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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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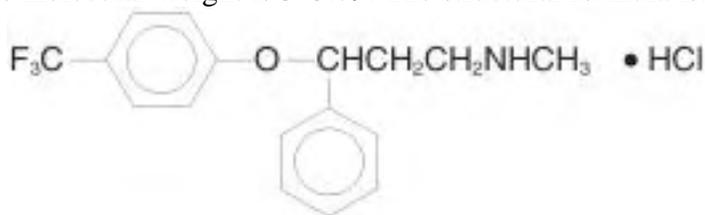
Suicidality and Antidepressant Drugs — Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use 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 or Neuroleptic Malignant Syndrome (NMS)-Like Reactions** — The
489 development of a potentially life-threatening serotonin syndrome, or Neuroleptic Malignant
490 Syndrome (NMS)-like reactions, has been reported with SNRIs and SSRIs alone, including
491 Prozac treatment, but particularly with concomitant use of serotonergic drugs (including triptans)
492 with drugs which impair metabolism of serotonin (including MAOIs), or with antipsychotics or
493 other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes
494 (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood
495 pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or
496 gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome, in its most
497 severe form, can resemble neuroleptic malignant syndrome, which includes hyperthermia,
498 muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental
499 status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-
500 like signs and symptoms.

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

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

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

508 Treatment with fluoxetine and any concomitant serotonergic or antidopaminergic agents,
509 including antipsychotics, should be discontinued immediately if the above events occur and
510 supportive symptomatic treatment should be initiated.

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

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

PRECAUTIONS

522

523 **General**

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

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

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

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

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

543 Among the most common adverse events associated with discontinuation (incidence at least
544 twice that for placebo and at least 1% for Prozac in clinical trials collecting only a primary event
545 associated with discontinuation) in US placebo-controlled fluoxetine clinical trials were anxiety
546 (2% in OCD), insomnia (1% in combined indications and 2% in bulimia), and nervousness (1%
547 in major depressive disorder) (*see Table 4*).

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

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

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

558 In US placebo-controlled clinical trials for bulimia nervosa, 8% of patients treated with Prozac
559 60 mg and 4% of patients treated with placebo reported anorexia (decreased appetite). Patients
560 treated with Prozac 60 mg on average lost 0.45 kg compared with a gain of 0.16 kg by patients
561 treated with placebo in the 16-week double-blind trial. Weight change should be monitored
562 during therapy.

563 **Activation of Mania/Hypomania** — In US placebo-controlled clinical trials for major
564 depressive disorder, mania/hypomania was reported in 0.1% of patients treated with Prozac and
565 0.1% of patients treated with placebo. Activation of mania/hypomania has also been reported in a
566 small proportion of patients with Major Affective Disorder treated with other marketed drugs

567 effective in the treatment of major depressive disorder (*see also* Pediatric Use *under*
568 PRECAUTIONS).

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

574 **Hyponatremia** — Hyponatremia may occur as a result of treatment with SSRIs and SNRIs,
575 including Prozac. In many cases, this hyponatremia appears to be the result of the syndrome of
576 inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than
577 110 mmol/L have been reported and appeared to be reversible when Prozac was discontinued.
578 Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also,
579 patients taking diuretics or who are otherwise volume depleted may be at greater risk (*see*
580 Geriatric Use). Discontinuation of Prozac should be considered in patients with symptomatic
581 hyponatremia and appropriate medical intervention should be instituted.

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

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

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

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

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

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

610 Studies in depressed patients on dialysis did not reveal excessive accumulation of fluoxetine or
611 norfluoxetine in plasma (*see* Renal disease *under* CLINICAL PHARMACOLOGY). Use of a

612 lower or less frequent dose for renally impaired patients is not routinely necessary (*see* DOSAGE
613 AND ADMINISTRATION).

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

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

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

637 **Information for Patients**

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

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

649 **Clinical Worsening and Suicide Risk** — Patients, their families, and their caregivers should
650 be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia,
651 irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness),
652 hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal
653 ideation, especially early during antidepressant treatment and when the dose is adjusted up or
654 down. Families and caregivers of patients should be advised to look for the emergence of such
655 symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be
656 reported to the patient’s prescriber or health professional, especially if they are severe, abrupt in
657 onset, or were not part of the patient’s presenting symptoms. Symptoms such as these may be

658 associated with an increased risk for suicidal thinking and behavior and indicate a need for very
659 close monitoring and possibly changes in the medication.

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

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

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

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

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

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

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

675 **Laboratory Tests**

676 There are no specific laboratory tests recommended.

677 **Drug Interactions**

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

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

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

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

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

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

713 Antipsychotics — Some clinical data suggests a possible pharmacodynamic and/or
714 pharmacokinetic interaction between SSRIs and antipsychotics. Elevation of blood levels of
715 haloperidol and clozapine has been observed in patients receiving concomitant fluoxetine.
716 Clinical studies of pimozide with other antidepressants demonstrate an increase in drug
717 interaction or QT_c prolongation. While a specific study with pimozide and fluoxetine has not
718 been conducted, the potential for drug interactions or QT_c prolongation warrants restricting the
719 concurrent use of pimozide and Prozac. Concomitant use of Prozac and pimozide is
720 contraindicated (*see* CONTRAINDICATIONS). For thioridazine, see CONTRAINDICATIONS
721 and WARNINGS.

