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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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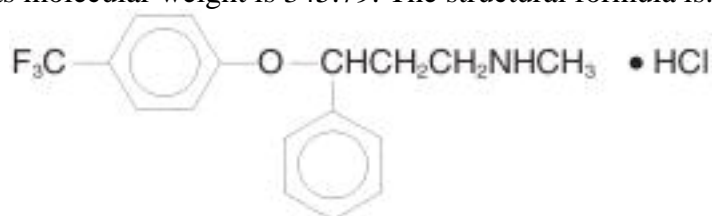
Suicidality and Antidepressant Drugs — Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use 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. 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 (\pm)-N-methyl-3-phenyl-3-[(α,α,α -trifluoro-*p*-tolyl)oxy]propylamine hydrochloride and has the empirical formula of $C_{17}H_{18}F_3NO \cdot HCl$. 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 μ mol), 20 mg (64.7 μ mol), or 40 mg (129.3 μ mol) 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 μ mol) 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
 413 **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

General

514 **Abnormal Bleeding** — SSRIs and SNRIs, including fluoxetine, may increase the risk of
515 bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and
516 other anti-coagulants may add to this risk. Case reports and epidemiological studies (case-control
517 and cohort design) have demonstrated an association between use of drugs that interfere with
518 serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to
519 SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to
520 life-threatening hemorrhages.
521

522 Patients should be cautioned about the risk of bleeding associated with the concomitant use of
523 fluoxetine and NSAIDs, aspirin, or other drugs that affect coagulation (*see Drug Interactions*).

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

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

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

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

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

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

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

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

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

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

565 **Hyponatremia** — Hyponatremia may occur as a result of treatment with SSRIs and SNRIs,
566 including Prozac. In many cases, this hyponatremia appears to be the result of the syndrome of
567 inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than
568 110 mmol/L have been reported and appeared to be reversible when Prozac was discontinued.
569 Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also,

570 patients taking diuretics or who are otherwise volume depleted may be at greater risk (*see*
571 Geriatric Use). Discontinuation of Prozac should be considered in patients with symptomatic
572 hyponatremia and appropriate medical intervention should be instituted.

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

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

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

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

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

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

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

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

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

614 **Discontinuation of Treatment with Prozac** — During marketing of Prozac and other SSRIs
615 and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous

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

628 **Information for Patients**

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

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

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

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

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

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

658 **Abnormal Bleeding** — Patients should be cautioned about the concomitant use of fluoxetine
659 and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of
660 psychotropic drugs that interfere with serotonin reuptake and these agents have been associated
661 with an increased risk of bleeding (*see* PRECAUTIONS, Abnormal Bleeding).

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

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

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

666 Laboratory Tests

667 There are no specific laboratory tests recommended.

668 Drug Interactions

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

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

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

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

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

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

704 Antipsychotics — Some clinical data suggests a possible pharmacodynamic and/or
705 pharmacokinetic interaction between SSRIs and antipsychotics. Elevation of blood levels of
706 haloperidol and clozapine has been observed in patients receiving concomitant fluoxetine.
707 Clinical studies of pimozide with other antidepressants demonstrate an increase in drug

708 interaction or QT_c prolongation. While a specific study with pimozone and fluoxetine has not
709 been conducted, the potential for drug interactions or QT_c prolongation warrants restricting the
710 concurrent use of pimozone and Prozac. Concomitant use of Prozac and pimozone is
711 contraindicated (*see* CONTRAINDICATIONS). For thioridazine, *see* CONTRAINDICATIONS
712 and WARNINGS.

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

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

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

724 Monoamine oxidase inhibitors — *See* CONTRAINDICATIONS.

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

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

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

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

748 Drugs that interfere with hemostasis (e.g., NSAIDs, Aspirin, Warfarin) — Serotonin release by
749 platelets plays an important role in hemostasis. Epidemiological studies of the case-control and
750 cohort design that have demonstrated an association between use of psychotropic drugs that
751 interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also
752 shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered
753 anticoagulant effects, including increased bleeding, have been reported when SSRIs or SNRIs

754 are coadministered with warfarin. Patients receiving warfarin therapy should be carefully
755 monitored when fluoxetine is initiated or discontinued.

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

759 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

771 Impairment of fertility — Two fertility studies conducted in adult rats at doses of up to 7.5 and
772 12.5 mg/kg/day (approximately 0.9 and 1.5 times the MRHD on a mg/m² basis) indicated that
773 fluoxetine had no adverse effects on fertility (*see* Pediatric Use).

