mg
Color	Peach & Light Yellow	Mustard Yellow & Light Yellow	Mustard Yellow & Light Grey	Red & Light Yellow	Red & Light Grey
Capsule No.	PU3230	PU3231	PU3233	PU3232	PU3234
Identification	Lilly 3230 3/25	Lilly 3231 6/25	Lilly 3233 6/50	Lilly 3232 12/25	Lilly 3234 12/50
NDC Codes					
Bottles 30	0002-3230-30	0002-3231-30	0002-3233-30	0002-3232-30	0002-3234-30
Bottles 100		0002-3231-02	0002-3233-02	0002-3232-02	0002-3234-02
Bottles 1000		0002-3231-04	0002-3233-04	0002-3232-04	0002-3234-04
Blisters ID ^b 100		0002-3231-33	0002-3233-33	0002-3232-33	0002-3234-33

1569 ^a Fluoxetine base equivalent.

1570 ^b IDENTI-DOSE[®], Unit Dose Medication, Lilly.

1571
 1572 Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room
 1573 Temperature].

1574 Keep tightly closed and protect from moisture.

1575 Literature revised January 16, 2008

Formatted: Not Highlight

1576 **Eli Lilly and Company**
 1577 **Indianapolis, IN 46285**

1578 **www.SYMBYAX.com**
 1579
 1580

Copyright © 2003, 2007, Eli Lilly and Company. All rights reserved.

PV 5420 AMP

PRINTED IN USA

1581