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

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

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

733 Monoamine oxidase inhibitors — See CONTRAINDICATIONS.

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

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

747 Triptans — There have been rare postmarketing reports of serotonin syndrome with use of an
748 SSRI and a triptan. If concomitant treatment of Prozac with a triptan is clinically warranted,

749 careful observation of the patient is advised, particularly during treatment initiation and dose
750 increases (*see* Serotonin Syndrome *under* WARNINGS).

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

757 Drugs that interfere with hemostasis (e.g., NSAIDs, Aspirin, Warfarin) — Serotonin release by
758 platelets plays an important role in hemostasis. Epidemiological studies of the case-control and
759 cohort design that have demonstrated an association between use of psychotropic drugs that
760 interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also
761 shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered
762 anticoagulant effects, including increased bleeding, have been reported when SSRIs or SNRIs
763 are coadministered with warfarin. Patients receiving warfarin therapy should be carefully
764 monitored when fluoxetine is initiated or discontinued.

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

768 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

780 Impairment of fertility — Two fertility studies conducted in adult rats at doses of up to 7.5 and
781 12.5 mg/kg/day (approximately 0.9 and 1.5 times the MRHD on a mg/m² basis) indicated that
782 fluoxetine had no adverse effects on fertility (*see* Pediatric Use).

783 **Pregnancy**

784 Pregnancy Category C — In embryo-fetal development studies in rats and rabbits, there was
785 no evidence of teratogenicity following administration of up to 12.5 and 15 mg/kg/day,
786 respectively (1.5 and 3.6 times, respectively, the MRHD of 80 mg on a mg/m² basis) throughout
787 organogenesis. However, in rat reproduction studies, an increase in stillborn pups, a decrease in
788 pup weight, and an increase in pup deaths during the first 7 days postpartum occurred following
789 maternal exposure to 12 mg/kg/day (1.5 times the MRHD on a mg/m² basis) during gestation or
790 7.5 mg/kg/day (0.9 times the MRHD on a mg/m² basis) during gestation and lactation. There was
791 no evidence of developmental neurotoxicity in the surviving offspring of rats treated with
792 12 mg/kg/day during gestation. The no-effect dose for rat pup mortality was 5 mg/kg/day (0.6
793 times the MRHD on a mg/m² basis). Prozac should be used during pregnancy only if the
794 potential benefit justifies the potential risk to the fetus.

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

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

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

822 **Labor and Delivery**

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

827 **Nursing Mothers**

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

834 **Pediatric Use**

835 The efficacy of Prozac for the treatment of major depressive disorder was demonstrated in two
836 8- to 9-week placebo-controlled clinical trials with 315 pediatric outpatients ages 8 to ≤18 (*see*
837 CLINICAL TRIALS).

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

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

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

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

850 Manic reaction, including mania and hypomania, was reported in 6 (1 mania, 5 hypomania) out
851 of 228 (2.6%) fluoxetine-treated patients and in 0 out of 190 (0%) placebo-treated patients.
852 Mania/hypomania led to the discontinuation of 4 (1.8%) fluoxetine-treated patients from the
853 acute phases of the 3 studies combined. Consequently, regular monitoring for the occurrence of
854 mania/hypomania is recommended.

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

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

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

869 In a study in which fluoxetine (3, 10, or 30 mg/kg) was orally administered to young rats from
870 weaning (Postnatal Day 21) through adulthood (Day 90), male and female sexual development
871 was delayed at all doses, and growth (body weight gain, femur length) was decreased during the
872 dosing period in animals receiving the highest dose. At the end of the treatment period, serum
873 levels of creatine kinase (marker of muscle damage) were increased at the intermediate and high
874 doses, and abnormal muscle and reproductive organ histopathology (skeletal muscle
875 degeneration and necrosis, testicular degeneration and necrosis, epididymal vacuolation and
876 hypospermia) was observed at the high dose. When animals were evaluated after a recovery
877 period (up to 11 weeks after cessation of dosing), neurobehavioral abnormalities (decreased
878 reactivity at all doses and learning deficit at the high dose) and reproductive functional
879 impairment (decreased mating at all doses and impaired fertility at the high dose) were seen; in
880 addition, testicular and epididymal microscopic lesions and decreased sperm concentrations were
881 found in the high dose group, indicating that the reproductive organ effects seen at the end of
882 treatment were irreversible. The reversibility of fluoxetine-induced muscle damage was not
883 assessed. Adverse effects similar to those observed in rats treated with fluoxetine during the

884 juvenile period have not been reported after administration of fluoxetine to adult animals. Plasma
885 exposures (AUC) to fluoxetine in juvenile rats receiving the low, intermediate, and high dose in
886 this study were approximately 0.1-0.2, 1-2, and 5-10 times, respectively, the average exposure in
887 pediatric patients receiving the maximum recommended dose (MRD) of 20 mg/day. Rat
888 exposures to the major metabolite, norfluoxetine, were approximately 0.3-0.8, 1-8, and 3-20
889 times, respectively, pediatric exposure at the MRD.

