

1  
2  
3  
4  
5

**PROZAC<sup>®</sup>**  
**FLUOXETINE CAPSULES, USP**  
**FLUOXETINE ORAL SOLUTION, USP**  
**FLUOXETINE DELAYED-RELEASE CAPSULES, USP**

6  
7

**WARNING**

8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22

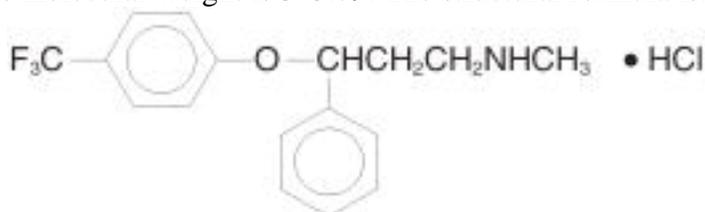
**Suicidality and Antidepressant Drugs — Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use 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.)**

23  
24

**DESCRIPTION**

25  
26  
27  
28

Prozac<sup>®</sup> (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<sup>®</sup>, fluoxetine hydrochloride). It is designated ( $\pm$ )-N-methyl-3-phenyl-3-[( $\alpha,\alpha,\alpha$ -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:



29  
30  
31

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

32  
33  
34  
35  
36

Each Pulvule<sup>®</sup> contains fluoxetine hydrochloride equivalent to 10 mg (32.3  $\mu$ mol), 20 mg (64.7  $\mu$ mol), or 40 mg (129.3  $\mu$ 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.

37  
38  
39

The oral solution contains fluoxetine hydrochloride equivalent to 20 mg/5 mL (64.7  $\mu$ 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  $\alpha_1$ -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  $\alpha_1$ -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 ( $\geq 60$  years of age) who received 20 mg fluoxetine for 6 weeks. Combined  
160 fluoxetine plus norfluoxetine plasma concentrations were  $209.3 \pm 85.7$  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 ( $\geq 18$  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 ( $\geq 60$  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  $\leq 8$ . 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  $\leq 7$  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  $\geq 14$  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  $\leq 18$ ) 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  $\leq 9$ , a CGI-Severity rating of  $\leq 2$ , 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 ( $\geq 18$  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**

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

414

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

513

## PRECAUTIONS

### 514 General

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

### 628 **Information for Patients**

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

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

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

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

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

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

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

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

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

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

### 666 **Laboratory Tests**

667 There are no specific laboratory tests recommended.

### 668 **Drug Interactions**

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

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

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

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

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

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

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

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

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

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

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

724 Monoamine oxidase inhibitors — *See* CONTRAINDICATIONS.

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

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

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

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

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

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

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

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

760 There is no evidence of carcinogenicity or mutagenicity from in vitro or animal studies.  
761 Impairment of fertility in adult animals at doses up to 12.5 mg/kg/day (approximately 1.5 times  
762 the MRHD on a mg/m<sup>2</sup> basis) was not observed.

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

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

771 Impairment of fertility — Two fertility studies conducted in adult rats at doses of up to 7.5 and  
772 12.5 mg/kg/day (approximately 0.9 and 1.5 times the MRHD on a mg/m<sup>2</sup> basis) indicated that  
773 fluoxetine had no adverse effects on fertility (*see* Pediatric Use).

### 774 **Pregnancy**

775 *Pregnancy Category C* — In embryo-fetal development studies in rats and rabbits, there was  
776 no evidence of teratogenicity following administration of up to 12.5 and 15 mg/kg/day,  
777 respectively (1.5 and 3.6 times, respectively, the MRHD of 80 mg on a mg/m<sup>2</sup> basis) throughout  
778 organogenesis. However, in rat reproduction studies, an increase in stillborn pups, a decrease in  
779 pup weight, and an increase in pup deaths during the first 7 days postpartum occurred following  
780 maternal exposure to 12 mg/kg/day (1.5 times the MRHD on a mg/m<sup>2</sup> basis) during gestation or  
781 7.5 mg/kg/day (0.9 times the MRHD on a mg/m<sup>2</sup> basis) during gestation and lactation. There was  
782 no evidence of developmental neurotoxicity in the surviving offspring of rats treated with  
783 12 mg/kg/day during gestation. The no-effect dose for rat pup mortality was 5 mg/kg/day (0.6  
784 times the MRHD on a mg/m<sup>2</sup> basis). Prozac should be used during pregnancy only if the  
785 potential benefit justifies the potential risk to the fetus.