774 **Pregnancy**

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

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

796 Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent
797 pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1-2 per 1000 live births in the
798 general population and is associated with substantial neonatal morbidity and mortality. In a
799 retrospective case-control study of 377 women whose infants were born with PPHN and 836

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

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

813 **Labor and Delivery**

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

818 **Nursing Mothers**

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

825 **Pediatric Use**

826 The efficacy of Prozac for the treatment of major depressive disorder was demonstrated in two
827 8- to 9-week placebo-controlled clinical trials with 315 pediatric outpatients ages 8 to ≤ 18 (*see*
828 CLINICAL TRIALS).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

897 Geriatric Use

898 US fluoxetine clinical trials included 687 patients ≥65 years of age and 93 patients ≥75 years
 899 of age. The efficacy in geriatric patients has been established (*see* CLINICAL TRIALS). For
 900 pharmacokinetic information in geriatric patients, see Age under CLINICAL
 901 PHARMACOLOGY. No overall differences in safety or effectiveness were observed between
 902 these subjects and younger subjects, and other reported clinical experience has not identified
 903 differences in responses between the elderly and younger patients, but greater sensitivity of some
 904 older individuals cannot be ruled out. SSRIs and SNRIs, including Prozac, have been associated
 905 with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk
 906 for this adverse event (*see* PRECAUTIONS, Hyponatremia).

907 ADVERSE REACTIONS

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

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

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

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

936 plus non-US panic disorder controlled clinical trials. Table 3 provides combined data for the pool
 937 of studies that are provided separately by indication in Table 2.
 938

939 **Table 2: Most Common Treatment-Emergent Adverse Events: Incidence in Major**
 940 **Depressive Disorder, OCD, Bulimia, and Panic Disorder Placebo-Controlled Clinical**
 941 **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

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

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

947 -- Incidence less than 1%.

948

949
950**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

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

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

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

965
 966 **Table 4: Most Common Adverse Events Associated with Discontinuation in Major**
 967 **Depressive Disorder, OCD, Bulimia, and Panic Disorder Placebo-Controlled Clinical**
 968 **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%)	--	--

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

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

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

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

990 Male and female sexual dysfunction with SSRIs — Although changes in sexual desire, sexual
 991 performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they
 992 may also be a consequence of pharmacologic treatment. In particular, some evidence suggests
 993 that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and
 994 severity of untoward experiences involving sexual desire, performance, and satisfaction are
 995 difficult to obtain, however, in part because patients and physicians may be reluctant to discuss
 996 them. Accordingly, estimates of the incidence of untoward sexual experience and performance,
 997 cited in product labeling, are likely to underestimate their actual incidence. In patients enrolled in
 998 US major depressive disorder, OCD, and bulimia placebo-controlled clinical trials, decreased
 999 libido was the only sexual side effect reported by at least 2% of patients taking fluoxetine (4%
 1000 fluoxetine, <1% placebo). There have been spontaneous reports in women taking fluoxetine of
 1001 orgasmic dysfunction, including anorgasmia.

1002 There are no adequate and well-controlled studies examining sexual dysfunction with
 1003 fluoxetine treatment.

1004 Priapism has been reported with all SSRIs.

1005 While it is difficult to know the precise risk of sexual dysfunction associated with the use of
 1006 SSRIs, physicians should routinely inquire about such possible side effects.

1007 **Other Events Observed in Clinical Trials**

1008 Following is a list of all treatment-emergent adverse events reported at anytime by individuals
 1009 taking fluoxetine in US clinical trials as of May 8, 1995 (10,782 patients) except (1) those listed
 1010 in the body or footnotes of Tables 2 or 3 above or elsewhere in labeling; (2) those for which the
 1011 COSTART terms were uninformative or misleading; (3) those events for which a causal
 1012 relationship to Prozac use was considered remote; and (4) events occurring in only 1 patient
 1013 treated with Prozac and which did not have a substantial probability of being acutely
 1014 life-threatening.

1015 Events are classified within body system categories using the following definitions: frequent
 1016 adverse events are defined as those occurring on one or more occasions in at least 1/100 patients;
 1017 infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those
 1018 occurring in less than 1/1000 patients.

1019 **Body as a Whole** — *Frequent*: chest pain, chills; *Infrequent*: chills and fever, face edema,
 1020 intentional overdose, malaise, pelvic pain, suicide attempt; *Rare*: acute abdominal syndrome,
 1021 hypothermia, intentional injury, neuroleptic malignant syndrome¹, photosensitivity reaction.