890 A specific effect of fluoxetine on bone development has been reported in mice treated with
891 fluoxetine during the juvenile period. When mice were treated with fluoxetine (5 or 20 mg/kg,
892 intraperitoneal) for 4 weeks starting at 4 weeks of age, bone formation was reduced resulting in
893 decreased bone mineral content and density. These doses did not affect overall growth (body
894 weight gain or femoral length). The doses administered to juvenile mice in this study are
895 approximately 0.5 and 2 times the MRD for pediatric patients on a body surface area (mg/m²)
896 basis.

897 In another mouse study, administration of fluoxetine (10 mg/kg intraperitoneal) during early
898 postnatal development (Postnatal Days 4 to 21) produced abnormal emotional behaviors
899 (decreased exploratory behavior in elevated plus-maze, increased shock avoidance latency) in
900 adulthood (12 weeks of age). The dose used in this study is approximately equal to the pediatric
901 MRD on a mg/m² basis. Because of the early dosing period in this study, the significance of
902 these findings to the approved pediatric use in humans is uncertain.

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

906 Geriatric Use

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

916 ADVERSE REACTIONS

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

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

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

937 Incidence in major depressive disorder, OCD, bulimia, and panic disorder placebo-controlled
 938 clinical trials (excluding data from extensions of trials) — Table 2 enumerates the most common
 939 treatment-emergent adverse events associated with the use of Prozac (incidence of at least 5% for
 940 Prozac and at least twice that for placebo within at least 1 of the indications) for the treatment of
 941 major depressive disorder, OCD, and bulimia in US controlled clinical trials and panic disorder
 942 in US plus non-US controlled trials. Table 3 enumerates treatment-emergent adverse events that
 943 occurred in 2% or more patients treated with Prozac and with incidence greater than placebo who
 944 participated in US major depressive disorder, OCD, and bulimia controlled clinical trials and US
 945 plus non-US panic disorder controlled clinical trials. Table 3 provides combined data for the pool
 946 of studies that are provided separately by indication in Table 2.

947
 948 **Table 2: Most Common Treatment-Emergent Adverse Events: Incidence in Major**
 949 **Depressive Disorder, OCD, Bulimia, and Panic Disorder Placebo-Controlled Clinical**
 950 **Trials¹**

	Percentage of Patients Reporting Event							
	Major Depressive Disorder		OCD		Bulimia		Panic Disorder	
Body System/ Adverse Event	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

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

956 -- Incidence less than 1%.

957

958 **Table 3: Treatment-Emergent Adverse Events: Incidence in Major Depressive Disorder,**
959 **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

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

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

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

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

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

Other adverse events in pediatric patients (children and adolescents) — Treatment-emergent adverse events were collected in 322 pediatric patients (180 fluoxetine-treated, 142 placebo-treated). The overall profile of adverse events was generally similar to that seen in adult studies, as shown in Tables 2 and 3. However, the following adverse events (excluding those which appear in the body or footnotes of Tables 2 and 3 and those for which the COSTART terms were uninformative or misleading) were reported at an incidence of at least 2% for

987 fluoxetine and greater than placebo: thirst, hyperkinesia, agitation, personality disorder,
988 epistaxis, urinary frequency, and menorrhagia.

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

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

999 Male and female sexual dysfunction with SSRIs — Although changes in sexual desire, sexual
1000 performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they
1001 may also be a consequence of pharmacologic treatment. In particular, some evidence suggests
1002 that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and
1003 severity of untoward experiences involving sexual desire, performance, and satisfaction are
1004 difficult to obtain, however, in part because patients and physicians may be reluctant to discuss
1005 them. Accordingly, estimates of the incidence of untoward sexual experience and performance,
1006 cited in product labeling, are likely to underestimate their actual incidence. In patients enrolled in
1007 US major depressive disorder, OCD, and bulimia placebo-controlled clinical trials, decreased
1008 libido was the only sexual side effect reported by at least 2% of patients taking fluoxetine (4%
1009 fluoxetine, <1% placebo). There have been spontaneous reports in women taking fluoxetine of
1010 orgasmic dysfunction, including anorgasmia.

1011 There are no adequate and well-controlled studies examining sexual dysfunction with
1012 fluoxetine treatment.

1013 Priapism has been reported with all SSRIs.

1014 While it is difficult to know the precise risk of sexual dysfunction associated with the use of
1015 SSRIs, physicians should routinely inquire about such possible side effects.

1016 **Other Events Observed in Clinical Trials**

1017 Following is a list of all treatment-emergent adverse events reported at anytime by individuals
1018 taking fluoxetine in US clinical trials as of May 8, 1995 (10,782 patients) except (1) those listed
1019 in the body or footnotes of Tables 2 or 3 above or elsewhere in labeling; (2) those for which the
1020 COSTART terms were uninformative or misleading; (3) those events for which a causal
1021 relationship to Prozac use was considered remote; and (4) events occurring in only 1 patient
1022 treated with Prozac and which did not have a substantial probability of being acutely
1023 life-threatening.

