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PROZAC[®]
FLUOXETINE CAPSULES, USP
FLUOXETINE ORAL SOLUTION, USP
FLUOXETINE DELAYED-RELEASE CAPSULES, USP

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WARNING

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Suicidality and Antidepressant Drugs — Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Prozac or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior.

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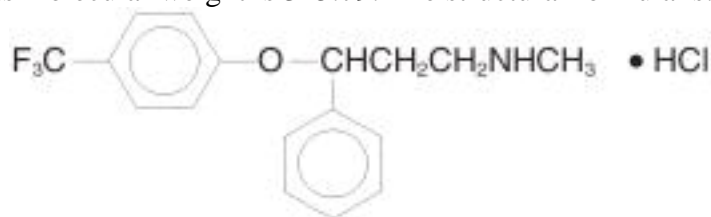
Families and caregivers should be advised of the need for close observation and communication with the prescriber. Prozac is approved for use in pediatric patients with MDD and obsessive compulsive disorder (OCD). (See WARNINGS, Clinical Worsening and Suicide Risk, PRECAUTIONS, Information for Patients, and PRECAUTIONS, Pediatric Use.)

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DESCRIPTION

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Prozac[®] (fluoxetine capsules, USP and fluoxetine oral solution, USP) is a psychotropic drug for oral administration. It is also marketed for the treatment of premenstrual dysphoric disorder (Sarafem[®], fluoxetine hydrochloride). It is designated (±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-*p*-tolyl)oxy]propylamine hydrochloride and has the empirical formula of C₁₇H₁₈F₃NO•HCl. Its molecular weight is 345.79. The structural formula is:



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

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Each Pulvule[®] contains fluoxetine hydrochloride equivalent to 10 mg (32.3 μmol), 20 mg (64.7 μmol), or 40 mg (129.3 μmol) of fluoxetine. The Pulvules also contain starch, gelatin, silicone, titanium dioxide, iron oxide, and other inactive ingredients. The 10- and 20-mg Pulvules also contain FD&C Blue No. 1, and the 40-mg Pulvule also contains FD&C Blue No. 1 and FD&C Yellow No. 6.

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The oral solution contains fluoxetine hydrochloride equivalent to 20 mg/5 mL (64.7 μmol) of fluoxetine. It also contains alcohol 0.23%, benzoic acid, flavoring agent, glycerin, purified water, and sucrose.

40 Prozac Weekly™ capsules, a delayed-release formulation, contain enteric-coated pellets of
41 fluoxetine hydrochloride equivalent to 90 mg (291 μmol) of fluoxetine. The capsules also
42 contain D&C Yellow No. 10, FD&C Blue No. 2, gelatin, hypromellose, hypromellose acetate
43 succinate, sodium lauryl sulfate, sucrose, sugar spheres, talc, titanium dioxide, triethyl citrate,
44 and other inactive ingredients.

45 CLINICAL PHARMACOLOGY

46 Pharmacodynamics

47 The antidepressant, antiobsessive compulsive, and antibulimic actions of fluoxetine are
48 presumed to be linked to its inhibition of CNS neuronal uptake of serotonin. Studies at clinically
49 relevant doses in man have demonstrated that fluoxetine blocks the uptake of serotonin into
50 human platelets. Studies in animals also suggest that fluoxetine is a much more potent uptake
51 inhibitor of serotonin than of norepinephrine.

52 Antagonism of muscarinic, histaminergic, and α_1 -adrenergic receptors has been hypothesized
53 to be associated with various anticholinergic, sedative, and cardiovascular effects of classical
54 tricyclic antidepressant (TCA) drugs. Fluoxetine binds to these and other membrane receptors
55 from brain tissue much less potently in vitro than do the tricyclic drugs.

56 Absorption, Distribution, Metabolism, and Excretion

57 **Systemic bioavailability** — In man, following a single oral 40-mg dose, peak plasma
58 concentrations of fluoxetine from 15 to 55 ng/mL are observed after 6 to 8 hours.

59 The Pulvule, oral solution, and Prozac Weekly capsule dosage forms of fluoxetine are
60 bioequivalent. Food does not appear to affect the systemic bioavailability of fluoxetine, although
61 it may delay its absorption by 1 to 2 hours, which is probably not clinically significant. Thus,
62 fluoxetine may be administered with or without food. Prozac Weekly capsules, a delayed-release
63 formulation, contain enteric-coated pellets that resist dissolution until reaching a segment of the
64 gastrointestinal tract where the pH exceeds 5.5. The enteric coating delays the onset of
65 absorption of fluoxetine 1 to 2 hours relative to the immediate-release formulations.

66 **Protein binding** — Over the concentration range from 200 to 1000 ng/mL, approximately
67 94.5% of fluoxetine is bound in vitro to human serum proteins, including albumin and
68 α_1 -glycoprotein. The interaction between fluoxetine and other highly protein-bound drugs has
69 not been fully evaluated, but may be important (*see* PRECAUTIONS).

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

74 **Metabolism** — Fluoxetine is extensively metabolized in the liver to norfluoxetine and a
75 number of other unidentified metabolites. The only identified active metabolite, norfluoxetine, is
76 formed by demethylation of fluoxetine. In animal models, *S*-norfluoxetine is a potent and
77 selective inhibitor of serotonin uptake and has activity essentially equivalent to *R*- or
78 *S*-fluoxetine. *R*-norfluoxetine is significantly less potent than the parent drug in the inhibition of
79 serotonin uptake. The primary route of elimination appears to be hepatic metabolism to inactive
80 metabolites excreted by the kidney.

81 **Clinical issues related to metabolism/elimination** — The complexity of the metabolism of
82 fluoxetine has several consequences that may potentially affect fluoxetine's clinical use.

83 **Variability in metabolism** — A subset (about 7%) of the population has reduced activity of the
84 drug-metabolizing enzyme cytochrome P450 2D6 (CYP2D6). Such individuals are referred to as

85 “poor metabolizers” of drugs such as debrisoquin, dextromethorphan, and the TCAs. In a study
86 involving labeled and unlabeled enantiomers administered as a racemate, these individuals
87 metabolized *S*-fluoxetine at a slower rate and thus achieved higher concentrations of
88 *S*-fluoxetine. Consequently, concentrations of *S*-norfluoxetine at steady state were lower. The
89 metabolism of *R*-fluoxetine in these poor metabolizers appears normal. When compared with
90 normal metabolizers, the total sum at steady state of the plasma concentrations of the 4 active
91 enantiomers was not significantly greater among poor metabolizers. Thus, the net
92 pharmacodynamic activities were essentially the same. Alternative, nonsaturable pathways
93 (non-2D6) also contribute to the metabolism of fluoxetine. This explains how fluoxetine
94 achieves a steady-state concentration rather than increasing without limit.

95 Because fluoxetine’s metabolism, like that of a number of other compounds including TCAs
96 and other selective serotonin reuptake inhibitors (SSRIs), involves the CYP2D6 system,
97 concomitant therapy with drugs also metabolized by this enzyme system (such as the TCAs) may
98 lead to drug interactions (*see Drug Interactions under PRECAUTIONS*).

99 Accumulation and slow elimination — The relatively slow elimination of fluoxetine
100 (elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic
101 administration) and its active metabolite, norfluoxetine (elimination half-life of 4 to 16 days after
102 acute and chronic administration), leads to significant accumulation of these active species in
103 chronic use and delayed attainment of steady state, even when a fixed dose is used. After 30 days
104 of dosing at 40 mg/day, plasma concentrations of fluoxetine in the range of 91 to 302 ng/mL and
105 norfluoxetine in the range of 72 to 258 ng/mL have been observed. Plasma concentrations of
106 fluoxetine were higher than those predicted by single-dose studies, because fluoxetine’s
107 metabolism is not proportional to dose. Norfluoxetine, however, appears to have linear
108 pharmacokinetics. Its mean terminal half-life after a single dose was 8.6 days and after multiple
109 dosing was 9.3 days. Steady-state levels after prolonged dosing are similar to levels seen at 4 to 5
110 weeks.

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

117 **Weekly dosing** — Administration of Prozac Weekly once weekly results in increased
118 fluctuation between peak and trough concentrations of fluoxetine and norfluoxetine compared
119 with once-daily dosing [for fluoxetine: 24% (daily) to 164% (weekly) and for norfluoxetine:
120 17% (daily) to 43% (weekly)]. Plasma concentrations may not necessarily be predictive of
121 clinical response. Peak concentrations from once-weekly doses of Prozac Weekly capsules of
122 fluoxetine are in the range of the average concentration for 20-mg once-daily dosing. Average
123 trough concentrations are 76% lower for fluoxetine and 47% lower for norfluoxetine than the
124 concentrations maintained by 20-mg once-daily dosing. Average steady-state concentrations of
125 either once-daily or once-weekly dosing are in relative proportion to the total dose administered.
126 Average steady-state fluoxetine concentrations are approximately 50% lower following the
127 once-weekly regimen compared with the once-daily regimen.

128 C_{\max} for fluoxetine following the 90-mg dose was approximately 1.7-fold higher than the C_{\max}
129 value for the established 20-mg once-daily regimen following transition the next day to the
130 once-weekly regimen. In contrast, when the first 90-mg once-weekly dose and the last 20-mg

131 once-daily dose were separated by 1 week, C_{max} values were similar. Also, there was a transient
132 increase in the average steady-state concentrations of fluoxetine observed following transition
133 the next day to the once-weekly regimen. From a pharmacokinetic perspective, it may be better
134 to separate the first 90-mg weekly dose and the last 20-mg once-daily dose by 1 week (*see*
135 DOSAGE AND ADMINISTRATION).

136 **Liver disease** — As might be predicted from its primary site of metabolism, liver impairment
137 can affect the elimination of fluoxetine. The elimination half-life of fluoxetine was prolonged in
138 a study of cirrhotic patients, with a mean of 7.6 days compared with the range of 2 to 3 days seen
139 in subjects without liver disease; norfluoxetine elimination was also delayed, with a mean
140 duration of 12 days for cirrhotic patients compared with the range of 7 to 9 days in normal
141 subjects. This suggests that the use of fluoxetine in patients with liver disease must be
142 approached with caution. If fluoxetine is administered to patients with liver disease, a lower or
143 less frequent dose should be used (*see* PRECAUTIONS *and* DOSAGE AND
144 ADMINISTRATION).

145 **Renal disease** — In depressed patients on dialysis (N=12), fluoxetine administered as 20 mg
146 once daily for 2 months produced steady-state fluoxetine and norfluoxetine plasma
147 concentrations comparable with those seen in patients with normal renal function. While the
148 possibility exists that renally excreted metabolites of fluoxetine may accumulate to higher levels
149 in patients with severe renal dysfunction, use of a lower or less frequent dose is not routinely
150 necessary in renally impaired patients (*see* Use in Patients with Concomitant Illness *under*
151 PRECAUTIONS *and* DOSAGE AND ADMINISTRATION).

152 Age

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

163 Pediatric pharmacokinetics (children and adolescents) — Fluoxetine pharmacokinetics were
164 evaluated in 21 pediatric patients (10 children ages 6 to <13, 11 adolescents ages 13 to <18)
165 diagnosed with major depressive disorder or obsessive compulsive disorder (OCD). Fluoxetine
166 20 mg/day was administered for up to 62 days. The average steady-state concentrations of
167 fluoxetine in these children were 2-fold higher than in adolescents (171 and 86 ng/mL,
168 respectively). The average norfluoxetine steady-state concentrations in these children were
169 1.5-fold higher than in adolescents (195 and 113 ng/mL, respectively). These differences can be
170 almost entirely explained by differences in weight. No gender-associated difference in fluoxetine
171 pharmacokinetics was observed. Similar ranges of fluoxetine and norfluoxetine plasma
172 concentrations were observed in another study in 94 pediatric patients (ages 8 to <18) diagnosed
173 with major depressive disorder.

174 Higher average steady-state fluoxetine and norfluoxetine concentrations were observed in
175 children relative to adults; however, these concentrations were within the range of concentrations
176 observed in the adult population. As in adults, fluoxetine and norfluoxetine accumulated

177 extensively following multiple oral dosing; steady-state concentrations were achieved within 3 to
178 4 weeks of daily dosing.

179

CLINICAL TRIALS

180 Major Depressive Disorder

181 Daily Dosing

182 Adult — The efficacy of Prozac for the treatment of patients with major depressive disorder
183 (≥ 18 years of age) has been studied in 5- and 6-week placebo-controlled trials. Prozac was
184 shown to be significantly more effective than placebo as measured by the Hamilton Depression
185 Rating Scale (HAM-D). Prozac was also significantly more effective than placebo on the
186 HAM-D subscores for depressed mood, sleep disturbance, and the anxiety subfactor.

