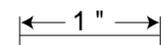




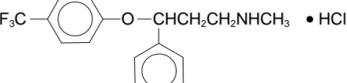
PV 3456 DPP  
PROZAC®  
FLUOXETINE  
HYDROCHLORIDE



PV 3456 DPP

**PROZAC®**  
**FLUOXETINE HYDROCHLORIDE**

DESCRIPTION  
Prozac® (fluoxetine hydrochloride) is a psychotropic drug for oral administration. It is also marketed for the treatment of premenstrual dysphoric disorder (Sarafen™, fluoxetine hydrochloride). It is designated (S)-N-methyl-3-phenyl-3-( $\alpha,\alpha$ -trifluoro-p-tolyl)oxypropylamine hydrochloride and has the empirical formula of C<sub>17</sub>H<sub>15</sub>F<sub>3</sub>NHCl. Its molecular weight is 345.79. The structural formula is:



Fluoxetine hydrochloride is a white to off-white crystalline solid with a solubility of 14 mg/mL in water. Each Pulvule® contains fluoxetine hydrochloride equivalent to 10 mg (32.3 µmol), 20 mg (64.7 µmol), or 40 mg (129.3 µmol) of fluoxetine. The Pulvules also contain starch, gelatin, silicon dioxide, 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.

Each tablet contains fluoxetine hydrochloride equivalent to 10 mg (32.3 µmol) of fluoxetine. The tablets also contain microcrystalline cellulose, magnesium stearate, croscarmellose sodium, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, and yellow iron oxide. In addition to the above ingredients, the 10-mg tablet contains FD&C Blue No. 1 aluminum lake and polyorbital 80.

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

Prozac Weekly™ capsules, a delayed-release formulation, contain enteric-coated pellets of fluoxetine hydrochloride equivalent to 90 mg (281 µmol) of fluoxetine. The capsules also contain D&C Yellow No. 10, FD&C Blue No. 2, gelatin, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose acetate succinate, sodium lauryl sulfate, sucrose, sugar spheres, talc, titanium dioxide, triethyl citrate, and other inactive ingredients.

**CLINICAL PHARMACOLOGY**

**Pharmacodynamics**  
The antidepressant, antidepressant-compulsive, and antimanic actions of fluoxetine are presumed to be linked to its inhibition of CNS neuronal uptake of serotonin. Studies in clinically relevant doses in man have demonstrated that fluoxetine blocks the uptake of serotonin into human platelets. Studies in animals also suggest that fluoxetine is a much more potent uptake inhibitor of serotonin than of norepinephrine.

Antagonism of muscarinic, histaminergic, and  $\alpha_1$ -adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects of classical tricyclic antidepressant (TCA) drugs. Fluoxetine binds to these and other membrane receptors from brain tissue much less potently than do the tricyclic drugs.

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

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

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

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

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

**Clinical issues related to metabolism/elimination** — The complexity of the metabolism of fluoxetine has several consequences that may potentially affect fluoxetine's clinical use.  
**Variability in metabolism** — A subset (about 7%) of the population has reduced activity of the drug metabolizing enzyme cytochrome P450 2D6 (CYP2D6). Such individuals are referred to as "poor metabolizers" of drugs such as desipramine, dextromethorphan, and the TCAs. In a study of 100 patients administered as a racemate, these individuals metabolized S-fluoxetine at a slower rate and thus achieved higher concentrations of S-fluoxetine. Consequently, concentrations of S-norfluoxetine at steady state were lower. The metabolism of R-fluoxetine in these poor metabolizers appears normal. When compared with normal metabolizers, the total sum at steady state of the plasma concentrations of the 4 active enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. Alternative, nonalterable pathways (non-2D6) contribute to the metabolism of fluoxetine. This explains how fluoxetine achieves a steady-state concentration rather than increasing without limit.

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

**Accumulation and slow elimination** — The relatively slow elimination of fluoxetine (elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration) and its active metabolite, norfluoxetine (elimination half-life of 4 to 16 days after acute and chronic administration), leads to significant accumulation of these active species in chronic use and delayed attainment of steady state, even when a fixed dose is used. Following a 40 mg daily plasma concentration of fluoxetine in the range of 11 to 302 ng/mL, and norfluoxetine in the range of 72 to 258 ng/mL, have been observed. Plasma concentrations of fluoxetine were higher than those predicted by single-dose studies, because fluoxetine's metabolism is not proportional to dose. Norfluoxetine, however, appears to have linear pharmacokinetics. Its mean terminal half-life after a single dose was 8.6 days and after multiple dosing was 9.3 days. Steady-state levels after prolonged dosing are similar to levels seen at 4 to 5 weeks.