1024 Events are classified within body system categories using the following definitions: frequent
1025 adverse events are defined as those occurring on one or more occasions in at least 1/100 patients;
1026 infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those
1027 occurring in less than 1/1000 patients.

1028 **Body as a Whole** — *Frequent*: chest pain, chills; *Infrequent*: chills and fever, face edema,
1029 intentional overdose, malaise, pelvic pain, suicide attempt; *Rare*: acute abdominal syndrome,
1030 hypothermia, intentional injury, neuroleptic malignant syndrome¹, photosensitivity reaction.

1031 **Cardiovascular System** — *Frequent*: hemorrhage, hypertension, palpitation; *Infrequent*:
1032 angina pectoris, arrhythmia, congestive heart failure, hypotension, migraine, myocardial infarct,

- 1033 postural hypotension, syncope, tachycardia, vascular headache; *Rare*: atrial fibrillation,
 1034 bradycardia, cerebral embolism, cerebral ischemia, cerebrovascular accident, extrasystoles, heart
 1035 arrest, heart block, pallor, peripheral vascular disorder, phlebitis, shock, thrombophlebitis,
 1036 thrombosis, vasospasm, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation.
- 1037 **Digestive System** — *Frequent*: increased appetite, nausea and vomiting; *Infrequent*: aphthous
 1038 stomatitis, cholelithiasis, colitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis,
 1039 glossitis, gum hemorrhage, hyperchlorhydria, increased salivation, liver function tests abnormal,
 1040 melena, mouth ulceration, nausea/vomiting/diarrhea, stomach ulcer, stomatitis, thirst; *Rare*:
 1041 biliary pain, bloody diarrhea, cholecystitis, duodenal ulcer, enteritis, esophageal ulcer, fecal
 1042 incontinence, gastrointestinal hemorrhage, hematemesis, hemorrhage of colon, hepatitis,
 1043 intestinal obstruction, liver fatty deposit, pancreatitis, peptic ulcer, rectal hemorrhage, salivary
 1044 gland enlargement, stomach ulcer hemorrhage, tongue edema.
- 1045 **Endocrine System** — *Infrequent*: hypothyroidism; *Rare*: diabetic acidosis, diabetes mellitus.
- 1046 **Hemic and Lymphatic System** — *Infrequent*: anemia, ecchymosis; *Rare*: blood dyscrasia,
 1047 hypochromic anemia, leukopenia, lymphedema, lymphocytosis, petechia, purpura,
 1048 thrombocythemia, thrombocytopenia.
- 1049 **Metabolic and Nutritional** — *Frequent*: weight gain; *Infrequent*: dehydration, generalized
 1050 edema, gout, hypercholesteremia, hyperlipemia, hypokalemia, peripheral edema; *Rare*: alcohol
 1051 intolerance, alkaline phosphatase increased, BUN increased, creatine phosphokinase increased,
 1052 hyperkalemia, hyperuricemia, hypocalcemia, iron deficiency anemia, SGPT increased.
- 1053 **Musculoskeletal System** — *Infrequent*: arthritis, bone pain, bursitis, leg cramps,
 1054 tenosynovitis; *Rare*: arthrosis, chondrodystrophy, myasthenia, myopathy, myositis,
 1055 osteomyelitis, osteoporosis, rheumatoid arthritis.
- 1056 **Nervous System** — *Frequent*: agitation, amnesia, confusion, emotional lability, sleep
 1057 disorder; *Infrequent*: abnormal gait, acute brain syndrome, akathisia, apathy, ataxia, buccoglossal
 1058 syndrome, CNS depression, CNS stimulation, depersonalization, euphoria, hallucinations,
 1059 hostility, hyperkinesia, hypertonia, hypesthesia, incoordination, libido increased, myoclonus,
 1060 neuralgia, neuropathy, neurosis, paranoid reaction, personality disorder², psychosis, vertigo;
 1061 *Rare*: abnormal electroencephalogram, antisocial reaction, circumoral paresthesia, coma,
 1062 delusions, dysarthria, dystonia, extrapyramidal syndrome, foot drop, hyperesthesia, neuritis,
 1063 paralysis, reflexes decreased, reflexes increased, stupor.
- 1064 **Respiratory System** — *Infrequent*: asthma, epistaxis, hiccup, hyperventilation; *Rare*: apnea,
 1065 atelectasis, cough decreased, emphysema, hemoptysis, hypoventilation, hypoxia, larynx edema,
 1066 lung edema, pneumothorax, stridor.
- 1067 **Skin and Appendages** — *Infrequent*: acne, alopecia, contact dermatitis, eczema,
 1068 maculopapular rash, skin discoloration, skin ulcer, vesiculobullous rash; *Rare*: furunculosis,
 1069 herpes zoster, hirsutism, petechial rash, psoriasis, purpuric rash, pustular rash, seborrhea.
- 1070 **Special Senses** — *Frequent*: ear pain, taste perversion, tinnitus; *Infrequent*: conjunctivitis, dry
 1071 eyes, mydriasis, photophobia; *Rare*: blepharitis, deafness, diplopia, exophthalmos, eye
 1072 hemorrhage, glaucoma, hyperacusis, iritis, parosmia, scleritis, strabismus, taste loss, visual field
 1073 defect.
- 1074 **Urogenital System** — *Frequent*: urinary frequency; *Infrequent*: abortion³, albuminuria,
 1075 amenorrhea³, anorgasmia, breast enlargement, breast pain, cystitis, dysuria, female lactation³,
 1076 fibrocystic breast³, hematuria, leukorrhea³, menorrhagia³, metrorrhagia³, nocturia, polyuria,
 1077 urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage³; *Rare*: breast

1078 engorgement, glycosuria, hypomenorrhea³, kidney pain, oliguria, priapism³, uterine
 1079 hemorrhage³, uterine fibroids enlarged³.