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

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

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

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

### 813 **Labor and Delivery**

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

### 818 **Nursing Mothers**

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

### 825 **Pediatric Use**

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

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

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

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

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

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

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

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

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

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

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

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

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

890 (decreased exploratory behavior in elevated plus-maze, increased shock avoidance latency) in  
891 adulthood (12 weeks of age). The dose used in this study is approximately equal to the pediatric  
892 MRD on a mg/m<sup>2</sup> basis. Because of the early dosing period in this study, the significance of  
893 these findings to the approved pediatric use in humans is uncertain.

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

### 897 **Geriatric Use**

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

### 907 **ADVERSE REACTIONS**

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

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

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

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

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

939 **Table 2: Most Common Treatment-Emergent Adverse Events: Incidence in Major**  
 940 **Depressive Disorder, OCD, Bulimia, and Panic Disorder Placebo-Controlled Clinical**  
 941 **Trials<sup>1</sup>**

Body System/ Adverse Event	Percentage of Patients Reporting Event							
	Major Depressive Disorder		OCD		Bulimia		Panic Disorder	
	Prozac (N=1728)	Placebo (N=975)	Prozac (N=266)	Placebo (N=89)	Prozac (N=450)	Placebo (N=267)	Prozac (N=425)	Placebo (N=342)
<b>Body as a Whole</b>								
Asthenia	9	5	15	11	21	9	7	7
Flu syndrome	3	4	10	7	8	3	5	5
<b>Cardiovascular System</b>								
Vasodilatation	3	2	5	--	2	1	1	--
<b>Digestive System</b>								
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
<b>Nervous System</b>								
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
<b>Respiratory System</b>								
Pharyngitis	3	3	11	9	10	5	3	3
Sinusitis	1	4	5	2	6	4	2	3
Yawn	--	--	7	--	11	--	1	--
<b>Skin and Appendages</b>								
Sweating	8	3	7	--	8	3	2	2
Rash	4	3	6	3	4	4	2	2
<b>Urogenital System</b>								
Impotence <sup>2</sup>	2	--	--	--	7	--	1	--
Abnormal ejaculation <sup>2</sup>	--	--	7	--	7	--	2	1

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

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

947 -- Incidence less than 1%.

948

949  
950**Table 3: Treatment-Emergent Adverse Events: Incidence in Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Placebo-Controlled Clinical Trials<sup>1</sup>**

	Percentage of Patients Reporting Event	
	Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Combined	
<b>Body System/ Adverse Event<sup>2</sup></b>	Prozac (N=2869)	Placebo (N=1673)
<b>Body as a Whole</b>		
Headache	21	19
Asthenia	11	6
Flu syndrome	5	4
Fever	2	1
<b>Cardiovascular System</b>		
Vasodilatation	2	1
<b>Digestive System</b>		
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
<b>Metabolic and Nutritional Disorders</b>		
Weight loss	2	1
<b>Nervous System</b>		
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
<b>Respiratory System</b>		
Yawn	3	--
<b>Skin and Appendages</b>		
Sweating	7	3
Rash	4	3
Pruritus	3	2
<b>Special Senses</b>		
Abnormal vision	2	1

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

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

965  
 966 **Table 4: Most Common Adverse Events Associated with Discontinuation in Major**  
 967 **Depressive Disorder, OCD, Bulimia, and Panic Disorder Placebo-Controlled Clinical**  
 968 **Trials<sup>1</sup>**

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

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

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

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

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

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

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

1004 Priapism has been reported with all SSRIs.

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

#### 1007 **Other Events Observed in Clinical Trials**

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

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

1019 **Body as a Whole** — *Frequent*: chest pain, chills; *Infrequent*: chills and fever, face edema,  
 1020 intentional overdose, malaise, pelvic pain, suicide attempt; *Rare*: acute abdominal syndrome,  
 1021 hypothermia, intentional injury, neuroleptic malignant syndrome<sup>1</sup>, photosensitivity reaction.