187 Two 6-week controlled studies (N=671, randomized) comparing Prozac 20 mg and placebo
188 have shown Prozac 20 mg daily to be effective in the treatment of elderly patients (≥ 60 years of
189 age) with major depressive disorder. In these studies, Prozac produced a significantly higher rate
190 of response and remission as defined, respectively, by a 50% decrease in the HAM-D score and a
191 total endpoint HAM-D score of ≤ 8 . Prozac was well tolerated and the rate of treatment
192 discontinuations due to adverse events did not differ between Prozac (12%) and placebo (9%).

193 A study was conducted involving depressed outpatients who had responded (modified
194 HAMD-17 score of ≤ 7 during each of the last 3 weeks of open-label treatment and absence of
195 major depressive disorder by DSM-III-R criteria) by the end of an initial 12-week
196 open-treatment phase on Prozac 20 mg/day. These patients (N=298) were randomized to
197 continuation on double-blind Prozac 20 mg/day or placebo. At 38 weeks (50 weeks total), a
198 statistically significantly lower relapse rate (defined as symptoms sufficient to meet a diagnosis
199 of major depressive disorder for 2 weeks or a modified HAMD-17 score of ≥ 14 for 3 weeks) was
200 observed for patients taking Prozac compared with those on placebo.

201 Pediatric (children and adolescents) — The efficacy of Prozac 20 mg/day for the treatment of
202 major depressive disorder in pediatric outpatients (N=315 randomized; 170 children ages 8 to
203 < 13 , 145 adolescents ages 13 to ≤ 18) has been studied in two 8- to 9-week placebo-controlled
204 clinical trials.

205 In both studies independently, Prozac produced a statistically significantly greater mean
206 change on the Childhood Depression Rating Scale-Revised (CDRS-R) total score from baseline
207 to endpoint than did placebo.

208 Subgroup analyses on the CDRS-R total score did not suggest any differential responsiveness
209 on the basis of age or gender.

210 Weekly dosing for maintenance/continuation treatment

211 A longer-term study was conducted involving adult outpatients meeting DSM-IV criteria for
212 major depressive disorder who had responded (defined as having a modified HAMD-17 score of
213 ≤ 9 , a CGI-Severity rating of ≤ 2 , and no longer meeting criteria for major depressive disorder) for
214 3 consecutive weeks at the end of 13 weeks of open-label treatment with Prozac 20 mg once
215 daily. These patients were randomized to double-blind, once-weekly continuation treatment with
216 Prozac Weekly, Prozac 20 mg once daily, or placebo. Prozac Weekly once weekly and Prozac
217 20 mg once daily demonstrated superior efficacy (having a significantly longer time to relapse of
218 depressive symptoms) compared with placebo for a period of 25 weeks. However, the
219 equivalence of these 2 treatments during continuation therapy has not been established.

220 **Obsessive Compulsive Disorder**

221 Adult — The effectiveness of Prozac for the treatment of obsessive compulsive disorder
 222 (OCD) was demonstrated in two 13-week, multicenter, parallel group studies (Studies 1 and 2) of
 223 adult outpatients who received fixed Prozac doses of 20, 40, or 60 mg/day (on a once-a-day
 224 schedule, in the morning) or placebo. Patients in both studies had moderate to severe OCD
 225 (DSM-III-R), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale
 226 (YBOCS, total score) ranging from 22 to 26. In Study 1, patients receiving Prozac experienced
 227 mean reductions of approximately 4 to 6 units on the YBOCS total score, compared with a 1-unit
 228 reduction for placebo patients. In Study 2, patients receiving Prozac experienced mean
 229 reductions of approximately 4 to 9 units on the YBOCS total score, compared with a 1-unit
 230 reduction for placebo patients. While there was no indication of a dose-response relationship for
 231 effectiveness in Study 1, a dose-response relationship was observed in Study 2, with numerically
 232 better responses in the 2 higher dose groups. The following table provides the outcome
 233 classification by treatment group on the Clinical Global Impression (CGI) improvement scale for
 234 Studies 1 and 2 combined:

235
 236 **Outcome Classification (%) on CGI Improvement Scale for**
 237 **Completers in Pool of Two OCD Studies**

Outcome Classification	Placebo	Prozac		
		20 mg	40 mg	60 mg
Worse	8%	0%	0%	0%
No change	64%	41%	33%	29%
Minimally improved	17%	23%	28%	24%
Much improved	8%	28%	27%	28%
Very much improved	3%	8%	12%	19%

238
 239 Exploratory analyses for age and gender effects on outcome did not suggest any differential
 240 responsiveness on the basis of age or sex.

241 Pediatric (children and adolescents) — In one 13-week clinical trial in pediatric patients
 242 (N=103 randomized; 75 children ages 7 to <13, 28 adolescents ages 13 to <18) with OCD,
 243 patients received Prozac 10 mg/day for 2 weeks, followed by 20 mg/day for 2 weeks. The dose
 244 was then adjusted in the range of 20 to 60 mg/day on the basis of clinical response and
 245 tolerability. Prozac produced a statistically significantly greater mean change from baseline to
 246 endpoint than did placebo as measured by the Children's Yale-Brown Obsessive Compulsive
 247 Scale (CY-BOCS).

248 Subgroup analyses on outcome did not suggest any differential responsiveness on the basis of
 249 age or gender.

250 **Bulimia Nervosa**

251 The effectiveness of Prozac for the treatment of bulimia was demonstrated in two 8-week and
 252 one 16-week, multicenter, parallel group studies of adult outpatients meeting DSM-III-R criteria
 253 for bulimia. Patients in the 8-week studies received either 20 or 60 mg/day of Prozac or placebo
 254 in the morning. Patients in the 16-week study received a fixed Prozac dose of 60 mg/day (once a
 255 day) or placebo. Patients in these 3 studies had moderate to severe bulimia with median
 256 binge-eating and vomiting frequencies ranging from 7 to 10 per week and 5 to 9 per week,
 257 respectively. In these 3 studies, Prozac 60 mg, but not 20 mg, was statistically significantly
 258 superior to placebo in reducing the number of binge-eating and vomiting episodes per week. The
 259 statistically significantly superior effect of 60 mg versus placebo was present as early as Week 1

260 and persisted throughout each study. The Prozac-related reduction in bulimic episodes appeared
261 to be independent of baseline depression as assessed by the Hamilton Depression Rating Scale.
262 In each of these 3 studies, the treatment effect, as measured by differences between Prozac
263 60 mg and placebo on median reduction from baseline in frequency of bulimic behaviors at
264 endpoint, ranged from 1 to 2 episodes per week for binge-eating and 2 to 4 episodes per week for
265 vomiting. The size of the effect was related to baseline frequency, with greater reductions seen in
266 patients with higher baseline frequencies. Although some patients achieved freedom from
267 binge-eating and purging as a result of treatment, for the majority, the benefit was a partial
268 reduction in the frequency of binge-eating and purging.

269 In a longer-term trial, 150 patients meeting DSM-IV criteria for bulimia nervosa, purging
270 subtype, who had responded during a single-blind, 8-week acute treatment phase with Prozac
271 60 mg/day, were randomized to continuation of Prozac 60 mg/day or placebo, for up to 52 weeks
272 of observation for relapse. Response during the single-blind phase was defined by having
273 achieved at least a 50% decrease in vomiting frequency compared with baseline. Relapse during
274 the double-blind phase was defined as a persistent return to baseline vomiting frequency or
275 physician judgment that the patient had relapsed. Patients receiving continued Prozac 60 mg/day
276 experienced a significantly longer time to relapse over the subsequent 52 weeks compared with
277 those receiving placebo.

278 **Panic Disorder**

279 The effectiveness of Prozac in the treatment of panic disorder was demonstrated in 2
280 double-blind, randomized, placebo-controlled, multicenter studies of adult outpatients who had a
281 primary diagnosis of panic disorder (DSM-IV), with or without agoraphobia.

282 Study 1 (N=180 randomized) was a 12-week flexible-dose study. Prozac was initiated at
283 10 mg/day for the first week, after which patients were dosed in the range of 20 to 60 mg/day on
284 the basis of clinical response and tolerability. A statistically significantly greater percentage of
285 Prozac-treated patients were free from panic attacks at endpoint than placebo-treated patients,
286 42% versus 28%, respectively.

287 Study 2 (N=214 randomized) was a 12-week flexible-dose study. Prozac was initiated at
288 10 mg/day for the first week, after which patients were dosed in a range of 20 to 60 mg/day on
289 the basis of clinical response and tolerability. A statistically significantly greater percentage of
290 Prozac-treated patients were free from panic attacks at endpoint than placebo-treated patients,
291 62% versus 44%, respectively.

292

INDICATIONS AND USAGE

293 **Major Depressive Disorder**

294 Prozac is indicated for the treatment of major depressive disorder.

295 Adult — The efficacy of Prozac was established in 5- and 6-week trials with depressed adult
296 and geriatric outpatients (≥ 18 years of age) whose diagnoses corresponded most closely to the
297 DSM-III (currently DSM-IV) category of major depressive disorder (*see* CLINICAL TRIALS).

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

304 The effects of Prozac in hospitalized depressed patients have not been adequately studied.

305 The efficacy of Prozac 20 mg once daily in maintaining a response in major depressive
306 disorder for up to 38 weeks following 12 weeks of open-label acute treatment (50 weeks total)
307 was demonstrated in a placebo-controlled trial.

308 The efficacy of Prozac Weekly once weekly in maintaining a response in major depressive
309 disorder has been demonstrated in a placebo-controlled trial for up to 25 weeks following
310 open-label acute treatment of 13 weeks with Prozac 20 mg daily for a total treatment of 38
311 weeks. However, it is unknown whether or not Prozac Weekly given on a once-weekly basis
312 provides the same level of protection from relapse as that provided by Prozac 20 mg daily
313 (*see CLINICAL TRIALS*).

314 Pediatric (children and adolescents) — The efficacy of Prozac in children and adolescents was
315 established in two 8- to 9-week placebo-controlled clinical trials in depressed outpatients whose
316 diagnoses corresponded most closely to the DSM-III-R or DSM-IV category of major depressive
317 disorder (*see CLINICAL TRIALS*).

318 The usefulness of the drug in adult and pediatric patients receiving fluoxetine for extended
319 periods should be reevaluated periodically.

320 **Obsessive Compulsive Disorder**

321 Adult — Prozac is indicated for the treatment of obsessions and compulsions in patients with
322 obsessive compulsive disorder (OCD), as defined in the DSM-III-R; i.e., the obsessions or
323 compulsions cause marked distress, are time-consuming, or significantly interfere with social or
324 occupational functioning.

325 The efficacy of Prozac was established in 13-week trials with obsessive compulsive outpatients
326 whose diagnoses corresponded most closely to the DSM-III-R category of OCD (*see CLINICAL*
327 *TRIALS*).

328 OCD is characterized by recurrent and persistent ideas, thoughts, impulses, or images
329 (obsessions) that are ego-dystonic and/or repetitive, purposeful, and intentional behaviors
330 (compulsions) that are recognized by the person as excessive or unreasonable.

331 The effectiveness of Prozac in long-term use, i.e., for more than 13 weeks, has not been
332 systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to use
333 Prozac for extended periods should periodically reevaluate the long-term usefulness of the drug
334 for the individual patient (*see DOSAGE AND ADMINISTRATION*).

335 Pediatric (children and adolescents) — The efficacy of Prozac in children and adolescents was
336 established in a 13-week, dose titration, clinical trial in patients with OCD, as defined in
337 DSM-IV (*see CLINICAL TRIALS*).

338 **Bulimia Nervosa**

339 Prozac is indicated for the treatment of binge-eating and vomiting behaviors in patients with
340 moderate to severe bulimia nervosa.

341 The efficacy of Prozac was established in 8- to 16-week trials for adult outpatients with
342 moderate to severe bulimia nervosa, i.e., at least 3 bulimic episodes per week for 6 months (*see*
343 *CLINICAL TRIALS*).

344 The efficacy of Prozac 60 mg/day in maintaining a response, in patients with bulimia who
345 responded during an 8-week acute treatment phase while taking Prozac 60 mg/day and were then
346 observed for relapse during a period of up to 52 weeks, was demonstrated in a placebo-controlled
347 trial (*see CLINICAL TRIALS*). Nevertheless, the physician who elects to use Prozac for
348 extended periods should periodically reevaluate the long-term usefulness of the drug for the
349 individual patient (*see DOSAGE AND ADMINISTRATION*).