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

**Weekly dosing** — Prozac Weekly once weekly results in increased fluctuation between peak and trough concentrations of fluoxetine and norfluoxetine compared with once-daily dosing [for fluoxetine: 24% (daily) to 164% (weekly) and for norfluoxetine: 17% (daily) to 43% (weekly)]. Plasma concentrations may not necessarily be predictive of clinical response. Peak concentrations from once-weekly doses of Prozac Weekly capsules of fluoxetine are in the range of the average concentration for 20-mg once-daily dosing. Average trough concentrations are 70% lower for fluoxetine and 47% lower for norfluoxetine than the concentrations maintained by 20-mg once-daily dosing. Average steady-state concentrations of either once-daily or once-weekly dosing are in relative proportion to the total dose administered. Average steady-state fluoxetine concentrations are approximately 50% lower following the once-weekly regimen compared with the once-daily regimen.

$C_{max}$  for fluoxetine following the 90-mg dose was approximately 1.7-fold higher than the  $C_{max}$  value for the established 20-mg once-daily regimen following transition the next day to the once-weekly regimen. In a study of 19 patients receiving Prozac Weekly capsules, the 90-mg dose were separated by 1 week.  $C_{max}$  values were similar. Also, there was a transient increase in the average steady-state concentrations of fluoxetine observed following transition the next day to the once-weekly regimen. From a pharmacokinetic perspective, it may be better to separate the first 90-mg weekly dose and the last 20-mg once-daily dose by 1 week (see DOSAGE AND ADMINISTRATION).

**Liver disease** — As might be expected, the long elimination half-lives of fluoxetine and norfluoxetine are affected by the elimination of fluoxetine. The elimination half-life of fluoxetine was prolonged in a study of cirrhotic patients, with a mean of 7.6 days compared with the range of 2 to 3 days seen in subjects without liver disease; norfluoxetine elimination was also delayed, with a mean duration of 12 days for cirrhotic patients compared with the range of 7 to 9 days in normal subjects. This suggests that the use of fluoxetine in patients with liver disease must be approached with caution. If fluoxetine is administered to patients with liver disease, a lower or less frequent dose should be used (see PRECAUTIONS AND DOSAGE AND ADMINISTRATION).

**Renal disease** — In depressed patients on dialysis (N=12), fluoxetine administered as 20 mg once daily for 2 months produced steady-state fluoxetine and norfluoxetine plasma concentrations comparable with those seen in patients with normal renal function. While the possibility exists that renally excreted metabolites of fluoxetine may accumulate in patients with severe renal dysfunction, the use of fluoxetine in these patients does not routinely necessitate renal monitoring. In renally impaired patients (see Use in patients with concomitant illness) PRECAUTIONS AND DOSAGE AND ADMINISTRATION.

**Age**  
**Geriatric pharmacokinetics** — The disposition of single doses of fluoxetine in healthy elderly subjects (>65 years of age) did not differ significantly from that in younger normal subjects. However, given the long half-life and nonlinear disposition of the drug, a single-dose study is not adequate to rule out the possibility of altered pharmacokinetics in the elderly, particularly if they have systemic illness or are receiving multiple drugs for concomitant diseases. The effects of age upon the metabolism of fluoxetine have been investigated in 260 elderly but otherwise healthy depressed patients (≥60 years of age) who received 20 mg fluoxetine for 6 weeks. Combined fluoxetine plus norfluoxetine plasma concentrations were 239.3 ± 85.7 ng/mL at the end of 6 weeks. No unusual age-associated pattern of adverse events was observed in these elderly patients.

**Pediatric pharmacokinetics (children and adolescents)** — Fluoxetine pharmacokinetics were evaluated in 21 pediatric patients (10 children ages 6 to <13, 11 adolescents ages 13 to <18) diagnosed with major depressive disorder or obsessive-compulsive disorder (OCD). Fluoxetine 20 mg/day was administered for up to 62 days. The average steady-state concentrations of fluoxetine in these children were 2-fold higher than in adolescents (171 and 88 ng/mL, respectively). The average norfluoxetine steady-state concentrations in these children were 1.5-fold higher than in adolescents (195 and 113 ng/mL, respectively). These differences can be almost entirely explained by differences in weight. No gender-associated difference in fluoxetine pharmacokinetics was observed. Similar ranges of fluoxetine and norfluoxetine plasma concentrations were observed in another study in 94 pediatric patients (ages 6 to <18) diagnosed with major depressive disorder.