1022 **Cardiovascular System** — *Frequent*: hemorrhage, hypertension, palpitation; *Infrequent*:
 1023 angina pectoris, arrhythmia, congestive heart failure, hypotension, migraine, myocardial infarct,
 1024 postural hypotension, syncope, tachycardia, vascular headache; *Rare*: atrial fibrillation,
 1025 bradycardia, cerebral embolism, cerebral ischemia, cerebrovascular accident, extrasystoles, heart
 1026 arrest, heart block, pallor, peripheral vascular disorder, phlebitis, shock, thrombophlebitis,
 1027 thrombosis, vasospasm, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation.

1028 **Digestive System** — *Frequent*: increased appetite, nausea and vomiting; *Infrequent*: aphthous
 1029 stomatitis, cholelithiasis, colitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis,
 1030 glossitis, gum hemorrhage, hyperchlorhydria, increased salivation, liver function tests abnormal,
 1031 melena, mouth ulceration, nausea/vomiting/diarrhea, stomach ulcer, stomatitis, thirst; *Rare*:
 1032 biliary pain, bloody diarrhea, cholecystitis, duodenal ulcer, enteritis, esophageal ulcer, fecal
 1033 incontinence, gastrointestinal hemorrhage, hematemesis, hemorrhage of colon, hepatitis,
 1034 intestinal obstruction, liver fatty deposit, pancreatitis, peptic ulcer, rectal hemorrhage, salivary
 1035 gland enlargement, stomach ulcer hemorrhage, tongue edema.

- 1036 **Endocrine System** — *Infrequent*: hypothyroidism; *Rare*: diabetic acidosis, diabetes mellitus.
- 1037 **Hemic and Lymphatic System** — *Infrequent*: anemia, ecchymosis; *Rare*: blood dyscrasia,
 1038 hypochromic anemia, leukopenia, lymphedema, lymphocytosis, petechia, purpura,
 1039 thrombocythemia, thrombocytopenia.
- 1040 **Metabolic and Nutritional** — *Frequent*: weight gain; *Infrequent*: dehydration, generalized
 1041 edema, gout, hypercholesteremia, hyperlipemia, hypokalemia, peripheral edema; *Rare*: alcohol
 1042 intolerance, alkaline phosphatase increased, BUN increased, creatine phosphokinase increased,
 1043 hyperkalemia, hyperuricemia, hypocalcemia, iron deficiency anemia, SGPT increased.
- 1044 **Musculoskeletal System** — *Infrequent*: arthritis, bone pain, bursitis, leg cramps,
 1045 tenosynovitis; *Rare*: arthrosis, chondrodystrophy, myasthenia, myopathy, myositis,
 1046 osteomyelitis, osteoporosis, rheumatoid arthritis.
- 1047 **Nervous System** — *Frequent*: agitation, amnesia, confusion, emotional lability, sleep
 1048 disorder; *Infrequent*: abnormal gait, acute brain syndrome, akathisia, apathy, ataxia, buccoglossal
 1049 syndrome, CNS depression, CNS stimulation, depersonalization, euphoria, hallucinations,
 1050 hostility, hyperkinesia, hypertonia, hypesthesia, incoordination, libido increased, myoclonus,
 1051 neuralgia, neuropathy, neurosis, paranoid reaction, personality disorder², psychosis, vertigo;
 1052 *Rare*: abnormal electroencephalogram, antisocial reaction, circumoral paresthesia, coma,
 1053 delusions, dysarthria, dystonia, extrapyramidal syndrome, foot drop, hyperesthesia, neuritis,
 1054 paralysis, reflexes decreased, reflexes increased, stupor.
- 1055 **Respiratory System** — *Infrequent*: asthma, epistaxis, hiccup, hyperventilation; *Rare*: apnea,
 1056 atelectasis, cough decreased, emphysema, hemoptysis, hypoventilation, hypoxia, larynx edema,
 1057 lung edema, pneumothorax, stridor.
- 1058 **Skin and Appendages** — *Infrequent*: acne, alopecia, contact dermatitis, eczema,
 1059 maculopapular rash, skin discoloration, skin ulcer, vesiculobullous rash; *Rare*: furunculosis,
 1060 herpes zoster, hirsutism, petechial rash, psoriasis, purpuric rash, pustular rash, seborrhea.
- 1061 **Special Senses** — *Frequent*: ear pain, taste perversion, tinnitus; *Infrequent*: conjunctivitis, dry
 1062 eyes, mydriasis, photophobia; *Rare*: blepharitis, deafness, diplopia, exophthalmos, eye
 1063 hemorrhage, glaucoma, hyperacusis, iritis, parosmia, scleritis, strabismus, taste loss, visual field
 1064 defect.
- 1065 **Urogenital System** — *Frequent*: urinary frequency; *Infrequent*: abortion³, albuminuria,
 1066 amenorrhea³, anorgasmia, breast enlargement, breast pain, cystitis, dysuria, female lactation³,
 1067 fibrocystic breast³, hematuria, leukorrhea³, menorrhagia³, metrorrhagia³, nocturia, polyuria,
 1068 urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage³; *Rare*: breast
 1069 engorgement, glycosuria, hypomenorrhea³, kidney pain, oliguria, priapism³, uterine
 1070 hemorrhage³, uterine fibroids enlarged³.
- 1071 ¹ Neuroleptic malignant syndrome is the COSTART term which best captures serotonin syndrome.
 1072 ² Personality disorder is the COSTART term for designating nonaggressive objectionable behavior.
 1073 ³ Adjusted for gender.
- 1074