350 **Panic Disorder**

351 Prozac is indicated for the treatment of panic disorder, with or without agoraphobia, as defined
 352 in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks, and
 353 associated concern about having additional attacks, worry about the implications or
 354 consequences of the attacks, and/or a significant change in behavior related to the attacks.

355 The efficacy of Prozac was established in two 12-week clinical trials in patients whose
 356 diagnoses corresponded to the DSM-IV category of panic disorder (*see* CLINICAL TRIALS).

357 Panic disorder (DSM-IV) is characterized by recurrent, unexpected panic attacks, i.e., a
 358 discrete period of intense fear or discomfort in which 4 or more of the following symptoms
 359 develop abruptly and reach a peak within 10 minutes: 1) palpitations, pounding heart, or
 360 accelerated heart rate; 2) sweating; 3) trembling or shaking; 4) sensations of shortness of breath
 361 or smothering; 5) feeling of choking; 6) chest pain or discomfort; 7) nausea or abdominal
 362 distress; 8) feeling dizzy, unsteady, lightheaded, or faint; 9) fear of losing control; 10) fear of
 363 dying; 11) paresthesias (numbness or tingling sensations); 12) chills or hot flashes.

364 The effectiveness of Prozac in long-term use, i.e., for more than 12 weeks, has not been
 365 established in placebo-controlled trials. Therefore, the physician who elects to use Prozac for
 366 extended periods should periodically reevaluate the long-term usefulness of the drug for the
 367 individual patient (*see* DOSAGE AND ADMINISTRATION).

368 **CONTRAINDICATIONS**

369 Prozac is contraindicated in patients known to be hypersensitive to it.

370 **Monoamine oxidase inhibitors** — There have been reports of serious, sometimes fatal,
 371 reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid
 372 fluctuations of vital signs, and mental status changes that include extreme agitation progressing
 373 to delirium and coma) in patients receiving fluoxetine in combination with a monoamine oxidase
 374 inhibitor (MAOI), and in patients who have recently discontinued fluoxetine and are then started
 375 on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome.
 376 Therefore, Prozac should not be used in combination with an MAOI, or within a minimum of 14
 377 days of discontinuing therapy with an MAOI. Since fluoxetine and its major metabolite have
 378 very long elimination half-lives, at least 5 weeks [perhaps longer, especially if fluoxetine has
 379 been prescribed chronically and/or at higher doses (*see* Accumulation and slow elimination
 380 *under* CLINICAL PHARMACOLOGY)] should be allowed after stopping Prozac before starting
 381 an MAOI.

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

384 **Thioridazine** — Thioridazine should not be administered with Prozac or within a minimum of
 385 5 weeks after Prozac has been discontinued (*see* WARNINGS).

386 **WARNINGS**

387 **Clinical Worsening and Suicide Risk** — Patients with major depressive disorder (MDD),
 388 both adult and pediatric, may experience worsening of their depression and/or the emergence of
 389 suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they
 390 are taking antidepressant medications, and this risk may persist until significant remission
 391 occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these
 392 disorders themselves are the strongest predictors of suicide. There has been a long-standing
 393 concern, however, that antidepressants may have a role in inducing worsening of depression and
 394 the emergence of suicidality in certain patients during the early phases of treatment. Pooled
 395 analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others)

396 showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in
 397 children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and
 398 other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality
 399 with antidepressants compared to placebo in adults beyond age 24; there was a reduction with
 400 antidepressants compared to placebo in adults aged 65 and older.

401 The pooled analyses of placebo-controlled trials in children and adolescents with MDD,
 402 obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24
 403 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of
 404 placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of
 405 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000
 406 patients. There was considerable variation in risk of suicidality among drugs, but a tendency
 407 toward an increase in the younger patients for almost all drugs studied. There were differences in
 408 absolute risk of suicidality across the different indications, with the highest incidence in MDD.
 409 The risk differences (drug versus placebo), however, were relatively stable within age strata and
 410 across indications. These risk differences (drug-placebo difference in the number of cases of
 411 suicidality per 1000 patients treated) are provided in Table 1.

412 **Table 1**

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

414
 415 No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but
 416 the number was not sufficient to reach any conclusion about drug effect on suicide.

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

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

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

431 Consideration should be given to changing the therapeutic regimen, including possibly
 432 discontinuing the medication, in patients whose depression is persistently worse, or who are

433 experiencing emergent suicidality or symptoms that might be precursors to worsening depression
434 or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the
435 patient's presenting symptoms.

436 If the decision has been made to discontinue treatment, medication should be tapered, as
437 rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with
438 certain symptoms (*see* PRECAUTIONS *and* DOSAGE AND ADMINISTRATION,
439 Discontinuation of Treatment with Prozac, for a description of the risks of discontinuation of
440 Prozac).

441 **Families and caregivers of patients being treated with antidepressants for major**
442 **depressive disorder or other indications, both psychiatric and nonpsychiatric, should be**
443 **alerted about the need to monitor patients for the emergence of agitation, irritability,**
444 **unusual changes in behavior, and the other symptoms described above, as well as the**
445 **emergence of suicidality, and to report such symptoms immediately to health care**
446 **providers. Such monitoring should include daily observation by families and caregivers.**
447 Prescriptions for Prozac should be written for the smallest quantity of capsules, or liquid
448 consistent with good patient management, in order to reduce the risk of overdose.

449 It should be noted that Prozac is approved in the pediatric population only for major depressive
450 disorder and obsessive compulsive disorder.

451 **Screening Patients for Bipolar Disorder** — A major depressive episode may be the initial
452 presentation of bipolar disorder. It is generally believed (though not established in controlled
453 trials) that treating such an episode with an antidepressant alone may increase the likelihood of
454 precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the
455 symptoms described above represent such a conversion is unknown. However, prior to initiating
456 treatment with an antidepressant, patients with depressive symptoms should be adequately
457 screened to determine if they are at risk for bipolar disorder; such screening should include a
458 detailed psychiatric history, including a family history of suicide, bipolar disorder, and
459 depression. It should be noted that Prozac is not approved for use in treating bipolar depression.

460 **Rash and Possibly Allergic Events** — In US fluoxetine clinical trials as of May 8, 1995, 7%
461 of 10,782 patients developed various types of rashes and/or urticaria. Among the cases of rash
462 and/or urticaria reported in premarketing clinical trials, almost a third were withdrawn from
463 treatment because of the rash and/or systemic signs or symptoms associated with the rash.
464 Clinical findings reported in association with rash include fever, leukocytosis, arthralgias,
465 edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild
466 transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine
467 and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these
468 events were reported to recover completely.

469 In premarketing clinical trials, 2 patients are known to have developed a serious cutaneous
470 systemic illness. In neither patient was there an unequivocal diagnosis, but one was considered to
471 have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was
472 considered variously to be a vasculitis or erythema multiforme. Other patients have had systemic
473 syndromes suggestive of serum sickness.

474 Since the introduction of Prozac, systemic events, possibly related to vasculitis and including
475 lupus-like syndrome, have developed in patients with rash. Although these events are rare, they
476 may be serious, involving the lung, kidney, or liver. Death has been reported to occur in
477 association with these systemic events.

478 Anaphylactoid events, including bronchospasm, angioedema, laryngospasm, and urticaria
479 alone and in combination, have been reported.

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

483 Whether these systemic events and rash have a common underlying cause or are due to
484 different etiologies or pathogenic processes is not known. Furthermore, a specific underlying
485 immunologic basis for these events has not been identified. Upon the appearance of rash or of
486 other possibly allergic phenomena for which an alternative etiology cannot be identified, Prozac
487 should be discontinued.

488 **Serotonin Syndrome** — The development of a potentially life-threatening serotonin syndrome
489 may occur with SNRIs and SSRIs, including Prozac treatment, particularly with concomitant use
490 of serotonergic drugs (including triptans) and with drugs which impair metabolism of serotonin
491 (including MAOIs). Serotonin syndrome symptoms may include mental status changes (e.g.,
492 agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure,
493 hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or
494 gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

495 The concomitant use of Prozac with MAOIs intended to treat depression is contraindicated (*see*
496 **CONTRAINDICATIONS and Drug Interactions under PRECAUTIONS**).

497 If concomitant treatment Prozac with a 5-hydroxytryptamine receptor agonist (triptan) is
498 clinically warranted, careful observation of the patient is advised, particularly during treatment
499 initiation and dose increases (*see Drug Interactions under PRECAUTIONS*).

500 The concomitant use of Prozac with serotonin precursors (such as tryptophan) is not
501 recommended (*see Drug Interactions under PRECAUTIONS*).

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

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

513

PRECAUTIONS

514 General

515 **Abnormal Bleeding** — Published case reports have documented the occurrence of bleeding
516 episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake.
517 Subsequent epidemiological studies, both of the case-control and cohort design, have
518 demonstrated an association between use of psychotropic drugs that interfere with serotonin
519 reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of
520 a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding (*see*
521 **DRUG INTERACTIONS**). Although these studies focused on upper gastrointestinal bleeding,
522 there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should

523 be cautioned regarding the risk of bleeding associated with the concomitant use of Prozac with
524 NSAIDs, aspirin, or other drugs that affect coagulation.

525 **Anxiety and Insomnia** — In US placebo-controlled clinical trials for major depressive
526 disorder, 12% to 16% of patients treated with Prozac and 7% to 9% of patients treated with
527 placebo reported anxiety, nervousness, or insomnia.

528 In US placebo-controlled clinical trials for OCD, insomnia was reported in 28% of patients
529 treated with Prozac and in 22% of patients treated with placebo. Anxiety was reported in 14% of
530 patients treated with Prozac and in 7% of patients treated with placebo.

531 In US placebo-controlled clinical trials for bulimia nervosa, insomnia was reported in 33% of
532 patients treated with Prozac 60 mg, and 13% of patients treated with placebo. Anxiety and
533 nervousness were reported, respectively, in 15% and 11% of patients treated with Prozac 60 mg
534 and in 9% and 5% of patients treated with placebo.

535 Among the most common adverse events associated with discontinuation (incidence at least
536 twice that for placebo and at least 1% for Prozac in clinical trials collecting only a primary event
537 associated with discontinuation) in US placebo-controlled fluoxetine clinical trials were anxiety
538 (2% in OCD), insomnia (1% in combined indications and 2% in bulimia), and nervousness (1%
539 in major depressive disorder) (*see* Table 4).

540 **Altered Appetite and Weight** — Significant weight loss, especially in underweight depressed
541 or bulimic patients may be an undesirable result of treatment with Prozac.

542 In US placebo-controlled clinical trials for major depressive disorder, 11% of patients treated
543 with Prozac and 2% of patients treated with placebo reported anorexia (decreased appetite).
544 Weight loss was reported in 1.4% of patients treated with Prozac and in 0.5% of patients treated
545 with placebo. However, only rarely have patients discontinued treatment with Prozac because of
546 anorexia or weight loss (*see also* Pediatric Use *under* PRECAUTIONS).

547 In US placebo-controlled clinical trials for OCD, 17% of patients treated with Prozac and 10%
548 of patients treated with placebo reported anorexia (decreased appetite). One patient discontinued
549 treatment with Prozac because of anorexia (*see also* Pediatric Use *under* PRECAUTIONS).

550 In US placebo-controlled clinical trials for bulimia nervosa, 8% of patients treated with Prozac
551 60 mg and 4% of patients treated with placebo reported anorexia (decreased appetite). Patients
552 treated with Prozac 60 mg on average lost 0.45 kg compared with a gain of 0.16 kg by patients
553 treated with placebo in the 16-week double-blind trial. Weight change should be monitored
554 during therapy.

555 **Activation of Mania/Hypomania** — In US placebo-controlled clinical trials for major
556 depressive disorder, mania/hypomania was reported in 0.1% of patients treated with Prozac and
557 0.1% of patients treated with placebo. Activation of mania/hypomania has also been reported in a
558 small proportion of patients with Major Affective Disorder treated with other marketed drugs
559 effective in the treatment of major depressive disorder (*see also* Pediatric Use *under*
560 PRECAUTIONS).

561 In US placebo-controlled clinical trials for OCD, mania/hypomania was reported in 0.8% of
562 patients treated with Prozac and no patients treated with placebo. No patients reported
563 mania/hypomania in US placebo-controlled clinical trials for bulimia. In all US Prozac clinical
564 trials as of May 8, 1995, 0.7% of 10,782 patients reported mania/hypomania (*see also* Pediatric
565 Use *under* PRECAUTIONS).