1080 ¹ Neuroleptic malignant syndrome is the COSTART term which best captures serotonin syndrome.

1081 ² Personality disorder is the COSTART term for designating nonaggressive objectionable behavior.

1082 ³ Adjusted for gender.

1083

1084 **Postintroduction Reports**

1085 Voluntary reports of adverse events temporally associated with Prozac that have been received
 1086 since market introduction and that may have no causal relationship with the drug include the
 1087 following: aplastic anemia, atrial fibrillation, cataract, cerebral vascular accident, cholestatic
 1088 jaundice, confusion, dyskinesia (including, for example, a case of buccal-lingual-masticatory
 1089 syndrome with involuntary tongue protrusion reported to develop in a 77-year-old female after 5
 1090 weeks of fluoxetine therapy and which completely resolved over the next few months following
 1091 drug discontinuation), eosinophilic pneumonia, epidermal necrolysis, erythema multiforme,
 1092 erythema nodosum, exfoliative dermatitis, gynecomastia, heart arrest, hepatic failure/necrosis,
 1093 hyperprolactinemia, hypoglycemia, immune-related hemolytic anemia, kidney failure,
 1094 misuse/abuse, movement disorders developing in patients with risk factors including drugs
 1095 associated with such events and worsening of preexisting movement disorders, optic neuritis,
 1096 pancreatitis, pancytopenia, priapism, pulmonary embolism, pulmonary hypertension, QT
 1097 prolongation, Stevens-Johnson syndrome, sudden unexpected death, suicidal ideation,
 1098 thrombocytopenia, thrombocytopenic purpura, vaginal bleeding after drug withdrawal,
 1099 ventricular tachycardia (including torsades de pointes-type arrhythmias), and violent behaviors.

1100

DRUG ABUSE AND DEPENDENCE

1101 **Controlled substance class** — Prozac is not a controlled substance.

1102 **Physical and psychological dependence** — Prozac has not been systematically studied, in
 1103 animals or humans, for its potential for abuse, tolerance, or physical dependence. While the
 1104 premarketing clinical experience with Prozac did not reveal any tendency for a withdrawal
 1105 syndrome or any drug seeking behavior, these observations were not systematic and it is not
 1106 possible to predict on the basis of this limited experience the extent to which a CNS active drug
 1107 will be misused, diverted, and/or abused once marketed. Consequently, physicians should
 1108 carefully evaluate patients for history of drug abuse and follow such patients closely, observing
 1109 them for signs of misuse or abuse of Prozac (e.g., development of tolerance, incrementation of
 1110 dose, drug-seeking behavior).

1111

OVERDOSAGE

Human Experience

1113 Worldwide exposure to fluoxetine hydrochloride is estimated to be over 38 million patients
 1114 (circa 1999). Of the 1578 cases of overdose involving fluoxetine hydrochloride, alone or with
 1115 other drugs, reported from this population, there were 195 deaths.

1116 Among 633 adult patients who overdosed on fluoxetine hydrochloride alone, 34 resulted in a
 1117 fatal outcome, 378 completely recovered, and 15 patients experienced sequelae after overdose,
 1118 including abnormal accommodation, abnormal gait, confusion, unresponsiveness, nervousness,
 1119 pulmonary dysfunction, vertigo, tremor, elevated blood pressure, impotence, movement disorder,
 1120 and hypomania. The remaining 206 patients had an unknown outcome. The most common signs
 1121 and symptoms associated with non-fatal overdose were seizures, somnolence, nausea,
 1122 tachycardia, and vomiting. The largest known ingestion of fluoxetine hydrochloride in adult

1123 patients was 8 grams in a patient who took fluoxetine alone and who subsequently recovered.
1124 However, in an adult patient who took fluoxetine alone, an ingestion as low as 520 mg has been
1125 associated with lethal outcome, but causality has not been established.

1126 Among pediatric patients (ages 3 months to 17 years), there were 156 cases of overdose
1127 involving fluoxetine alone or in combination with other drugs. Six patients died, 127 patients
1128 completely recovered, 1 patient experienced renal failure, and 22 patients had an unknown
1129 outcome. One of the six fatalities was a 9-year-old boy who had a history of OCD, Tourette's
1130 syndrome with tics, attention deficit disorder, and fetal alcohol syndrome. He had been receiving
1131 100 mg of fluoxetine daily for 6 months in addition to clonidine, methylphenidate, and
1132 promethazine. Mixed-drug ingestion or other methods of suicide complicated all 6 overdoses in
1133 children that resulted in fatalities. The largest ingestion in pediatric patients was 3 grams which
1134 was nonlethal.