1075 Postintroduction Reports

1076 Voluntary reports of adverse events temporally associated with Prozac that have been received
 1077 since market introduction and that may have no causal relationship with the drug include the
 1078 following: aplastic anemia, atrial fibrillation, cataract, cerebral vascular accident, cholestatic
 1079 jaundice, confusion, dyskinesia (including, for example, a case of buccal-lingual-masticatory
 1080 syndrome with involuntary tongue protrusion reported to develop in a 77-year-old female after 5
 1081 weeks of fluoxetine therapy and which completely resolved over the next few months following
 1082 drug discontinuation), eosinophilic pneumonia, epidermal necrolysis, erythema multiforme,

1083 erythema nodosum, exfoliative dermatitis, gynecomastia, heart arrest, hepatic failure/necrosis,
 1084 hyperprolactinemia, hypoglycemia, immune-related hemolytic anemia, kidney failure,
 1085 misuse/abuse, movement disorders developing in patients with risk factors including drugs
 1086 associated with such events and worsening of preexisting movement disorders, neuroleptic
 1087 malignant syndrome-like events, optic neuritis, pancreatitis, pancytopenia, priapism, pulmonary
 1088 embolism, pulmonary hypertension, QT prolongation, serotonin syndrome (a range of signs and
 1089 symptoms that can rarely, in its most severe form, resemble neuroleptic malignant syndrome),
 1090 Stevens-Johnson syndrome, sudden unexpected death, suicidal ideation, thrombocytopenia,
 1091 thrombocytopenic purpura, vaginal bleeding after drug withdrawal, ventricular tachycardia
 1092 (including torsades de pointes-type arrhythmias), and violent behaviors.

1093 **DRUG ABUSE AND DEPENDENCE**

1094 **Controlled substance class** — Prozac is not a controlled substance.

1095 **Physical and psychological dependence** — Prozac has not been systematically studied, in
 1096 animals or humans, for its potential for abuse, tolerance, or physical dependence. While the
 1097 premarketing clinical experience with Prozac did not reveal any tendency for a withdrawal
 1098 syndrome or any drug seeking behavior, these observations were not systematic and it is not
 1099 possible to predict on the basis of this limited experience the extent to which a CNS active drug
 1100 will be misused, diverted, and/or abused once marketed. Consequently, physicians should
 1101 carefully evaluate patients for history of drug abuse and follow such patients closely, observing
 1102 them for signs of misuse or abuse of Prozac (e.g., development of tolerance, incrementation of
 1103 dose, drug-seeking behavior).

1104 **OVERDOSAGE**

1105 **Human Experience**

1106 Worldwide exposure to fluoxetine hydrochloride is estimated to be over 38 million patients
 1107 (circa 1999). Of the 1578 cases of overdose involving fluoxetine hydrochloride, alone or with
 1108 other drugs, reported from this population, there were 195 deaths.

1109 Among 633 adult patients who overdosed on fluoxetine hydrochloride alone, 34 resulted in a
 1110 fatal outcome, 378 completely recovered, and 15 patients experienced sequelae after overdose,
 1111 including abnormal accommodation, abnormal gait, confusion, unresponsiveness, nervousness,
 1112 pulmonary dysfunction, vertigo, tremor, elevated blood pressure, impotence, movement disorder,
 1113 and hypomania. The remaining 206 patients had an unknown outcome. The most common signs
 1114 and symptoms associated with non-fatal overdose were seizures, somnolence, nausea,
 1115 tachycardia, and vomiting. The largest known ingestion of fluoxetine hydrochloride in adult
 1116 patients was 8 grams in a patient who took fluoxetine alone and who subsequently recovered.
 1117 However, in an adult patient who took fluoxetine alone, an ingestion as low as 520 mg has been
 1118 associated with lethal outcome, but causality has not been established.