566 **Hyponatremia** — Cases of hyponatremia (some with serum sodium lower than 110 mmol/L)
567 have been reported. The hyponatremia appeared to be reversible when Prozac was discontinued.
568 Although these cases were complex with varying possible etiologies, some were possibly due to

569 the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these
570 occurrences have been in older patients and in patients taking diuretics or who were otherwise
571 volume depleted. In two 6-week controlled studies in patients ≥ 60 years of age, 10 of 323
572 fluoxetine patients and 6 of 327 placebo recipients had a lowering of serum sodium below the
573 reference range; this difference was not statistically significant. The lowest observed
574 concentration was 129 mmol/L. The observed decreases were not clinically significant.

575 **Seizures** — In US placebo-controlled clinical trials for major depressive disorder, convulsions
576 (or events described as possibly having been seizures) were reported in 0.1% of patients treated
577 with Prozac and 0.2% of patients treated with placebo. No patients reported convulsions in US
578 placebo-controlled clinical trials for either OCD or bulimia. In all US Prozac clinical trials as of
579 May 8, 1995, 0.2% of 10,782 patients reported convulsions. The percentage appears to be similar
580 to that associated with other marketed drugs effective in the treatment of major depressive
581 disorder. Prozac should be introduced with care in patients with a history of seizures.

582 **The Long Elimination Half-Lives of Fluoxetine and its Metabolites** — Because of the long
583 elimination half-lives of the parent drug and its major active metabolite, changes in dose will not
584 be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose
585 and withdrawal from treatment (*see* CLINICAL PHARMACOLOGY *and* DOSAGE AND
586 ADMINISTRATION).

587 **Use in Patients with Concomitant Illness** — Clinical experience with Prozac in patients with
588 concomitant systemic illness is limited. Caution is advisable in using Prozac in patients with
589 diseases or conditions that could affect metabolism or hemodynamic responses.

590 Fluoxetine has not been evaluated or used to any appreciable extent in patients with a recent
591 history of myocardial infarction or unstable heart disease. Patients with these diagnoses were
592 systematically excluded from clinical studies during the product's premarket testing. However,
593 the electrocardiograms of 312 patients who received Prozac in double-blind trials were
594 retrospectively evaluated; no conduction abnormalities that resulted in heart block were
595 observed. The mean heart rate was reduced by approximately 3 beats/min.

596 In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite,
597 norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A
598 lower or less frequent dose should be used in patients with cirrhosis.

599 Studies in depressed patients on dialysis did not reveal excessive accumulation of fluoxetine or
600 norfluoxetine in plasma (*see* Renal disease *under* CLINICAL PHARMACOLOGY). Use of a
601 lower or less frequent dose for renally impaired patients is not routinely necessary (*see* DOSAGE
602 AND ADMINISTRATION).

603 In patients with diabetes, Prozac may alter glycemic control. Hypoglycemia has occurred
604 during therapy with Prozac, and hyperglycemia has developed following discontinuation of the
605 drug. As is true with many other types of medication when taken concurrently by patients with
606 diabetes, insulin and/or oral hypoglycemic dosage may need to be adjusted when therapy with
607 Prozac is instituted or discontinued.

608 **Interference with Cognitive and Motor Performance** — Any psychoactive drug may impair
609 judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous
610 machinery, including automobiles, until they are reasonably certain that the drug treatment does
611 not affect them adversely.

612 **Discontinuation of Treatment with Prozac** — During marketing of Prozac and other SSRIs
613 and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous
614 reports of adverse events occurring upon discontinuation of these drugs, particularly when

615 abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory
616 disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache,
617 lethargy, emotional lability, insomnia, and hypomania. While these events are generally
618 self-limiting, there have been reports of serious discontinuation symptoms. Patients should be
619 monitored for these symptoms when discontinuing treatment with Prozac. A gradual reduction in
620 the dose rather than abrupt cessation is recommended whenever possible. If intolerable
621 symptoms occur following a decrease in the dose or upon discontinuation of treatment, then
622 resuming the previously prescribed dose may be considered. Subsequently, the physician may
623 continue decreasing the dose but at a more gradual rate. Plasma fluoxetine and norfluoxetine
624 concentration decrease gradually at the conclusion of therapy, which may minimize the risk of
625 discontinuation symptoms with this drug (*see* DOSAGE AND ADMINISTRATION).

626 **Information for Patients**

627 Prescribers or other health professionals should inform patients, their families, and their
628 caregivers about the benefits and risks associated with treatment with Prozac and should counsel
629 them in its appropriate use. A patient Medication Guide about “Antidepressant Medicines,
630 Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions” is available for
631 Prozac. The prescriber or health professional should instruct patients, their families, and their
632 caregivers to read the Medication Guide and should assist them in understanding its contents.
633 Patients should be given the opportunity to discuss the contents of the Medication Guide and to
634 obtain answers to any questions they may have. The complete text of the Medication Guide is
635 reprinted at the end of this document.

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

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

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

651 Because Prozac may impair judgment, thinking, or motor skills, patients should be advised to
652 avoid driving a car or operating hazardous machinery until they are reasonably certain that their
653 performance is not affected.

654 Patients should be advised to inform their physician if they are taking or plan to take any
655 prescription or over-the-counter drugs, or alcohol.

656 Patients should be cautioned about the concomitant use of fluoxetine and NSAIDs, aspirin, or
657 other drugs that affect coagulation since combined use of psychotropic drugs that interfere with
658 serotonin reuptake and these agents have been associated with an increased risk of bleeding.

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

661 Patients should be advised to notify their physician if they are breast-feeding an infant.

662 Patients should be advised to notify their physician if they develop a rash or hives.

663 **Laboratory Tests**

664 There are no specific laboratory tests recommended.

665 **Drug Interactions**

666 As with all drugs, the potential for interaction by a variety of mechanisms (e.g.,
667 pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc.) is a possibility (*see*
668 Accumulation and slow elimination *under* CLINICAL PHARMACOLOGY).

669 Drugs metabolized by CYP2D6 — Fluoxetine inhibits the activity of CYP2D6, and may make
670 individuals with normal CYP2D6 metabolic activity resemble a poor metabolizer.

671 Coadministration of fluoxetine with other drugs that are metabolized by CYP2D6, including
672 certain antidepressants (e.g., TCAs), antipsychotics (e.g., phenothiazines and most atypicals),
673 and antiarrhythmics (e.g., propafenone, flecainide, and others) should be approached with
674 caution. Therapy with medications that are predominantly metabolized by the CYP2D6 system
675 and that have a relatively narrow therapeutic index (see list below) should be initiated at the low
676 end of the dose range if a patient is receiving fluoxetine concurrently or has taken it in the
677 previous 5 weeks. Thus, his/her dosing requirements resemble those of poor metabolizers. If
678 fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by
679 CYP2D6, the need for decreased dose of the original medication should be considered. Drugs
680 with a narrow therapeutic index represent the greatest concern (e.g., flecainide, propafenone,
681 vinblastine, and TCAs). Due to the risk of serious ventricular arrhythmias and sudden death
682 potentially associated with elevated plasma levels of thioridazine, thioridazine should not be
683 administered with fluoxetine or within a minimum of 5 weeks after fluoxetine has been
684 discontinued (*see* CONTRAINDICATIONS *and* WARNINGS).

685 Drugs metabolized by CYP3A4 — In an in vivo interaction study involving coadministration
686 of fluoxetine with single doses of terfenadine (a CYP3A4 substrate), no increase in plasma
687 terfenadine concentrations occurred with concomitant fluoxetine. In addition, in vitro studies
688 have shown ketoconazole, a potent inhibitor of CYP3A4 activity, to be at least 100 times more
689 potent than fluoxetine or norfluoxetine as an inhibitor of the metabolism of several substrates for
690 this enzyme, including astemizole, cisapride, and midazolam. These data indicate that
691 fluoxetine's extent of inhibition of CYP3A4 activity is not likely to be of clinical significance.

692 CNS active drugs — The risk of using Prozac in combination with other CNS active drugs has
693 not been systematically evaluated. Nonetheless, caution is advised if the concomitant
694 administration of Prozac and such drugs is required. In evaluating individual cases, consideration
695 should be given to using lower initial doses of the concomitantly administered drugs, using
696 conservative titration schedules, and monitoring of clinical status (*see* Accumulation and slow
697 elimination *under* CLINICAL PHARMACOLOGY).

698 Anticonvulsants — Patients on stable doses of phenytoin and carbamazepine have developed
699 elevated plasma anticonvulsant concentrations and clinical anticonvulsant toxicity following
700 initiation of concomitant fluoxetine treatment.

701 Antipsychotics — Some clinical data suggests a possible pharmacodynamic and/or
702 pharmacokinetic interaction between SSRIs and antipsychotics. Elevation of blood levels of
703 haloperidol and clozapine has been observed in patients receiving concomitant fluoxetine.
704 Clinical studies of pimozide with other antidepressants demonstrate an increase in drug
705 interaction or QT_c prolongation. While a specific study with pimozide and fluoxetine has not
706 been conducted, the potential for drug interactions or QT_c prolongation warrants restricting the

707 concurrent use of pimozide and Prozac. Concomitant use of Prozac and pimozide is
708 contraindicated (*see* CONTRAINDICATIONS). For thioridazine, *see* CONTRAINDICATIONS
709 and WARNINGS.

710 Benzodiazepines — The half-life of concurrently administered diazepam may be prolonged in
711 some patients (*see* Accumulation and slow elimination *under* CLINICAL PHARMACOLOGY).
712 Coadministration of alprazolam and fluoxetine has resulted in increased alprazolam plasma
713 concentrations and in further psychomotor performance decrement due to increased alprazolam
714 levels.

715 Lithium — There have been reports of both increased and decreased lithium levels when
716 lithium was used concomitantly with fluoxetine. Cases of lithium toxicity and increased
717 serotonergic effects have been reported. Lithium levels should be monitored when these drugs
718 are administered concomitantly.

719 Tryptophan — Five patients receiving Prozac in combination with tryptophan experienced
720 adverse reactions, including agitation, restlessness, and gastrointestinal distress.

721 Monoamine oxidase inhibitors — *See* CONTRAINDICATIONS.

722 Other drugs effective in the treatment of major depressive disorder — In 2 studies, previously
723 stable plasma levels of imipramine and desipramine have increased greater than 2- to 10-fold
724 when fluoxetine has been administered in combination. This influence may persist for 3 weeks or
725 longer after fluoxetine is discontinued. Thus, the dose of TCA may need to be reduced and
726 plasma TCA concentrations may need to be monitored temporarily when fluoxetine is
727 coadministered or has been recently discontinued (*see* Accumulation and slow elimination *under*
728 CLINICAL PHARMACOLOGY, *and* Drugs metabolized by CYP2D6 *under* Drug Interactions).

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

735 Triptans — There have been rare postmarketing reports of serotonin syndrome with use of an
736 SSRI and a triptan. If concomitant treatment of Prozac with a triptan is clinically warranted,
737 careful observation of the patient is advised, particularly during treatment initiation and dose
738 increases (*see* Serotonin Syndrome *under* WARNINGS).

739 Potential effects of coadministration of drugs tightly bound to plasma proteins — Because
740 fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking
741 another drug that is tightly bound to protein (e.g., Coumadin, digitoxin) may cause a shift in
742 plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may
743 result from displacement of protein-bound fluoxetine by other tightly-bound drugs (*see*
744 Accumulation and slow elimination *under* CLINICAL PHARMACOLOGY).

745 Drugs that interfere with hemostasis (NSAIDs, aspirin, warfarin, etc.) — Serotonin release by
746 platelets plays an important role in hemostasis. Epidemiological studies of the case-control and
747 cohort design that have demonstrated an association between use of psychotropic drugs that
748 interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also
749 shown that concurrent use of an NSAID or aspirin potentiated the risk of bleeding. Thus, patients
750 should be cautioned about the use of such drugs concurrently with fluoxetine.

751 Warfarin — Altered anticoagulant effects, including increased bleeding, have been reported
752 when fluoxetine is coadministered with warfarin. Patients receiving warfarin therapy should
753 receive careful coagulation monitoring when fluoxetine is initiated or stopped.

754 Electroconvulsive therapy (ECT) — There are no clinical studies establishing the benefit of the
755 combined use of ECT and fluoxetine. There have been rare reports of prolonged seizures in
756 patients on fluoxetine receiving ECT treatment.

757 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

758 There is no evidence of carcinogenicity or mutagenicity from in vitro or animal studies.
759 Impairment of fertility in adult animals at doses up to 12.5 mg/kg/day (approximately 1.5 times
760 the MRHD on a mg/m² basis) was not observed.

761 Carcinogenicity — The dietary administration of fluoxetine to rats and mice for 2 years at
762 doses of up to 10 and 12 mg/kg/day, respectively [approximately 1.2 and 0.7 times, respectively,
763 the maximum recommended human dose (MRHD) of 80 mg on a mg/m² basis], produced no
764 evidence of carcinogenicity.