1135 Other important adverse events reported with fluoxetine overdose (single or multiple drugs)
1136 include coma, delirium, ECG abnormalities (such as QT interval prolongation and ventricular
1137 tachycardia, including torsades de pointes-type arrhythmias), hypotension, mania, neuroleptic
1138 malignant syndrome-like events, pyrexia, stupor, and syncope.

1139 **Animal Experience**

1140 Studies in animals do not provide precise or necessarily valid information about the treatment
1141 of human overdose. However, animal experiments can provide useful insights into possible
1142 treatment strategies.

1143 The oral median lethal dose in rats and mice was found to be 452 and 248 mg/kg, respectively.
1144 Acute high oral doses produced hyperirritability and convulsions in several animal species.

1145 Among 6 dogs purposely overdosed with oral fluoxetine, 5 experienced grand mal seizures.
1146 Seizures stopped immediately upon the bolus intravenous administration of a standard veterinary
1147 dose of diazepam. In this short-term study, the lowest plasma concentration at which a seizure
1148 occurred was only twice the maximum plasma concentration seen in humans taking 80 mg/day,
1149 chronically.

1150 In a separate single-dose study, the ECG of dogs given high doses did not reveal prolongation
1151 of the PR, QRS, or QT intervals. Tachycardia and an increase in blood pressure were observed.
1152 Consequently, the value of the ECG in predicting cardiac toxicity is unknown. Nonetheless, the
1153 ECG should ordinarily be monitored in cases of human overdose (*see* Management of
1154 Overdose).

1155 **Management of Overdose**

1156 Treatment should consist of those general measures employed in the management of
1157 overdosage with any drug effective in the treatment of major depressive disorder.

1158 Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital
1159 signs. General supportive and symptomatic measures are also recommended. Induction of emesis
1160 is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway
1161 protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic
1162 patients.

1163 Activated charcoal should be administered. Due to the large volume of distribution of this
1164 drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of
1165 benefit. No specific antidotes for fluoxetine are known.

1166 A specific caution involves patients who are taking or have recently taken fluoxetine and might
1167 ingest excessive quantities of a TCA. In such a case, accumulation of the parent tricyclic and/or
1168 an active metabolite may increase the possibility of clinically significant sequelae and extend the

1169 time needed for close medical observation (*see* Other drugs effective in the treatment of major
1170 depressive disorder *under* PRECAUTIONS).

1171 Based on experience in animals, which may not be relevant to humans, fluoxetine-induced
1172 seizures that fail to remit spontaneously may respond to diazepam.

1173 In managing overdosage, consider the possibility of multiple drug involvement. The physician
1174 should consider contacting a poison control center for additional information on the treatment of
1175 any overdose. Telephone numbers for certified poison control centers are listed in the
1176 *Physicians' Desk Reference (PDR)*.

1177 **DOSAGE AND ADMINISTRATION**

1178 **Major Depressive Disorder**

1179 Initial Treatment

1180 Adult — In controlled trials used to support the efficacy of fluoxetine, patients were
1181 administered morning doses ranging from 20 to 80 mg/day. Studies comparing fluoxetine 20, 40,
1182 and 60 mg/day to placebo indicate that 20 mg/day is sufficient to obtain a satisfactory response
1183 in major depressive disorder in most cases. Consequently, a dose of 20 mg/day, administered in
1184 the morning, is recommended as the initial dose.

1185 A dose increase may be considered after several weeks if insufficient clinical improvement is
1186 observed. Doses above 20 mg/day may be administered on a once-a-day (morning) or BID
1187 schedule (i.e., morning and noon) and should not exceed a maximum dose of 80 mg/day.

1188 Pediatric (children and adolescents) — In the short-term (8 to 9 week) controlled clinical trials
1189 of fluoxetine supporting its effectiveness in the treatment of major depressive disorder, patients
1190 were administered fluoxetine doses of 10 to 20 mg/day (*see* CLINICAL TRIALS). Treatment
1191 should be initiated with a dose of 10 or 20 mg/day. After 1 week at 10 mg/day, the dose should
1192 be increased to 20 mg/day.

1193 However, due to higher plasma levels in lower weight children, the starting and target dose in
1194 this group may be 10 mg/day. A dose increase to 20 mg/day may be considered after several
1195 weeks if insufficient clinical improvement is observed.

1196 All patients — As with other drugs effective in the treatment of major depressive disorder, the
1197 full effect may be delayed until 4 weeks of treatment or longer.

1198 As with many other medications, a lower or less frequent dosage should be used in patients
1199 with hepatic impairment. A lower or less frequent dosage should also be considered for the
1200 elderly (*see* Geriatric Use *under* PRECAUTIONS), and for patients with concurrent disease or
1201 on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely
1202 necessary (*see* Liver disease *and* Renal disease *under* CLINICAL PHARMACOLOGY, *and* Use
1203 in Patients with Concomitant Illness *under* PRECAUTIONS).