1119 Among pediatric patients (ages 3 months to 17 years), there were 156 cases of overdose
 1120 involving fluoxetine alone or in combination with other drugs. Six patients died, 127 patients
 1121 completely recovered, 1 patient experienced renal failure, and 22 patients had an unknown
 1122 outcome. One of the six fatalities was a 9-year-old boy who had a history of OCD, Tourette's
 1123 syndrome with tics, attention deficit disorder, and fetal alcohol syndrome. He had been receiving
 1124 100 mg of fluoxetine daily for 6 months in addition to clonidine, methylphenidate, and
 1125 promethazine. Mixed-drug ingestion or other methods of suicide complicated all 6 overdoses in
 1126 children that resulted in fatalities. The largest ingestion in pediatric patients was 3 grams which
 1127 was nonlethal.

1128 Other important adverse events reported with fluoxetine overdose (single or multiple drugs)
1129 include coma, delirium, ECG abnormalities (such as QT interval prolongation and ventricular
1130 tachycardia, including torsades de pointes-type arrhythmias), hypotension, mania, neuroleptic
1131 malignant syndrome-like events, pyrexia, stupor, and syncope.

1132 **Animal Experience**

1133 Studies in animals do not provide precise or necessarily valid information about the treatment
1134 of human overdose. However, animal experiments can provide useful insights into possible
1135 treatment strategies.

1136 The oral median lethal dose in rats and mice was found to be 452 and 248 mg/kg, respectively.
1137 Acute high oral doses produced hyperirritability and convulsions in several animal species.

1138 Among 6 dogs purposely overdosed with oral fluoxetine, 5 experienced grand mal seizures.
1139 Seizures stopped immediately upon the bolus intravenous administration of a standard veterinary
1140 dose of diazepam. In this short-term study, the lowest plasma concentration at which a seizure
1141 occurred was only twice the maximum plasma concentration seen in humans taking 80 mg/day,
1142 chronically.

1143 In a separate single-dose study, the ECG of dogs given high doses did not reveal prolongation
1144 of the PR, QRS, or QT intervals. Tachycardia and an increase in blood pressure were observed.
1145 Consequently, the value of the ECG in predicting cardiac toxicity is unknown. Nonetheless, the
1146 ECG should ordinarily be monitored in cases of human overdose (*see* Management of
1147 Overdose).

1148 **Management of Overdose**

1149 Treatment should consist of those general measures employed in the management of
1150 overdosage with any drug effective in the treatment of major depressive disorder.

1151 Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital
1152 signs. General supportive and symptomatic measures are also recommended. Induction of emesis
1153 is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway
1154 protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic
1155 patients.

1156 Activated charcoal should be administered. Due to the large volume of distribution of this
1157 drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of
1158 benefit. No specific antidotes for fluoxetine are known.

1159 A specific caution involves patients who are taking or have recently taken fluoxetine and might
1160 ingest excessive quantities of a TCA. In such a case, accumulation of the parent tricyclic and/or
1161 an active metabolite may increase the possibility of clinically significant sequelae and extend the
1162 time needed for close medical observation (*see* Other drugs effective in the treatment of major
1163 depressive disorder *under* PRECAUTIONS).

1164 Based on experience in animals, which may not be relevant to humans, fluoxetine-induced
1165 seizures that fail to remit spontaneously may respond to diazepam.

1166 In managing overdosage, consider the possibility of multiple drug involvement. The physician
1167 should consider contacting a poison control center for additional information on the treatment of
1168 any overdose. Telephone numbers for certified poison control centers are listed in the
1169 *Physicians' Desk Reference (PDR)*.

DOSAGE AND ADMINISTRATION

1170

1171 Major Depressive Disorder

1172 Initial Treatment

1173 Adult — In controlled trials used to support the efficacy of fluoxetine, patients were
1174 administered morning doses ranging from 20 to 80 mg/day. Studies comparing fluoxetine 20, 40,
1175 and 60 mg/day to placebo indicate that 20 mg/day is sufficient to obtain a satisfactory response
1176 in major depressive disorder in most cases. Consequently, a dose of 20 mg/day, administered in
1177 the morning, is recommended as the initial dose.

1178 A dose increase may be considered after several weeks if insufficient clinical improvement is
1179 observed. Doses above 20 mg/day may be administered on a once-a-day (morning) or BID
1180 schedule (i.e., morning and noon) and should not exceed a maximum dose of 80 mg/day.

1181 Pediatric (children and adolescents) — In the short-term (8 to 9 week) controlled clinical trials
1182 of fluoxetine supporting its effectiveness in the treatment of major depressive disorder, patients
1183 were administered fluoxetine doses of 10 to 20 mg/day (*see CLINICAL TRIALS*). Treatment
1184 should be initiated with a dose of 10 or 20 mg/day. After 1 week at 10 mg/day, the dose should
1185 be increased to 20 mg/day.