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

769 Impairment of fertility — Two fertility studies conducted in adult rats at doses of up to 7.5 and
770 12.5 mg/kg/day (approximately 0.9 and 1.5 times the MRHD on a mg/m² basis) indicated that
771 fluoxetine had no adverse effects on fertility (*see* Pediatric Use).

772 **Pregnancy**

773 Pregnancy Category C — In embryo-fetal development studies in rats and rabbits, there was
774 no evidence of teratogenicity following administration of up to 12.5 and 15 mg/kg/day,
775 respectively (1.5 and 3.6 times, respectively, the MRHD of 80 mg on a mg/m² basis) throughout
776 organogenesis. However, in rat reproduction studies, an increase in stillborn pups, a decrease in
777 pup weight, and an increase in pup deaths during the first 7 days postpartum occurred following
778 maternal exposure to 12 mg/kg/day (1.5 times the MRHD on a mg/m² basis) during gestation or
779 7.5 mg/kg/day (0.9 times the MRHD on a mg/m² basis) during gestation and lactation. There was
780 no evidence of developmental neurotoxicity in the surviving offspring of rats treated with
781 12 mg/kg/day during gestation. The no-effect dose for rat pup mortality was 5 mg/kg/day (0.6
782 times the MRHD on a mg/m² basis). Prozac should be used during pregnancy only if the
783 potential benefit justifies the potential risk to the fetus.

784 Nonteratogenic Effects — Neonates exposed to Prozac and other SSRIs or serotonin and
785 norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed
786 complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such
787 complications can arise immediately upon delivery. Reported clinical findings have included
788 respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty,
789 vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and
790 constant crying. These features are consistent with either a direct toxic effect of SSRIs and
791 SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the
792 clinical picture is consistent with serotonin syndrome (*see* Monoamine oxidase inhibitors *under*
793 CONTRAINDICATIONS).

794 Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent
795 pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1-2 per 1000 live births in the
796 general population and is associated with substantial neonatal morbidity and mortality. In a

797 retrospective case-control study of 377 women whose infants were born with PPHN and 836
798 women whose infants were born healthy, the risk for developing PPHN was approximately
799 six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants
800 who had not been exposed to antidepressants during pregnancy. There is currently no
801 corroborative evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy;
802 this is the first study that has investigated the potential risk. The study did not include enough
803 cases with exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN
804 risk.

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

811 **Labor and Delivery**

812 The effect of Prozac on labor and delivery in humans is unknown. However, because
813 fluoxetine crosses the placenta and because of the possibility that fluoxetine may have adverse
814 effects on the newborn, fluoxetine should be used during labor and delivery only if the potential
815 benefit justifies the potential risk to the fetus.

816 **Nursing Mothers**

817 Because Prozac is excreted in human milk, nursing while on Prozac is not recommended. In
818 one breast-milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng/mL. The
819 concentration in the mother's plasma was 295.0 ng/mL. No adverse effects on the infant were
820 reported. In another case, an infant nursed by a mother on Prozac developed crying, sleep
821 disturbance, vomiting, and watery stools. The infant's plasma drug levels were 340 ng/mL of
822 fluoxetine and 208 ng/mL of norfluoxetine on the second day of feeding.

823 **Pediatric Use**

824 The efficacy of Prozac for the treatment of major depressive disorder was demonstrated in two
825 8- to 9-week placebo-controlled clinical trials with 315 pediatric outpatients ages 8 to ≤ 18 (*see*
826 CLINICAL TRIALS).

827 The efficacy of Prozac for the treatment of OCD was demonstrated in one 13-week
828 placebo-controlled clinical trial with 103 pediatric outpatients ages 7 to < 18 (*see* CLINICAL
829 TRIALS).

830 The safety and effectiveness in pediatric patients < 8 years of age in major depressive disorder
831 and < 7 years of age in OCD have not been established.

832 Fluoxetine pharmacokinetics were evaluated in 21 pediatric patients (ages 6 to ≤ 18) with major
833 depressive disorder or OCD (*see* Pharmacokinetics *under* CLINICAL PHARMACOLOGY).

834 The acute adverse event profiles observed in the 3 studies (N=418 randomized; 228
835 fluoxetine-treated, 190 placebo-treated) were generally similar to that observed in adult studies
836 with fluoxetine. The longer-term adverse event profile observed in the 19-week major depressive
837 disorder study (N=219 randomized; 109 fluoxetine-treated, 110 placebo-treated) was also similar
838 to that observed in adult trials with fluoxetine (*see* ADVERSE REACTIONS).

839 Manic reaction, including mania and hypomania, was reported in 6 (1 mania, 5 hypomania) out
840 of 228 (2.6%) fluoxetine-treated patients and in 0 out of 190 (0%) placebo-treated patients.
841 Mania/hypomania led to the discontinuation of 4 (1.8%) fluoxetine-treated patients from the

842 acute phases of the 3 studies combined. Consequently, regular monitoring for the occurrence of
843 mania/hypomania is recommended.

844 As with other SSRIs, decreased weight gain has been observed in association with the use of
845 fluoxetine in children and adolescent patients. After 19 weeks of treatment in a clinical trial,
846 pediatric subjects treated with fluoxetine gained an average of 1.1 cm less in height ($p=0.004$)
847 and 1.1 kg less in weight ($p=0.008$) than subjects treated with placebo. In addition, fluoxetine
848 treatment was associated with a decrease in alkaline phosphatase levels. The safety of fluoxetine
849 treatment for pediatric patients has not been systematically assessed for chronic treatment longer
850 than several months in duration. In particular, there are no studies that directly evaluate the
851 longer-term effects of fluoxetine on the growth, development, and maturation of children and
852 adolescent patients. Therefore, height and weight should be monitored periodically in pediatric
853 patients receiving fluoxetine.

854 (*See WARNINGS, Clinical Worsening and Suicide Risk.*)

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

858 In a study in which fluoxetine (3, 10, or 30 mg/kg) was orally administered to young rats from
859 weaning (Postnatal Day 21) through adulthood (Day 90), male and female sexual development
860 was delayed at all doses, and growth (body weight gain, femur length) was decreased during the
861 dosing period in animals receiving the highest dose. At the end of the treatment period, serum
862 levels of creatine kinase (marker of muscle damage) were increased at the intermediate and high
863 doses, and abnormal muscle and reproductive organ histopathology (skeletal muscle
864 degeneration and necrosis, testicular degeneration and necrosis, epididymal vacuolation and
865 hypospermia) was observed at the high dose. When animals were evaluated after a recovery
866 period (up to 11 weeks after cessation of dosing), neurobehavioral abnormalities (decreased
867 reactivity at all doses and learning deficit at the high dose) and reproductive functional
868 impairment (decreased mating at all doses and impaired fertility at the high dose) were seen; in
869 addition, testicular and epididymal microscopic lesions and decreased sperm concentrations were
870 found in the high dose group, indicating that the reproductive organ effects seen at the end of
871 treatment were irreversible. The reversibility of fluoxetine-induced muscle damage was not
872 assessed. Adverse effects similar to those observed in rats treated with fluoxetine during the
873 juvenile period have not been reported after administration of fluoxetine to adult animals. Plasma
874 exposures (AUC) to fluoxetine in juvenile rats receiving the low, intermediate, and high dose in
875 this study were approximately 0.1-0.2, 1-2, and 5-10 times, respectively, the average exposure in
876 pediatric patients receiving the maximum recommended dose (MRD) of 20 mg/day. Rat
877 exposures to the major metabolite, norfluoxetine, were approximately 0.3-0.8, 1-8, and 3-20
878 times, respectively, pediatric exposure at the MRD.

879 A specific effect of fluoxetine on bone development has been reported in mice treated with
880 fluoxetine during the juvenile period. When mice were treated with fluoxetine (5 or 20 mg/kg,
881 intraperitoneal) for 4 weeks starting at 4 weeks of age, bone formation was reduced resulting in
882 decreased bone mineral content and density. These doses did not affect overall growth (body
883 weight gain or femoral length). The doses administered to juvenile mice in this study are
884 approximately 0.5 and 2 times the MRD for pediatric patients on a body surface area (mg/m^2)
885 basis.

886 In another mouse study, administration of fluoxetine (10 mg/kg intraperitoneal) during early
887 postnatal development (Postnatal Days 4 to 21) produced abnormal emotional behaviors

888 (decreased exploratory behavior in elevated plus-maze, increased shock avoidance latency) in
889 adulthood (12 weeks of age). The dose used in this study is approximately equal to the pediatric
890 MRD on a mg/m² basis. Because of the early dosing period in this study, the significance of
891 these findings to the approved pediatric use in humans is uncertain.

892 Prozac is approved for use in pediatric patients with MDD and OCD (*see* BOX WARNING
893 *and* WARNINGS, Clinical Worsening and Suicide Risk). Anyone considering the use of Prozac
894 in a child or adolescent must balance the potential risks with the clinical need.

895 **Geriatric Use**

896 US fluoxetine clinical trials as of May 8, 1995 (10,782 patients) included 687 patients ≥65
897 years of age and 93 patients ≥75 years of age. The efficacy in geriatric patients has been
898 established (*see* CLINICAL TRIALS). For pharmacokinetic information in geriatric patients, see
899 Age under CLINICAL PHARMACOLOGY. No overall differences in safety or effectiveness
900 were observed between these subjects and younger subjects, and other reported clinical
901 experience has not identified differences in responses between the elderly and younger patients,
902 but greater sensitivity of some older individuals cannot be ruled out. As with other SSRIs,
903 fluoxetine has been associated with cases of clinically significant hyponatremia in elderly
904 patients (*see* Hyponatremia *under* PRECAUTIONS).

905 **ADVERSE REACTIONS**

906 Multiple doses of Prozac had been administered to 10,782 patients with various diagnoses in
907 US clinical trials as of May 8, 1995. In addition, there have been 425 patients administered
908 Prozac in panic clinical trials. Adverse events were recorded by clinical investigators using
909 descriptive terminology of their own choosing. Consequently, it is not possible to provide a
910 meaningful estimate of the proportion of individuals experiencing adverse events without first
911 grouping similar types of events into a limited (i.e., reduced) number of standardized event
912 categories.

913 In the tables and tabulations that follow, COSTART Dictionary terminology has been used to
914 classify reported adverse events. The stated frequencies represent the proportion of individuals
915 who experienced, at least once, a treatment-emergent adverse event of the type listed. An event
916 was considered treatment-emergent if it occurred for the first time or worsened while receiving
917 therapy following baseline evaluation. It is important to emphasize that events reported during
918 therapy were not necessarily caused by it.

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

926 Incidence in major depressive disorder, OCD, bulimia, and panic disorder placebo-controlled
927 clinical trials (excluding data from extensions of trials) — Table 2 enumerates the most common
928 treatment-emergent adverse events associated with the use of Prozac (incidence of at least 5% for
929 Prozac and at least twice that for placebo within at least 1 of the indications) for the treatment of
930 major depressive disorder, OCD, and bulimia in US controlled clinical trials and panic disorder
931 in US plus non-US controlled trials. Table 3 enumerates treatment-emergent adverse events that
932 occurred in 2% or more patients treated with Prozac and with incidence greater than placebo who
933 participated in US major depressive disorder, OCD, and bulimia controlled clinical trials and US

934 plus non-US panic disorder controlled clinical trials. Table 3 provides combined data for the pool
 935 of studies that are provided separately by indication in Table 2.

936
 937
 938
 939

Table 2: Most Common Treatment-Emergent Adverse Events: Incidence in Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Placebo-Controlled Clinical Trials¹

Body System/ Adverse Event	Percentage of Patients Reporting Event							
	Major Depressive Disorder		OCD		Bulimia		Panic Disorder	
	Prozac (N=1728)	Placebo (N=975)	Prozac (N=266)	Placebo (N=89)	Prozac (N=450)	Placebo (N=267)	Prozac (N=425)	Placebo (N=342)
Body as a Whole								
Asthenia	9	5	15	11	21	9	7	7
Flu syndrome	3	4	10	7	8	3	5	5
Cardiovascular System								
Vasodilatation	3	2	5	--	2	1	1	--
Digestive System								
Nausea	21	9	26	13	29	11	12	7
Diarrhea	12	8	18	13	8	6	9	4
Anorexia	11	2	17	10	8	4	4	1
Dry mouth	10	7	12	3	9	6	4	4
Dyspepsia	7	5	10	4	10	6	6	2
Nervous System								
Insomnia	16	9	28	22	33	13	10	7
Anxiety	12	7	14	7	15	9	6	2
Nervousness	14	9	14	15	11	5	8	6
Somnolence	13	6	17	7	13	5	5	2
Tremor	10	3	9	1	13	1	3	1
Libido decreased	3	--	11	2	5	1	1	2
Abnormal dreams	1	1	5	2	5	3	1	1
Respiratory System								
Pharyngitis	3	3	11	9	10	5	3	3
Sinusitis	1	4	5	2	6	4	2	3
Yawn	--	--	7	--	11	--	1	--
Skin and Appendages								
Sweating	8	3	7	--	8	3	2	2
Rash	4	3	6	3	4	4	2	2
Urogenital System								
Impotence ²	2	--	--	--	7	--	1	--
Abnormal ejaculation ²	--	--	7	--	7	--	2	1

940 ¹ Includes US data for major depressive disorder, OCD, bulimia, and panic disorder clinical trials, plus non-US
 941 data for panic disorder clinical trials.