Higher average steady-state fluoxetine and norfluoxetine concentrations were observed in children relative to adults; however, these concentrations were within the range of concentrations observed in the adult population. As in adults, fluoxetine and norfluoxetine accumulated extensively following multiple oral dosing; steady-state concentrations were achieved within 3 to 4 weeks of daily dosing.

**CLINICAL TRIALS**

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

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

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

**Pediatric (children and adolescents)** — The efficacy of Prozac 20 mg/day for the treatment of major depressive disorder in pediatric outpatients (N=315 randomized; 170 children ages 6 to <13, 145 adolescents ages 13 to <18) has been studied in two 8- to 9-week placebo-controlled clinical trials.

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

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

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

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

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

| Outcome Classification | Placebo |       | Prozac |       |
|------------------------|---------|-------|--------|-------|
|                        | 20 mg   | 40 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%    | 26%   |
| Very much improved     | 3%      | 8%    | 12%    | 19%   |

Exploratory analyses for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or sex.  
**Pediatric (children and adolescents)** — In one 13-week clinical trial in pediatric patients (N=103 randomized; 75 children ages 7 to <13, 28 adolescents ages 13 to <18) with OCD, patients received Prozac 10 mg/day for 2 weeks, followed by 20 mg/day for 2 weeks. The dose was then adjusted in the range of 20 to 60 mg/day on the basis of clinical response and tolerability. Prozac produced a statistically significantly greater mean reduction from baseline to endpoint than did placebo as measured by the Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS).

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

**Bulimia Nervosa**  
The effectiveness of Prozac for the treatment of bulimia was demonstrated in two 8-week and one 16-week, multicenter, parallel group studies of adult outpatients meeting DSM-III-R criteria for bulimia. Patients in the 8-week studies received either 20 or 60 mg/day of Prozac or placebo in the morning. Patients in the 16-week study received a fixed Prozac dose of 60 mg/day (once a day) or placebo. Patients in these 3 studies had moderate to severe bulimia with median binge-eating and vomiting frequencies ranging from 7 to 10 per week and 5 to 9 per week, respectively. In these 3 studies, Prozac 60 mg, but not 20 mg, was statistically significantly superior to placebo in reducing the number of binge-eating and vomiting episodes per week. The statistically significantly superior effect of 60 mg versus placebo was present as early as Week 1 and persisted throughout each study. The Prozac-related reduction in bulimic episodes appeared to be independent of baseline depression as assessed by the Hamilton Depression Rating Scale. In each of these 3 studies, the treatment effect, as measured by differences between Prozac 60 mg and placebo on median reduction from baseline in frequency of bulimic behaviors at endpoint, ranged from 1 to 2 episodes per week for binge-eating and 2 to 4 episodes per week for vomiting. The size of the effect was related to baseline frequency, with greater reductions seen in patients with higher baseline frequencies. Although some patients achieved freedom from binge-eating and purging as a result of treatment, for the majority, the benefit was a partial reduction in the frequency of binge-eating and purging.

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

**Panic Disorder**  
The effectiveness of Prozac in the treatment of panic disorder was demonstrated in 2 double-blind, randomized, placebo-controlled, multicenter studies of adult outpatients who had a primary diagnosis of panic disorder (DSM-IV), with or without agoraphobia.  
Study 1 (N=180 randomized) was a 12-week flexible-dose study. Prozac was initiated at 10 mg/day for the first week, after which patients were dosed in the range of 20 to 60 mg/day on the basis of clinical response and tolerability. A statistically significantly greater percentage of Prozac-treated patients were free from panic attacks at endpoint than placebo-treated patients, 62% versus 44%, respectively.

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

**INDICATIONS AND USAGE**

**Major Depressive Disorder**  
Prozac is indicated for the treatment of major depressive disorder.

**Adult** — The efficacy of Prozac was established in 5- and 6-week trials with depressed adult and geriatric outpatients (≥18 years of age) whose diagnoses corresponded most closely to the DSM-III (currently DSM-IV) category of major depressive disorder (see CLINICAL TRIALS).  
A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

The effects of Prozac in hospitalized depressed patients have not been adequately studied.  
The efficacy of Prozac 20 mg once daily in maintaining a response in major depressive disorder for up to 38 weeks following a 12-week of open-label acute treatment (50 weeks total) was demonstrated in a placebo-controlled trial.  
The efficacy of Prozac Weekly once weekly in maintaining a response in major depressive disorder has been demonstrated in a placebo-controlled trial for up to 25 weeks following open-label acute treatment of 13 weeks with Prozac 20 mg daily for a total treatment of 38 weeks. However, it is unknown whether or not Prozac Weekly given on a once-weekly basis provides the same level of protection for relapse as that provided by Prozac 20 mg daily (see CLINICAL TRIALS).