1204 Maintenance/Continuation/Extended Treatment

1205 It is generally agreed that acute episodes of major depressive disorder require several months
1206 or longer of sustained pharmacologic therapy. Whether the dose needed to induce remission is
1207 identical to the dose needed to maintain and/or sustain euthymia is unknown.

1208 Daily Dosing

1209 Systematic evaluation of Prozac in adult patients has shown that its efficacy in major
1210 depressive disorder is maintained for periods of up to 38 weeks following 12 weeks of
1211 open-label acute treatment (50 weeks total) at a dose of 20 mg/day (*see* CLINICAL TRIALS).

1212 Weekly Dosing

1213 Systematic evaluation of Prozac Weekly in adult patients has shown that its efficacy in major
1214 depressive disorder is maintained for periods of up to 25 weeks with once-weekly dosing
1215 following 13 weeks of open-label treatment with Prozac 20 mg once daily. However, therapeutic
1216 equivalence of Prozac Weekly given on a once-weekly basis with Prozac 20 mg given daily for
1217 delaying time to relapse has not been established (*see CLINICAL TRIALS*).

1218 Weekly dosing with Prozac Weekly capsules is recommended to be initiated 7 days after the
1219 last daily dose of Prozac 20 mg (*see Weekly dosing under CLINICAL PHARMACOLOGY*).

1220 If satisfactory response is not maintained with Prozac Weekly, consider reestablishing a daily
1221 dosing regimen (*see CLINICAL TRIALS*).

1222 Switching Patients to a Tricyclic Antidepressant (TCA)

1223 Dosage of a TCA may need to be reduced, and plasma TCA concentrations may need to be
1224 monitored temporarily when fluoxetine is coadministered or has been recently discontinued (*see*
1225 *Other drugs effective in the treatment of major depressive disorder under PRECAUTIONS, Drug*
1226 *Interactions*).

1227 Switching Patients to or from a Monoamine Oxidase Inhibitor (MAOI)

1228 At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy
1229 with Prozac. In addition, at least 5 weeks, perhaps longer, should be allowed after stopping
1230 Prozac before starting an MAOI (*see CONTRAINDICATIONS and PRECAUTIONS*).

1231 Obsessive Compulsive Disorder

1232 Initial Treatment

1233 Adult — In the controlled clinical trials of fluoxetine supporting its effectiveness in the
1234 treatment of OCD, patients were administered fixed daily doses of 20, 40, or 60 mg of fluoxetine
1235 or placebo (*see CLINICAL TRIALS*). In 1 of these studies, no dose-response relationship for
1236 effectiveness was demonstrated. Consequently, a dose of 20 mg/day, administered in the
1237 morning, is recommended as the initial dose. Since there was a suggestion of a possible
1238 dose-response relationship for effectiveness in the second study, a dose increase may be
1239 considered after several weeks if insufficient clinical improvement is observed. The full
1240 therapeutic effect may be delayed until 5 weeks of treatment or longer.

1241 Doses above 20 mg/day may be administered on a once-a-day (i.e., morning) or BID schedule
1242 (i.e., morning and noon). A dose range of 20 to 60 mg/day is recommended; however, doses of
1243 up to 80 mg/day have been well tolerated in open studies of OCD. The maximum fluoxetine dose
1244 should not exceed 80 mg/day.

1245 Pediatric (children and adolescents) — In the controlled clinical trial of fluoxetine supporting
1246 its effectiveness in the treatment of OCD, patients were administered fluoxetine doses in the
1247 range of 10 to 60 mg/day (*see CLINICAL TRIALS*).

1248 In adolescents and higher weight children, treatment should be initiated with a dose of
1249 10 mg/day. After 2 weeks, the dose should be increased to 20 mg/day. Additional dose increases
1250 may be considered after several more weeks if insufficient clinical improvement is observed. A
1251 dose range of 20 to 60 mg/day is recommended.

1252 In lower weight children, treatment should be initiated with a dose of 10 mg/day. Additional
1253 dose increases may be considered after several more weeks if insufficient clinical improvement
1254 is observed. A dose range of 20 to 30 mg/day is recommended. Experience with daily doses
1255 greater than 20 mg is very minimal, and there is no experience with doses greater than 60 mg.

1256 All patients — As with the use of Prozac in the treatment of major depressive disorder, a lower
1257 or less frequent dosage should be used in patients with hepatic impairment. A lower or less
1258 frequent dosage should also be considered for the elderly (*see Geriatric Use under*
1259 PRECAUTIONS), and for patients with concurrent disease or on multiple concomitant
1260 medications. Dosage adjustments for renal impairment are not routinely necessary (*see Liver*
1261 *disease and Renal disease under CLINICAL PHARMACOLOGY, and Use in Patients with*
1262 *Concomitant Illness under PRECAUTIONS*).

1263 Maintenance/Continuation Treatment

1264 While there are no systematic studies that answer the question of how long to continue Prozac,
1265 OCD is a chronic condition and it is reasonable to consider continuation for a responding patient.
1266 Although the efficacy of Prozac after 13 weeks has not been documented in controlled trials,
1267 adult patients have been continued in therapy under double-blind conditions for up to an
1268 additional 6 months without loss of benefit. However, dosage adjustments should be made to
1269 maintain the patient on the lowest effective dosage, and patients should be periodically
1270 reassessed to determine the need for treatment.