942 ² Denominator used was for males only (N=690 Prozac major depressive disorder; N=410 placebo major
 943 depressive disorder; N=116 Prozac OCD; N=43 placebo OCD; N=14 Prozac bulimia; N=1 placebo bulimia;
 944 N=162 Prozac panic; N=121 placebo panic).

945 -- Incidence less than 1%.

946

947
948**Table 3: Treatment-Emergent Adverse Events: Incidence in Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Placebo-Controlled Clinical Trials¹**

	Percentage of Patients Reporting Event	
	Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Combined	
Body System/ Adverse Event²	Prozac (N=2869)	Placebo (N=1673)
Body as a Whole		
Headache	21	19
Asthenia	11	6
Flu syndrome	5	4
Fever	2	1
Cardiovascular System		
Vasodilatation	2	1
Digestive System		
Nausea	22	9
Diarrhea	11	7
Anorexia	10	3
Dry mouth	9	6
Dyspepsia	8	4
Constipation	5	4
Flatulence	3	2
Vomiting	3	2
Metabolic and Nutritional Disorders		
Weight loss	2	1
Nervous System		
Insomnia	19	10
Nervousness	13	8
Anxiety	12	6
Somnolence	12	5
Dizziness	9	6
Tremor	9	2
Libido decreased	4	1
Thinking abnormal	2	1
Respiratory System		
Yawn	3	--
Skin and Appendages		
Sweating	7	3
Rash	4	3
Pruritus	3	2
Special Senses		
Abnormal vision	2	1

949 ¹ Includes US data for major depressive disorder, OCD, bulimia, and panic disorder clinical trials, plus non-US
950 data for panic disorder clinical trials.

951 ² Included are events reported by at least 2% of patients taking Prozac, except the following events, which had an
952 incidence on placebo \geq Prozac (major depressive disorder, OCD, bulimia, and panic disorder combined):
953 abdominal pain, abnormal dreams, accidental injury, back pain, cough increased, major depressive disorder
954 (includes suicidal thoughts), dysmenorrhea, infection, myalgia, pain, paresthesia, pharyngitis, rhinitis, sinusitis.
955 -- Incidence less than 1%.

956
957 Associated with discontinuation in major depressive disorder, OCD, bulimia, and panic
958 disorder placebo-controlled clinical trials (excluding data from extensions of trials) — Table 4
959 lists the adverse events associated with discontinuation of Prozac treatment (incidence at least
960 twice that for placebo and at least 1% for Prozac in clinical trials collecting only a primary event
961 associated with discontinuation) in major depressive disorder, OCD, bulimia, and panic disorder
962 clinical trials, plus non-US panic disorder clinical trials.

963
964 **Table 4: Most Common Adverse Events Associated with Discontinuation in Major**
965 **Depressive Disorder, OCD, Bulimia, and Panic Disorder Placebo-Controlled Clinical**
966 **Trials¹**

Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Combined (N=1533)	Major Depressive Disorder (N=392)	OCD (N=266)	Bulimia (N=450)	Panic Disorder (N=425)
Anxiety (1%)	--	Anxiety (2%)	--	Anxiety (2%)
--	--	--	Insomnia (2%)	--
--	Nervousness (1%)	--	--	Nervousness (1%)
--	--	Rash (1%)	--	--

967 ¹ Includes US major depressive disorder, OCD, bulimia, and panic disorder clinical trials, plus non-US panic
968 disorder clinical trials.

969
970 Other adverse events in pediatric patients (children and adolescents) — Treatment-emergent
971 adverse events were collected in 322 pediatric patients (180 fluoxetine-treated, 142
972 placebo-treated). The overall profile of adverse events was generally similar to that seen in adult
973 studies, as shown in Tables 2 and 3. However, the following adverse events (excluding those
974 which appear in the body or footnotes of Tables 2 and 3 and those for which the COSTART
975 terms were uninformative or misleading) were reported at an incidence of at least 2% for
976 fluoxetine and greater than placebo: thirst, hyperkinesia, agitation, personality disorder,
977 epistaxis, urinary frequency, and menorrhagia.

978 The most common adverse event (incidence at least 1% for fluoxetine and greater than
979 placebo) associated with discontinuation in 3 pediatric placebo-controlled trials (N=418
980 randomized; 228 fluoxetine-treated; 190 placebo-treated) was mania/hypomania (1.8% for
981 fluoxetine-treated, 0% for placebo-treated). In these clinical trials, only a primary event
982 associated with discontinuation was collected.

983 Events observed in Prozac Weekly clinical trials — Treatment-emergent adverse events in
984 clinical trials with Prozac Weekly were similar to the adverse events reported by patients in
985 clinical trials with Prozac daily. In a placebo-controlled clinical trial, more patients taking Prozac
986 Weekly reported diarrhea than patients taking placebo (10% versus 3%, respectively) or taking
987 Prozac 20 mg daily (10% versus 5%, respectively).

988 Male and female sexual dysfunction with SSRIs — Although changes in sexual desire, sexual
 989 performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they
 990 may also be a consequence of pharmacologic treatment. In particular, some evidence suggests
 991 that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and
 992 severity of untoward experiences involving sexual desire, performance, and satisfaction are
 993 difficult to obtain, however, in part because patients and physicians may be reluctant to discuss
 994 them. Accordingly, estimates of the incidence of untoward sexual experience and performance,
 995 cited in product labeling, are likely to underestimate their actual incidence. In patients enrolled in
 996 US major depressive disorder, OCD, and bulimia placebo-controlled clinical trials, decreased
 997 libido was the only sexual side effect reported by at least 2% of patients taking fluoxetine (4%
 998 fluoxetine, <1% placebo). There have been spontaneous reports in women taking fluoxetine of
 999 orgasmic dysfunction, including anorgasmia.

1000 There are no adequate and well-controlled studies examining sexual dysfunction with
 1001 fluoxetine treatment.

1002 Priapism has been reported with all SSRIs.

1003 While it is difficult to know the precise risk of sexual dysfunction associated with the use of
 1004 SSRIs, physicians should routinely inquire about such possible side effects.

1005 **Other Events Observed in Clinical Trials**

1006 Following is a list of all treatment-emergent adverse events reported at anytime by individuals
 1007 taking fluoxetine in US clinical trials as of May 8, 1995 (10,782 patients) except (1) those listed
 1008 in the body or footnotes of Tables 2 or 3 above or elsewhere in labeling; (2) those for which the
 1009 COSTART terms were uninformative or misleading; (3) those events for which a causal
 1010 relationship to Prozac use was considered remote; and (4) events occurring in only 1 patient
 1011 treated with Prozac and which did not have a substantial probability of being acutely
 1012 life-threatening.

1013 Events are classified within body system categories using the following definitions: frequent
 1014 adverse events are defined as those occurring on one or more occasions in at least 1/100 patients;
 1015 infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those
 1016 occurring in less than 1/1000 patients.

1017 **Body as a Whole** — *Frequent*: chest pain, chills; *Infrequent*: chills and fever, face edema,
 1018 intentional overdose, malaise, pelvic pain, suicide attempt; *Rare*: acute abdominal syndrome,
 1019 hypothermia, intentional injury, neuroleptic malignant syndrome¹, photosensitivity reaction.

1020 **Cardiovascular System** — *Frequent*: hemorrhage, hypertension, palpitation; *Infrequent*:
 1021 angina pectoris, arrhythmia, congestive heart failure, hypotension, migraine, myocardial infarct,
 1022 postural hypotension, syncope, tachycardia, vascular headache; *Rare*: atrial fibrillation,
 1023 bradycardia, cerebral embolism, cerebral ischemia, cerebrovascular accident, extrasystoles, heart
 1024 arrest, heart block, pallor, peripheral vascular disorder, phlebitis, shock, thrombophlebitis,
 1025 thrombosis, vasospasm, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation.

1026 **Digestive System** — *Frequent*: increased appetite, nausea and vomiting; *Infrequent*: aphthous
 1027 stomatitis, cholelithiasis, colitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis,
 1028 glossitis, gum hemorrhage, hyperchlorhydria, increased salivation, liver function tests abnormal,
 1029 melena, mouth ulceration, nausea/vomiting/diarrhea, stomach ulcer, stomatitis, thirst; *Rare*:
 1030 biliary pain, bloody diarrhea, cholecystitis, duodenal ulcer, enteritis, esophageal ulcer, fecal
 1031 incontinence, gastrointestinal hemorrhage, hematemesis, hemorrhage of colon, hepatitis,
 1032 intestinal obstruction, liver fatty deposit, pancreatitis, peptic ulcer, rectal hemorrhage, salivary
 1033 gland enlargement, stomach ulcer hemorrhage, tongue edema.

- 1034 **Endocrine System** — *Infrequent*: hypothyroidism; *Rare*: diabetic acidosis, diabetes mellitus.
- 1035 **Hemic and Lymphatic System** — *Infrequent*: anemia, ecchymosis; *Rare*: blood dyscrasia,
 1036 hypochromic anemia, leukopenia, lymphedema, lymphocytosis, petechia, purpura,
 1037 thrombocythemia, thrombocytopenia.
- 1038 **Metabolic and Nutritional** — *Frequent*: weight gain; *Infrequent*: dehydration, generalized
 1039 edema, gout, hypercholesteremia, hyperlipemia, hypokalemia, peripheral edema; *Rare*: alcohol
 1040 intolerance, alkaline phosphatase increased, BUN increased, creatine phosphokinase increased,
 1041 hyperkalemia, hyperuricemia, hypocalcemia, iron deficiency anemia, SGPT increased.
- 1042 **Musculoskeletal System** — *Infrequent*: arthritis, bone pain, bursitis, leg cramps,
 1043 tenosynovitis; *Rare*: arthrosis, chondrodystrophy, myasthenia, myopathy, myositis,
 1044 osteomyelitis, osteoporosis, rheumatoid arthritis.
- 1045 **Nervous System** — *Frequent*: agitation, amnesia, confusion, emotional lability, sleep
 1046 disorder; *Infrequent*: abnormal gait, acute brain syndrome, akathisia, apathy, ataxia, buccoglossal
 1047 syndrome, CNS depression, CNS stimulation, depersonalization, euphoria, hallucinations,
 1048 hostility, hyperkinesia, hypertonia, hypesthesia, incoordination, libido increased, myoclonus,
 1049 neuralgia, neuropathy, neurosis, paranoid reaction, personality disorder², psychosis, vertigo;
 1050 *Rare*: abnormal electroencephalogram, antisocial reaction, circumoral paresthesia, coma,
 1051 delusions, dysarthria, dystonia, extrapyramidal syndrome, foot drop, hyperesthesia, neuritis,
 1052 paralysis, reflexes decreased, reflexes increased, stupor.
- 1053 **Respiratory System** — *Infrequent*: asthma, epistaxis, hiccup, hyperventilation; *Rare*: apnea,
 1054 atelectasis, cough decreased, emphysema, hemoptysis, hypoventilation, hypoxia, larynx edema,
 1055 lung edema, pneumothorax, stridor.
- 1056 **Skin and Appendages** — *Infrequent*: acne, alopecia, contact dermatitis, eczema,
 1057 maculopapular rash, skin discoloration, skin ulcer, vesiculobullous rash; *Rare*: furunculosis,
 1058 herpes zoster, hirsutism, petechial rash, psoriasis, purpuric rash, pustular rash, seborrhea.
- 1059 **Special Senses** — *Frequent*: ear pain, taste perversion, tinnitus; *Infrequent*: conjunctivitis, dry
 1060 eyes, mydriasis, photophobia; *Rare*: blepharitis, deafness, diplopia, exophthalmos, eye
 1061 hemorrhage, glaucoma, hyperacusis, iritis, parosmia, scleritis, strabismus, taste loss, visual field
 1062 defect.
- 1063 **Urogenital System** — *Frequent*: urinary frequency; *Infrequent*: abortion³, albuminuria,
 1064 amenorrhea³, anorgasmia, breast enlargement, breast pain, cystitis, dysuria, female lactation³,
 1065 fibrocystic breast³, hematuria, leukorrhea³, menorrhagia³, metrorrhagia³, nocturia, polyuria,
 1066 urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage³; *Rare*: breast
 1067 engorgement, glycosuria, hypomenorrhea³, kidney pain, oliguria, priapism³, uterine
 1068 hemorrhage³, uterine fibroids enlarged³.
- 1069 ¹ Neuroleptic malignant syndrome is the COSTART term which best captures serotonin syndrome.
 1070 ² Personality disorder is the COSTART term for designating nonaggressive objectionable behavior.
 1071 ³ Adjusted for gender.
- 1072