1186 However, due to higher plasma levels in lower weight children, the starting and target dose in
1187 this group may be 10 mg/day. A dose increase to 20 mg/day may be considered after several
1188 weeks if insufficient clinical improvement is observed.

1189 All patients — As with other drugs effective in the treatment of major depressive disorder, the
1190 full effect may be delayed until 4 weeks of treatment or longer.

1191 As with many other medications, a lower or less frequent dosage should be used in patients
1192 with hepatic impairment. A lower or less frequent dosage should also be considered for the
1193 elderly (*see Geriatric Use under PRECAUTIONS*), and for patients with concurrent disease or
1194 on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely
1195 necessary (*see Liver disease and Renal disease under CLINICAL PHARMACOLOGY, and Use*
1196 *in Patients with Concomitant Illness under PRECAUTIONS*).

1197 Maintenance/Continuation/Extended Treatment

1198 It is generally agreed that acute episodes of major depressive disorder require several months
1199 or longer of sustained pharmacologic therapy. Whether the dose needed to induce remission is
1200 identical to the dose needed to maintain and/or sustain euthymia is unknown.

1201 Daily Dosing

1202 Systematic evaluation of Prozac in adult patients has shown that its efficacy in major
1203 depressive disorder is maintained for periods of up to 38 weeks following 12 weeks of
1204 open-label acute treatment (50 weeks total) at a dose of 20 mg/day (*see CLINICAL TRIALS*).

1205 Weekly Dosing

1206 Systematic evaluation of Prozac Weekly in adult patients has shown that its efficacy in major
1207 depressive disorder is maintained for periods of up to 25 weeks with once-weekly dosing
1208 following 13 weeks of open-label treatment with Prozac 20 mg once daily. However, therapeutic
1209 equivalence of Prozac Weekly given on a once-weekly basis with Prozac 20 mg given daily for
1210 delaying time to relapse has not been established (*see CLINICAL TRIALS*).

1211 Weekly dosing with Prozac Weekly capsules is recommended to be initiated 7 days after the
1212 last daily dose of Prozac 20 mg (*see Weekly dosing under CLINICAL PHARMACOLOGY*).

1213 If satisfactory response is not maintained with Prozac Weekly, consider reestablishing a daily
1214 dosing regimen (*see CLINICAL TRIALS*).

1215 Switching Patients to a Tricyclic Antidepressant (TCA)

1216 Dosage of a TCA may need to be reduced, and plasma TCA concentrations may need to be
1217 monitored temporarily when fluoxetine is coadministered or has been recently discontinued (*see*
1218 Other drugs effective in the treatment of major depressive disorder *under* PRECAUTIONS, Drug
1219 Interactions).

1220 Switching Patients to or from a Monoamine Oxidase Inhibitor (MAOI)

1221 At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy
1222 with Prozac. In addition, at least 5 weeks, perhaps longer, should be allowed after stopping
1223 Prozac before starting an MAOI (*see* CONTRAINDICATIONS *and* PRECAUTIONS).

1224 Obsessive Compulsive Disorder

1225 Initial Treatment

1226 Adult — In the controlled clinical trials of fluoxetine supporting its effectiveness in the
1227 treatment of OCD, patients were administered fixed daily doses of 20, 40, or 60 mg of fluoxetine
1228 or placebo (*see* CLINICAL TRIALS). In 1 of these studies, no dose-response relationship for
1229 effectiveness was demonstrated. Consequently, a dose of 20 mg/day, administered in the
1230 morning, is recommended as the initial dose. Since there was a suggestion of a possible
1231 dose-response relationship for effectiveness in the second study, a dose increase may be
1232 considered after several weeks if insufficient clinical improvement is observed. The full
1233 therapeutic effect may be delayed until 5 weeks of treatment or longer.

1234 Doses above 20 mg/day may be administered on a once-a-day (i.e., morning) or BID schedule
1235 (i.e., morning and noon). A dose range of 20 to 60 mg/day is recommended; however, doses of
1236 up to 80 mg/day have been well tolerated in open studies of OCD. The maximum fluoxetine dose
1237 should not exceed 80 mg/day.

1238 Pediatric (children and adolescents) — In the controlled clinical trial of fluoxetine supporting
1239 its effectiveness in the treatment of OCD, patients were administered fluoxetine doses in the
1240 range of 10 to 60 mg/day (*see* CLINICAL TRIALS).