1271 **Bulimia Nervosa**

1272 Initial Treatment

1273 In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of
1274 bulimia nervosa, patients were administered fixed daily fluoxetine doses of 20 or 60 mg, or
1275 placebo (*see CLINICAL TRIALS*). Only the 60-mg dose was statistically significantly superior
1276 to placebo in reducing the frequency of binge-eating and vomiting. Consequently, the
1277 recommended dose is 60 mg/day, administered in the morning. For some patients it may be
1278 advisable to titrate up to this target dose over several days. Fluoxetine doses above 60 mg/day
1279 have not been systematically studied in patients with bulimia.

1280 As with the use of Prozac in the treatment of major depressive disorder and OCD, a lower or
1281 less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent
1282 dosage should also be considered for the elderly (*see Geriatric Use under PRECAUTIONS*), and
1283 for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments
1284 for renal impairment are not routinely necessary (*see Liver disease and Renal disease under*
1285 *CLINICAL PHARMACOLOGY, and Use in Patients with Concomitant Illness under*
1286 *PRECAUTIONS*).

1287 Maintenance/Continuation Treatment

1288 Systematic evaluation of continuing Prozac 60 mg/day for periods of up to 52 weeks in
1289 patients with bulimia who have responded while taking Prozac 60 mg/day during an 8-week
1290 acute treatment phase has demonstrated a benefit of such maintenance treatment (*see CLINICAL*
1291 *TRIALS*). Nevertheless, patients should be periodically reassessed to determine the need for
1292 maintenance treatment.

1293 **Panic Disorder**

1294 Initial Treatment

1295 In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of
1296 panic disorder, patients were administered fluoxetine doses in the range of 10 to 60 mg/day (*see*
1297 *CLINICAL TRIALS*). Treatment should be initiated with a dose of 10 mg/day. After 1 week, the
1298 dose should be increased to 20 mg/day. The most frequently administered dose in the 2
1299 flexible-dose clinical trials was 20 mg/day.

1300 A dose increase may be considered after several weeks if no clinical improvement is observed.
 1301 Fluoxetine doses above 60 mg/day have not been systematically evaluated in patients with panic
 1302 disorder.

1303 As with the use of Prozac in other indications, a lower or less frequent dosage should be used
 1304 in patients with hepatic impairment. A lower or less frequent dosage should also be considered
 1305 for the elderly (*see Geriatric Use under PRECAUTIONS*), and for patients with concurrent
 1306 disease or on multiple concomitant medications. Dosage adjustments for renal impairment are
 1307 not routinely necessary (*see Liver disease and Renal disease under CLINICAL*
 1308 *PHARMACOLOGY, and Use in Patients with Concomitant Illness under PRECAUTIONS*).

1309 Maintenance/Continuation Treatment

1310 While there are no systematic studies that answer the question of how long to continue Prozac,
 1311 panic disorder is a chronic condition and it is reasonable to consider continuation for a
 1312 responding patient. Nevertheless, patients should be periodically reassessed to determine the
 1313 need for continued treatment.

1314 Special Populations

1315 Treatment of Pregnant Women During the Third Trimester

1316 Neonates exposed to Prozac and other SSRIs or SNRIs, late in the third trimester have
 1317 developed complications requiring prolonged hospitalization, respiratory support, and tube
 1318 feeding (*see PRECAUTIONS*). When treating pregnant women with Prozac during the third
 1319 trimester, the physician should carefully consider the potential risks and benefits of treatment.
 1320 The physician may consider tapering Prozac in the third trimester.

1321 Discontinuation of Treatment with Prozac

1322 Symptoms associated with discontinuation of Prozac and other SSRIs and SNRIs, have been
 1323 reported (*see PRECAUTIONS*). Patients should be monitored for these symptoms when
 1324 discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is
 1325 recommended whenever possible. If intolerable symptoms occur following a decrease in the dose
 1326 or upon discontinuation of treatment, then resuming the previously prescribed dose may be
 1327 considered. Subsequently, the physician may continue decreasing the dose but at a more gradual
 1328 rate. Plasma fluoxetine and norfluoxetine concentration decrease gradually at the conclusion of
 1329 therapy which may minimize the risk of discontinuation symptoms with this drug.

1330 HOW SUPPLIED

1331 The following products are manufactured by Eli Lilly and Company for Dista Products
 1332 Company.

1333

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

1334

1335 ¹ Fluoxetine base equivalent.1336 ² Protect from light.1337 ³ Dispense in a tight, light-resistant container.

1338

1339 Store at Controlled Room Temperature, 15° to 30°C (59° to 86°F).

1340

ANIMAL TOXICOLOGY

1341 Phospholipids are increased in some tissues of mice, rats, and dogs given fluoxetine
1342 chronically. This effect is reversible after cessation of fluoxetine treatment. Phospholipid
1343 accumulation in animals has been observed with many cationic amphiphilic drugs, including
1344 fenfluramine, imipramine, and ranitidine. The significance of this effect in humans is unknown.

1345 Literature revised MMM DD, 2009

1346

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