1073 Postintroduction Reports

- 1074 Voluntary reports of adverse events temporally associated with Prozac that have been received
 1075 since market introduction and that may have no causal relationship with the drug include the
 1076 following: aplastic anemia, atrial fibrillation, cataract, cerebral vascular accident, cholestatic
 1077 jaundice, confusion, dyskinesia (including, for example, a case of buccal-lingual-masticatory
 1078 syndrome with involuntary tongue protrusion reported to develop in a 77-year-old female after 5
 1079 weeks of fluoxetine therapy and which completely resolved over the next few months following
 1080 drug discontinuation), eosinophilic pneumonia, epidermal necrolysis, erythema multiforme,

1081 erythema nodosum, exfoliative dermatitis, gynecomastia, heart arrest, hepatic failure/necrosis,
 1082 hyperprolactinemia, hypoglycemia, immune-related hemolytic anemia, kidney failure,
 1083 misuse/abuse, movement disorders developing in patients with risk factors including drugs
 1084 associated with such events and worsening of preexisting movement disorders, neuroleptic
 1085 malignant syndrome-like events, optic neuritis, pancreatitis, pancytopenia, priapism, pulmonary
 1086 embolism, pulmonary hypertension, QT prolongation, serotonin syndrome (a range of signs and
 1087 symptoms that can rarely, in its most severe form, resemble neuroleptic malignant syndrome),
 1088 Stevens-Johnson syndrome, sudden unexpected death, suicidal ideation, thrombocytopenia,
 1089 thrombocytopenic purpura, vaginal bleeding after drug withdrawal, ventricular tachycardia
 1090 (including torsades de pointes-type arrhythmias), and violent behaviors.

1091 **DRUG ABUSE AND DEPENDENCE**

1092 **Controlled substance class** — Prozac is not a controlled substance.

1093 **Physical and psychological dependence** — Prozac has not been systematically studied, in
 1094 animals or humans, for its potential for abuse, tolerance, or physical dependence. While the
 1095 premarketing clinical experience with Prozac did not reveal any tendency for a withdrawal
 1096 syndrome or any drug seeking behavior, these observations were not systematic and it is not
 1097 possible to predict on the basis of this limited experience the extent to which a CNS active drug
 1098 will be misused, diverted, and/or abused once marketed. Consequently, physicians should
 1099 carefully evaluate patients for history of drug abuse and follow such patients closely, observing
 1100 them for signs of misuse or abuse of Prozac (e.g., development of tolerance, incrementation of
 1101 dose, drug-seeking behavior).

1102 **OVERDOSAGE**

1103 **Human Experience**

1104 Worldwide exposure to fluoxetine hydrochloride is estimated to be over 38 million patients
 1105 (circa 1999). Of the 1578 cases of overdose involving fluoxetine hydrochloride, alone or with
 1106 other drugs, reported from this population, there were 195 deaths.

1107 Among 633 adult patients who overdosed on fluoxetine hydrochloride alone, 34 resulted in a
 1108 fatal outcome, 378 completely recovered, and 15 patients experienced sequelae after overdose,
 1109 including abnormal accommodation, abnormal gait, confusion, unresponsiveness, nervousness,
 1110 pulmonary dysfunction, vertigo, tremor, elevated blood pressure, impotence, movement disorder,
 1111 and hypomania. The remaining 206 patients had an unknown outcome. The most common signs
 1112 and symptoms associated with non-fatal overdose were seizures, somnolence, nausea,
 1113 tachycardia, and vomiting. The largest known ingestion of fluoxetine hydrochloride in adult
 1114 patients was 8 grams in a patient who took fluoxetine alone and who subsequently recovered.
 1115 However, in an adult patient who took fluoxetine alone, an ingestion as low as 520 mg has been
 1116 associated with lethal outcome, but causality has not been established.

1117 Among pediatric patients (ages 3 months to 17 years), there were 156 cases of overdose
 1118 involving fluoxetine alone or in combination with other drugs. Six patients died, 127 patients
 1119 completely recovered, 1 patient experienced renal failure, and 22 patients had an unknown
 1120 outcome. One of the six fatalities was a 9-year-old boy who had a history of OCD, Tourette's
 1121 syndrome with tics, attention deficit disorder, and fetal alcohol syndrome. He had been receiving
 1122 100 mg of fluoxetine daily for 6 months in addition to clonidine, methylphenidate, and
 1123 promethazine. Mixed-drug ingestion or other methods of suicide complicated all 6 overdoses in
 1124 children that resulted in fatalities. The largest ingestion in pediatric patients was 3 grams which
 1125 was nonlethal.

1126 Other important adverse events reported with fluoxetine overdose (single or multiple drugs)
1127 include coma, delirium, ECG abnormalities (such as QT interval prolongation and ventricular
1128 tachycardia, including torsades de pointes-type arrhythmias), hypotension, mania, neuroleptic
1129 malignant syndrome-like events, pyrexia, stupor, and syncope.

1130 **Animal Experience**

1131 Studies in animals do not provide precise or necessarily valid information about the treatment
1132 of human overdose. However, animal experiments can provide useful insights into possible
1133 treatment strategies.

1134 The oral median lethal dose in rats and mice was found to be 452 and 248 mg/kg, respectively.
1135 Acute high oral doses produced hyperirritability and convulsions in several animal species.

1136 Among 6 dogs purposely overdosed with oral fluoxetine, 5 experienced grand mal seizures.
1137 Seizures stopped immediately upon the bolus intravenous administration of a standard veterinary
1138 dose of diazepam. In this short-term study, the lowest plasma concentration at which a seizure
1139 occurred was only twice the maximum plasma concentration seen in humans taking 80 mg/day,
1140 chronically.

1141 In a separate single-dose study, the ECG of dogs given high doses did not reveal prolongation
1142 of the PR, QRS, or QT intervals. Tachycardia and an increase in blood pressure were observed.
1143 Consequently, the value of the ECG in predicting cardiac toxicity is unknown. Nonetheless, the
1144 ECG should ordinarily be monitored in cases of human overdose (*see* Management of
1145 Overdose).

1146 **Management of Overdose**

1147 Treatment should consist of those general measures employed in the management of
1148 overdosage with any drug effective in the treatment of major depressive disorder.

1149 Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital
1150 signs. General supportive and symptomatic measures are also recommended. Induction of emesis
1151 is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway
1152 protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic
1153 patients.

1154 Activated charcoal should be administered. Due to the large volume of distribution of this
1155 drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of
1156 benefit. No specific antidotes for fluoxetine are known.

1157 A specific caution involves patients who are taking or have recently taken fluoxetine and might
1158 ingest excessive quantities of a TCA. In such a case, accumulation of the parent tricyclic and/or
1159 an active metabolite may increase the possibility of clinically significant sequelae and extend the
1160 time needed for close medical observation (*see* Other drugs effective in the treatment of major
1161 depressive disorder *under* PRECAUTIONS).

1162 Based on experience in animals, which may not be relevant to humans, fluoxetine-induced
1163 seizures that fail to remit spontaneously may respond to diazepam.

1164 In managing overdosage, consider the possibility of multiple drug involvement. The physician
1165 should consider contacting a poison control center for additional information on the treatment of
1166 any overdose. Telephone numbers for certified poison control centers are listed in the
1167 *Physicians' Desk Reference (PDR)*.

DOSAGE AND ADMINISTRATION

1168

1169 Major Depressive Disorder

1170 Initial Treatment

1171 Adult — In controlled trials used to support the efficacy of fluoxetine, patients were
1172 administered morning doses ranging from 20 to 80 mg/day. Studies comparing fluoxetine 20, 40,
1173 and 60 mg/day to placebo indicate that 20 mg/day is sufficient to obtain a satisfactory response
1174 in major depressive disorder in most cases. Consequently, a dose of 20 mg/day, administered in
1175 the morning, is recommended as the initial dose.

1176 A dose increase may be considered after several weeks if insufficient clinical improvement is
1177 observed. Doses above 20 mg/day may be administered on a once-a-day (morning) or BID
1178 schedule (i.e., morning and noon) and should not exceed a maximum dose of 80 mg/day.

1179 Pediatric (children and adolescents) — In the short-term (8 to 9 week) controlled clinical trials
1180 of fluoxetine supporting its effectiveness in the treatment of major depressive disorder, patients
1181 were administered fluoxetine doses of 10 to 20 mg/day (*see CLINICAL TRIALS*). Treatment
1182 should be initiated with a dose of 10 or 20 mg/day. After 1 week at 10 mg/day, the dose should
1183 be increased to 20 mg/day.

1184 However, due to higher plasma levels in lower weight children, the starting and target dose in
1185 this group may be 10 mg/day. A dose increase to 20 mg/day may be considered after several
1186 weeks if insufficient clinical improvement is observed.

1187 All patients — As with other drugs effective in the treatment of major depressive disorder, the
1188 full effect may be delayed until 4 weeks of treatment or longer.

1189 As with many other medications, a lower or less frequent dosage should be used in patients
1190 with hepatic impairment. A lower or less frequent dosage should also be considered for the
1191 elderly (*see Geriatric Use under PRECAUTIONS*), and for patients with concurrent disease or
1192 on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely
1193 necessary (*see Liver disease and Renal disease under CLINICAL PHARMACOLOGY, and Use*
1194 *in Patients with Concomitant Illness under PRECAUTIONS*).

1195 Maintenance/Continuation/Extended Treatment

1196 It is generally agreed that acute episodes of major depressive disorder require several months
1197 or longer of sustained pharmacologic therapy. Whether the dose needed to induce remission is
1198 identical to the dose needed to maintain and/or sustain euthymia is unknown.

1199 Daily Dosing

1200 Systematic evaluation of Prozac in adult patients has shown that its efficacy in major
1201 depressive disorder is maintained for periods of up to 38 weeks following 12 weeks of
1202 open-label acute treatment (50 weeks total) at a dose of 20 mg/day (*see CLINICAL TRIALS*).

1203 Weekly Dosing

1204 Systematic evaluation of Prozac Weekly in adult patients has shown that its efficacy in major
1205 depressive disorder is maintained for periods of up to 25 weeks with once-weekly dosing
1206 following 13 weeks of open-label treatment with Prozac 20 mg once daily. However, therapeutic
1207 equivalence of Prozac Weekly given on a once-weekly basis with Prozac 20 mg given daily for
1208 delaying time to relapse has not been established (*see CLINICAL TRIALS*).

1209 Weekly dosing with Prozac Weekly capsules is recommended to be initiated 7 days after the
1210 last daily dose of Prozac 20 mg (*see Weekly dosing under CLINICAL PHARMACOLOGY*).

1211 If satisfactory response is not maintained with Prozac Weekly, consider reestablishing a daily
1212 dosing regimen (*see CLINICAL TRIALS*).

1213 Switching Patients to a Tricyclic Antidepressant (TCA)

1214 Dosage of a TCA may need to be reduced, and plasma TCA concentrations may need to be
1215 monitored temporarily when fluoxetine is coadministered or has been recently discontinued (*see*
1216 Other drugs effective in the treatment of major depressive disorder *under* PRECAUTIONS, Drug
1217 Interactions).

1218 Switching Patients to or from a Monoamine Oxidase Inhibitor (MAOI)

1219 At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy
1220 with Prozac. In addition, at least 5 weeks, perhaps longer, should be allowed after stopping
1221 Prozac before starting an MAOI (*see* CONTRAINDICATIONS *and* PRECAUTIONS).