1241 In adolescents and higher weight children, treatment should be initiated with a dose of
1242 10 mg/day. After 2 weeks, the dose should be increased to 20 mg/day. Additional dose increases
1243 may be considered after several more weeks if insufficient clinical improvement is observed. A
1244 dose range of 20 to 60 mg/day is recommended.

1245 In lower weight children, treatment should be initiated with a dose of 10 mg/day. Additional
1246 dose increases may be considered after several more weeks if insufficient clinical improvement
1247 is observed. A dose range of 20 to 30 mg/day is recommended. Experience with daily doses
1248 greater than 20 mg is very minimal, and there is no experience with doses greater than 60 mg.

1249 All patients — As with the use of Prozac in the treatment of major depressive disorder, a lower
1250 or less frequent dosage should be used in patients with hepatic impairment. A lower or less
1251 frequent dosage should also be considered for the elderly (*see* Geriatric Use *under*
1252 PRECAUTIONS), and for patients with concurrent disease or on multiple concomitant
1253 medications. Dosage adjustments for renal impairment are not routinely necessary (*see* Liver
1254 disease *and* Renal disease *under* CLINICAL PHARMACOLOGY, *and* Use in Patients with
1255 Concomitant Illness *under* PRECAUTIONS).

1256 Maintenance/Continuation Treatment

1257 While there are no systematic studies that answer the question of how long to continue Prozac,
1258 OCD is a chronic condition and it is reasonable to consider continuation for a responding patient.
1259 Although the efficacy of Prozac after 13 weeks has not been documented in controlled trials,

1260 adult patients have been continued in therapy under double-blind conditions for up to an
1261 additional 6 months without loss of benefit. However, dosage adjustments should be made to
1262 maintain the patient on the lowest effective dosage, and patients should be periodically
1263 reassessed to determine the need for treatment.

1264 **Bulimia Nervosa**

1265 Initial Treatment

1266 In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of
1267 bulimia nervosa, patients were administered fixed daily fluoxetine doses of 20 or 60 mg, or
1268 placebo (*see* CLINICAL TRIALS). Only the 60-mg dose was statistically significantly superior
1269 to placebo in reducing the frequency of binge-eating and vomiting. Consequently, the
1270 recommended dose is 60 mg/day, administered in the morning. For some patients it may be
1271 advisable to titrate up to this target dose over several days. Fluoxetine doses above 60 mg/day
1272 have not been systematically studied in patients with bulimia.

1273 As with the use of Prozac in the treatment of major depressive disorder and OCD, a lower or
1274 less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent
1275 dosage should also be considered for the elderly (*see* Geriatric Use *under* PRECAUTIONS), and
1276 for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments
1277 for renal impairment are not routinely necessary (*see* Liver disease *and* Renal disease *under*
1278 CLINICAL PHARMACOLOGY, *and* Use in Patients with Concomitant Illness *under*
1279 PRECAUTIONS).

1280 Maintenance/Continuation Treatment

1281 Systematic evaluation of continuing Prozac 60 mg/day for periods of up to 52 weeks in
1282 patients with bulimia who have responded while taking Prozac 60 mg/day during an 8-week
1283 acute treatment phase has demonstrated a benefit of such maintenance treatment (*see* CLINICAL
1284 TRIALS). Nevertheless, patients should be periodically reassessed to determine the need for
1285 maintenance treatment.

1286 **Panic Disorder**

1287 Initial Treatment

1288 In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of
1289 panic disorder, patients were administered fluoxetine doses in the range of 10 to 60 mg/day (*see*
1290 CLINICAL TRIALS). Treatment should be initiated with a dose of 10 mg/day. After 1 week, the
1291 dose should be increased to 20 mg/day. The most frequently administered dose in the 2
1292 flexible-dose clinical trials was 20 mg/day.

1293 A dose increase may be considered after several weeks if no clinical improvement is observed.
1294 Fluoxetine doses above 60 mg/day have not been systematically evaluated in patients with panic
1295 disorder.

1296 As with the use of Prozac in other indications, a lower or less frequent dosage should be used
1297 in patients with hepatic impairment. A lower or less frequent dosage should also be considered
1298 for the elderly (*see* Geriatric Use *under* PRECAUTIONS), and for patients with concurrent
1299 disease or on multiple concomitant medications. Dosage adjustments for renal impairment are
1300 not routinely necessary (*see* Liver disease *and* Renal disease *under* CLINICAL
1301 PHARMACOLOGY, *and* Use in Patients with Concomitant Illness *under* PRECAUTIONS).

1302 Maintenance/Continuation Treatment

1303 While there are no systematic studies that answer the question of how long to continue Prozac,
 1304 panic disorder is a chronic condition and it is reasonable to consider continuation for a
 1305 responding patient. Nevertheless, patients should be periodically reassessed to determine the
 1306 need for continued treatment.