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

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

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

## 1075 Postintroduction Reports

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

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

### 1093 **DRUG ABUSE AND DEPENDENCE**

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

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

### 1104 **OVERDOSAGE**

#### 1105 **Human Experience**

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

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

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

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

### 1132 **Animal Experience**

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

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

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

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

### 1148 **Management of Overdose**

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

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

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

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

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

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

## DOSAGE AND ADMINISTRATION

1170

### 1171 Major Depressive Disorder

#### 1172 Initial Treatment

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

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

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

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

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

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

#### 1197 Maintenance/Continuation/Extended Treatment

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

#### 1201 Daily Dosing

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

#### 1205 Weekly Dosing

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

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

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

### 1215 Switching Patients to a Tricyclic Antidepressant (TCA)

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

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

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

## 1224 Obsessive Compulsive Disorder

### 1225 Initial Treatment

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

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

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

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

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

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

### 1256 Maintenance/Continuation Treatment

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

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

## 1264 **Bulimia Nervosa**

### 1265 Initial Treatment

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

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

### 1280 Maintenance/Continuation Treatment

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

## 1286 **Panic Disorder**

### 1287 Initial Treatment

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

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

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

1302 Maintenance/Continuation Treatment

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

1307 **Special Populations**

1308 Treatment of Pregnant Women During the Third Trimester

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

1314 **Discontinuation of Treatment with Prozac**

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

1323 **HOW SUPPLIED**

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

1326

Prozac<sup>®</sup> Pulvules<sup>®</sup>, USP, are available in:

The 10-mg<sup>1</sup>, 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 (PU3104<sup>2</sup>) - Bottles of 100

The 20-mg<sup>1</sup> 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 (PU3105<sup>2</sup>) - Bottles of 30

NDC 0777-3105-02 (PU3105<sup>2</sup>) - Bottles of 100

NDC 0777-3105-07 (PU3105<sup>2</sup>) - Bottles of 2000

The 40-mg<sup>1</sup> 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 (PU3107<sup>2</sup>) - 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 mg<sup>1</sup> per 5 mL with mint flavor:

NDC 0777-5120-58 (MS-5120<sup>3</sup>) - Bottles of 120 mL

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

Prozac<sup>®</sup> Weekly<sup>™</sup> Capsules are available in:

The 90-mg<sup>1</sup> capsule is an opaque green cap and clear body containing discretely visible white pellets through the clear body of the capsule, imprinted with Lilly on the cap and 3004 and 90 mg on the body.

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

1327

1328

<sup>1</sup> Fluoxetine base equivalent.

1329

<sup>2</sup> Protect from light.

1330

<sup>3</sup> Dispense in a tight, light-resistant container.

1331

1332

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

1333

### ANIMAL TOXICOLOGY

1334

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

1335

1336

1337

1338

Literature revised January 16, 2008

1339

1340

1341

1342

**Eli Lilly and Company  
Indianapolis, IN 46285, USA**

[www.lilly.com](http://www.lilly.com)

PV 5326 DPP

PRINTED IN USA

1343

1344

## Medication Guide

1345

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

1346

1347

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

1348

1349

1350

1351

- all risks and benefits of treatment with antidepressant medicines

1352

- all treatment choices for depression or other serious mental illness

1353

1354

1355

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

1356

1357

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

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

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

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

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

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

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

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

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

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

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

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

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

1403 Patient Information revised June 21, 2007

PV 5083 AMP

1404