1222 **Obsessive Compulsive Disorder**

1223 Initial Treatment

1224 Adult — In the controlled clinical trials of fluoxetine supporting its effectiveness in the
1225 treatment of OCD, patients were administered fixed daily doses of 20, 40, or 60 mg of fluoxetine
1226 or placebo (*see* CLINICAL TRIALS). In 1 of these studies, no dose-response relationship for
1227 effectiveness was demonstrated. Consequently, a dose of 20 mg/day, administered in the
1228 morning, is recommended as the initial dose. Since there was a suggestion of a possible
1229 dose-response relationship for effectiveness in the second study, a dose increase may be
1230 considered after several weeks if insufficient clinical improvement is observed. The full
1231 therapeutic effect may be delayed until 5 weeks of treatment or longer.

1232 Doses above 20 mg/day may be administered on a once-a-day (i.e., morning) or BID schedule
1233 (i.e., morning and noon). A dose range of 20 to 60 mg/day is recommended; however, doses of
1234 up to 80 mg/day have been well tolerated in open studies of OCD. The maximum fluoxetine dose
1235 should not exceed 80 mg/day.

1236 Pediatric (children and adolescents) — In the controlled clinical trial of fluoxetine supporting
1237 its effectiveness in the treatment of OCD, patients were administered fluoxetine doses in the
1238 range of 10 to 60 mg/day (*see* CLINICAL TRIALS).

1239 In adolescents and higher weight children, treatment should be initiated with a dose of
1240 10 mg/day. After 2 weeks, the dose should be increased to 20 mg/day. Additional dose increases
1241 may be considered after several more weeks if insufficient clinical improvement is observed. A
1242 dose range of 20 to 60 mg/day is recommended.

1243 In lower weight children, treatment should be initiated with a dose of 10 mg/day. Additional
1244 dose increases may be considered after several more weeks if insufficient clinical improvement
1245 is observed. A dose range of 20 to 30 mg/day is recommended. Experience with daily doses
1246 greater than 20 mg is very minimal, and there is no experience with doses greater than 60 mg.

1247 All patients — As with the use of Prozac in the treatment of major depressive disorder, a lower
1248 or less frequent dosage should be used in patients with hepatic impairment. A lower or less
1249 frequent dosage should also be considered for the elderly (*see* Geriatric Use *under*
1250 PRECAUTIONS), and for patients with concurrent disease or on multiple concomitant
1251 medications. Dosage adjustments for renal impairment are not routinely necessary (*see* Liver
1252 disease *and* Renal disease *under* CLINICAL PHARMACOLOGY, *and* Use in Patients with
1253 Concomitant Illness *under* PRECAUTIONS).

1254 Maintenance/Continuation Treatment

1255 While there are no systematic studies that answer the question of how long to continue Prozac,
1256 OCD is a chronic condition and it is reasonable to consider continuation for a responding patient.
1257 Although the efficacy of Prozac after 13 weeks has not been documented in controlled trials,

1258 adult patients have been continued in therapy under double-blind conditions for up to an
1259 additional 6 months without loss of benefit. However, dosage adjustments should be made to
1260 maintain the patient on the lowest effective dosage, and patients should be periodically
1261 reassessed to determine the need for treatment.

1262 **Bulimia Nervosa**

1263 Initial Treatment

1264 In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of
1265 bulimia nervosa, patients were administered fixed daily fluoxetine doses of 20 or 60 mg, or
1266 placebo (*see* CLINICAL TRIALS). Only the 60-mg dose was statistically significantly superior
1267 to placebo in reducing the frequency of binge-eating and vomiting. Consequently, the
1268 recommended dose is 60 mg/day, administered in the morning. For some patients it may be
1269 advisable to titrate up to this target dose over several days. Fluoxetine doses above 60 mg/day
1270 have not been systematically studied in patients with bulimia.

1271 As with the use of Prozac in the treatment of major depressive disorder and OCD, a lower or
1272 less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent
1273 dosage should also be considered for the elderly (*see* Geriatric Use *under* PRECAUTIONS), and
1274 for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments
1275 for renal impairment are not routinely necessary (*see* Liver disease *and* Renal disease *under*
1276 CLINICAL PHARMACOLOGY, *and* Use in Patients with Concomitant Illness *under*
1277 PRECAUTIONS).

1278 Maintenance/Continuation Treatment

1279 Systematic evaluation of continuing Prozac 60 mg/day for periods of up to 52 weeks in
1280 patients with bulimia who have responded while taking Prozac 60 mg/day during an 8-week
1281 acute treatment phase has demonstrated a benefit of such maintenance treatment (*see* CLINICAL
1282 TRIALS). Nevertheless, patients should be periodically reassessed to determine the need for
1283 maintenance treatment.

1284 **Panic Disorder**

1285 Initial Treatment

1286 In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of
1287 panic disorder, patients were administered fluoxetine doses in the range of 10 to 60 mg/day (*see*
1288 CLINICAL TRIALS). Treatment should be initiated with a dose of 10 mg/day. After 1 week, the
1289 dose should be increased to 20 mg/day. The most frequently administered dose in the 2
1290 flexible-dose clinical trials was 20 mg/day.

1291 A dose increase may be considered after several weeks if no clinical improvement is observed.
1292 Fluoxetine doses above 60 mg/day have not been systematically evaluated in patients with panic
1293 disorder.

1294 As with the use of Prozac in other indications, a lower or less frequent dosage should be used
1295 in patients with hepatic impairment. A lower or less frequent dosage should also be considered
1296 for the elderly (*see* Geriatric Use *under* PRECAUTIONS), and for patients with concurrent
1297 disease or on multiple concomitant medications. Dosage adjustments for renal impairment are
1298 not routinely necessary (*see* Liver disease *and* Renal disease *under* CLINICAL
1299 PHARMACOLOGY, *and* Use in Patients with Concomitant Illness *under* PRECAUTIONS).

1300 Maintenance/Continuation Treatment

1301 While there are no systematic studies that answer the question of how long to continue Prozac,
 1302 panic disorder is a chronic condition and it is reasonable to consider continuation for a
 1303 responding patient. Nevertheless, patients should be periodically reassessed to determine the
 1304 need for continued treatment.

1305 **Special Populations**

1306 Treatment of Pregnant Women During the Third Trimester

1307 Neonates exposed to Prozac and other SSRIs or SNRIs, late in the third trimester have
 1308 developed complications requiring prolonged hospitalization, respiratory support, and tube
 1309 feeding (*see* PRECAUTIONS). When treating pregnant women with Prozac during the third
 1310 trimester, the physician should carefully consider the potential risks and benefits of treatment.
 1311 The physician may consider tapering Prozac in the third trimester.

1312 **Discontinuation of Treatment with Prozac**

1313 Symptoms associated with discontinuation of Prozac and other SSRIs and SNRIs, have been
 1314 reported (*see* PRECAUTIONS). Patients should be monitored for these symptoms when
 1315 discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is
 1316 recommended whenever possible. If intolerable symptoms occur following a decrease in the dose
 1317 or upon discontinuation of treatment, then resuming the previously prescribed dose may be
 1318 considered. Subsequently, the physician may continue decreasing the dose but at a more gradual
 1319 rate. Plasma fluoxetine and norfluoxetine concentration decrease gradually at the conclusion of
 1320 therapy which may minimize the risk of discontinuation symptoms with this drug.

1321 **HOW SUPPLIED**

1322 The following products are manufactured by Eli Lilly and Company for Dista Products
 1323 Company.

1324

Prozac[®] Pulvules[®], USP, are available in:

The 10-mg¹, Pulvule is opaque green cap and opaque green body, imprinted with
 DISTA 3104 on the cap and Prozac 10 mg on the body:

NDC 0777-3104-02 (PU3104²) - Bottles of 100

The 20-mg¹ Pulvule is an opaque green cap and opaque yellow body, imprinted
 with DISTA 3105 on the cap and Prozac 20 mg on the body:

NDC 0777-3105-30 (PU3105²) - Bottles of 30

NDC 0777-3105-02 (PU3105²) - Bottles of 100

NDC 0777-3105-07 (PU3105²) - Bottles of 2000

The 40-mg¹ Pulvule is an opaque green cap and opaque orange body, imprinted
 with DISTA 3107 on the cap and Prozac 40 mg on the body:

NDC 0777-3107-30 (PU3107²) - Bottles of 30

The following is manufactured by OSG Norwich Pharmaceuticals, Inc., North
 Norwich, NY, 13814, for Dista Products Company:

Liquid, Oral Solution is available in:

20 mg¹ per 5 mL with mint flavor:

NDC 0777-5120-58 (MS-5120³) - Bottles of 120 mL

The following product is manufactured and distributed by Eli Lilly and Company:

Prozac[®] Weekly[™] Capsules are available in:

The 90-mg¹ capsule is an opaque green cap and clear body containing discretely visible white pellets through the clear body of the capsule, imprinted with Lilly on the cap and 3004 and 90 mg on the body.

NDC 0002-3004-75 (PU3004) - Blister package of 4

1325

1326 ¹ Fluoxetine base equivalent.1327 ² Protect from light.1328 ³ Dispense in a tight, light-resistant container.

1329

1330 Store at Controlled Room Temperature, 15° to 30°C (59° to 86°F).

1331

ANIMAL TOXICOLOGY

1332 Phospholipids are increased in some tissues of mice, rats, and dogs given fluoxetine
1333 chronically. This effect is reversible after cessation of fluoxetine treatment. Phospholipid
1334 accumulation in animals has been observed with many cationic amphiphilic drugs, including
1335 fenfluramine, imipramine, and ranitidine. The significance of this effect in humans is unknown.

1336 Literature revised June 21, 2007

1337

Eli Lilly and Company
Indianapolis, IN 46285, USA

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www.lilly.com

PV 5324 DPP

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Medication Guide

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

1343

1344

1345 Read the Medication Guide that comes with your or your family member's antidepressant
1346 medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with
1347 antidepressant medicines. **Talk to your, or your family member's, healthcare provider**
1348 **about:**

1349

- all risks and benefits of treatment with antidepressant medicines

1350

- all treatment choices for depression or other serious mental illness

1351 **What is the most important information I should know about antidepressant**1352 **medicines, depression and other serious mental illnesses, and suicidal thoughts**
1353 **or actions?**

1354 **1. Antidepressant medicines may increase suicidal thoughts or actions in some children,**
1355 **teenagers, and young adults within the first few months of treatment.**

1356 **2. Depression and other serious mental illnesses are the most important causes of**
 1357 **suicidal thoughts and actions. Some people may have a particularly high risk of**
 1358 **having suicidal thoughts or actions.** These include people who have (or have a family
 1359 history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or
 1360 actions.

1361 **3. How can I watch for and try to prevent suicidal thoughts and actions in myself or a**
 1362 **family member?**

1363 • Pay close attention to any changes, especially sudden changes, in mood, behaviors,
 1364 thoughts, or feelings. This is very important when an antidepressant medicine is
 1365 started or when the dose is changed.

1366 • Call the healthcare provider right away to report new or sudden changes in mood,
 1367 behavior, thoughts, or feelings.

1368 • Keep all follow-up visits with the healthcare provider as scheduled. Call the
 1369 healthcare provider between visits as needed, especially if you have concerns about
 1370 symptoms.

1371 **Call a healthcare provider right away if you or your family member has any of the**
 1372 **following symptoms, especially if they are new, worse, or worry you:**

- 1373 • thoughts about suicide or dying
- 1374 • attempts to commit suicide
- 1375 • new or worse depression
- 1376 • new or worse anxiety
- 1377 • feeling very agitated or restless
- 1378 • panic attacks
- 1379 • trouble sleeping (insomnia)
- 1380 • new or worse irritability
- 1381 • acting aggressive, being angry, or violent
- 1382 • acting on dangerous impulses
- 1383 • an extreme increase in activity and talking (mania)
- 1384 • other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- 1385 • **Never stop an antidepressant medicine without first talking to a healthcare provider.**
 1386 Stopping an antidepressant medicine suddenly can cause other symptoms.
- 1387 • **Antidepressants are medicines used to treat depression and other illnesses.** It is
 1388 important to discuss all the risks of treating depression and also the risks of not treating it.
 1389 Patients and their families or other caregivers should discuss all treatment choices with the
 1390 healthcare provider, not just the use of antidepressants.
 1391

- 1392 • **Antidepressant medicines have other side effects.** Talk to the healthcare provider about
1393 the side effects of the medicine prescribed for you or your family member.
- 1394 • **Antidepressant medicines can interact with other medicines.** Know all of the medicines
1395 that you or your family member takes. Keep a list of all medicines to show the healthcare
1396 provider. Do not start new medicines without first checking with your healthcare provider.
- 1397 • **Not all antidepressant medicines prescribed for children are FDA approved for use in**
1398 **children.** Talk to your child's healthcare provider for more information.

1399 *This Medication Guide has been approved by the US Food and Drug Administration for*
1400 *all antidepressants.*

1401 Patient Information revised June 21, 2007

PV 5083 AMP

1402