1307 **Special Populations**

1308 Treatment of Pregnant Women During the Third Trimester

1309 Neonates exposed to Prozac and other SSRIs or SNRIs, late in the third trimester have
 1310 developed complications requiring prolonged hospitalization, respiratory support, and tube
 1311 feeding (*see* PRECAUTIONS). When treating pregnant women with Prozac during the third
 1312 trimester, the physician should carefully consider the potential risks and benefits of treatment.
 1313 The physician may consider tapering Prozac in the third trimester.

1314 **Discontinuation of Treatment with Prozac**

1315 Symptoms associated with discontinuation of Prozac and other SSRIs and SNRIs, have been
 1316 reported (*see* PRECAUTIONS). Patients should be monitored for these symptoms when
 1317 discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is
 1318 recommended whenever possible. If intolerable symptoms occur following a decrease in the dose
 1319 or upon discontinuation of treatment, then resuming the previously prescribed dose may be
 1320 considered. Subsequently, the physician may continue decreasing the dose but at a more gradual
 1321 rate. Plasma fluoxetine and norfluoxetine concentration decrease gradually at the conclusion of
 1322 therapy which may minimize the risk of discontinuation symptoms with this drug.

1323 **HOW SUPPLIED**

1324 The following products are manufactured by Eli Lilly and Company for Dista Products
 1325 Company.

1326

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

1327

1328

¹ Fluoxetine base equivalent.

1329

² Protect from light.

1330

³ Dispense in a tight, light-resistant container.

1331

1332

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

1333

ANIMAL TOXICOLOGY

1334

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

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Literature revised January 16, 2008

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Medication Guide

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

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

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1351

- all risks and benefits of treatment with antidepressant medicines

1352

- all treatment choices for depression or other serious mental illness

1353

1354

1355

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

1356

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

1357

1358 **2. Depression and other serious mental illnesses are the most important causes of**
 1359 **suicidal thoughts and actions. Some people may have a particularly high risk of**
 1360 **having suicidal thoughts or actions.** These include people who have (or have a family
 1361 history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or
 1362 actions.

1363 **3. How can I watch for and try to prevent suicidal thoughts and actions in myself or a**
 1364 **family member?**

1365 • Pay close attention to any changes, especially sudden changes, in mood, behaviors,
 1366 thoughts, or feelings. This is very important when an antidepressant medicine is
 1367 started or when the dose is changed.

1368 • Call the healthcare provider right away to report new or sudden changes in mood,
 1369 behavior, thoughts, or feelings.

1370 • Keep all follow-up visits with the healthcare provider as scheduled. Call the
 1371 healthcare provider between visits as needed, especially if you have concerns about
 1372 symptoms.

1373 **Call a healthcare provider right away if you or your family member has any of the**
 1374 **following symptoms, especially if they are new, worse, or worry you:**

- 1375 • thoughts about suicide or dying
- 1376 • attempts to commit suicide
- 1377 • new or worse depression
- 1378 • new or worse anxiety
- 1379 • feeling very agitated or restless
- 1380 • panic attacks
- 1381 • trouble sleeping (insomnia)
- 1382 • new or worse irritability
- 1383 • acting aggressive, being angry, or violent
- 1384 • acting on dangerous impulses
- 1385 • an extreme increase in activity and talking (mania)
- 1386 • other unusual changes in behavior or mood

1387 **What else do I need to know about antidepressant medicines?**

1388 • **Never stop an antidepressant medicine without first talking to a healthcare provider.**
 1389 Stopping an antidepressant medicine suddenly can cause other symptoms.

1390 • **Antidepressants are medicines used to treat depression and other illnesses.** It is
 1391 important to discuss all the risks of treating depression and also the risks of not treating it.
 1392 Patients and their families or other caregivers should discuss all treatment choices with the
 1393 healthcare provider, not just the use of antidepressants.

- 1394 • **Antidepressant medicines have other side effects.** Talk to the healthcare provider about
1395 the side effects of the medicine prescribed for you or your family member.
- 1396 • **Antidepressant medicines can interact with other medicines.** Know all of the medicines
1397 that you or your family member takes. Keep a list of all medicines to show the healthcare
1398 provider. Do not start new medicines without first checking with your healthcare provider.
- 1399 • **Not all antidepressant medicines prescribed for children are FDA approved for use in**
1400 **children.** Talk to your child's healthcare provider for more information.

1401 *This Medication Guide has been approved by the US Food and Drug Administration for*
1402 *all antidepressants.*

1403 Patient Information revised June 21, 2007

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