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

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

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

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

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

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

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

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

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

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

**Panic Disorder**  
Prozac is indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks, and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.  
The efficacy of Prozac was established in two 12-week clinical trials in patients whose diagnoses corresponded to the DSM-IV category of panic disorder (see CLINICAL TRIALS).

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

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

**CONTRAINDICATIONS**

Prozac is contraindicated in patients known to be hypersensitive to it.  
**Monooamine oxidase inhibitors** — There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) in patients who have received MAOIs and MAOIs and pediatric patients being treated with antidepressants for major depressive disorder and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, Prozac should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI. Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks after the last dose, especially if fluoxetine has been prescribed chronically and/or at higher doses (see Accumulation and slow elimination under CLINICAL PHARMACOLOGY) should be allowed after stopping Prozac before starting an MAOI.

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

**WARNINGS**

**Clinical worsening and suicide risk** — Patients with major depressive disorder, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality), whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Although there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and nonpsychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and nonpsychiatric disorders.  
The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

**Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, and the other symptoms, described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers.** Prescriptions for Prozac should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS AND DOSAGE AND ADMINISTRATION, Discontinuation of Treatment with Prozac, for a description of the risks of discontinuation of Prozac).  
It should be noted that Prozac is approved in the pediatric population only for major depressive disorder and obsessive compulsive disorder.

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with Prozac, a description of the risks of discontinuation of Prozac, and a determination of the extent of the risk of bipolar disorder, such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Prozac is not approved for use in treating bipolar depression.

**Rash and possibly allergic events** — In US fluoxetine clinical trials as of May 8, 1995, 7% of 10,782 patients developed various types of rashes and skin reactions. Anaphylactic shock, angioedema, and urticaria have been reported in clinical trials, and in a third who were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, cardiac tunnel syndrome, respiratory distress, lymphadenopathy, prothrombin, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events recovered completely.

In premarketing clinical trials, 2 patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but one was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Other patients have had systemic syndromes suggestive of serum sickness.  
Since the introduction of Prozac, systemic events, possibly related to vasculitis, including angitis-like syndrome, have developed in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported in association with these systemic events.

Anaphylactic events, including bronchospasm, angioedema, laryngospasm, and urticaria alone and in combination, have been reported.

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

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

**Potential interaction with thioridazine** — In a study of 19 healthy male subjects, which included 6 slow and 13 rapid hydroxylators of debrisoquine and 10 normal metabolizers of thioridazine, the oral administration of a 2.4-fold higher  $C_{max}$  and a 4.5-fold higher AUC for thioridazine in the slow hydroxylators compared with the rapid hydroxylators. The rate of debrisoquine hydroxylation is felt to depend on the level of CYP2D6 isozyme activity. Thus, this study suggests that drugs which inhibit CYP2D6, such as certain SSRIs, including fluoxetine, will produce elevated plasma levels of thioridazine (see PRECAUTIONS).

Thioridazine administration produces a dose-related prolongation of the QT<sub>c</sub> interval, which is associated with serious ventricular arrhythmias, such as torsades de pointes-type arrhythmias, and sudden death. This risk is expected to increase with fluoxetine-induced inhibition of thioridazine metabolism (see CONTRAINDICATIONS).

**PRECAUTIONS**

**General**  
**Abnormal Bleeding** — Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In US placebo-controlled clinical trials for either OCD or bulimia, in all US Prozac clinical trials as of May 8, 1995, 0.2% of 10,782 patients reported interactions. Although the data are limited to upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of Prozac with NSAIDs, aspirin, or other drugs that affect coagulation.

**Anxiety and insomnia** — In US placebo-controlled clinical trials for major depressive disorder, 12% to 16% of patients treated with Prozac and 7% to 10% of patients treated with placebo reported anxiety and insomnia.  
In US placebo-controlled clinical trials for OCD, insomnia was reported in 28% of patients treated with Prozac and in 22% of patients treated with placebo. Anxiety was reported in 14% of patients treated with Prozac and in 7% of patients treated with placebo.

In US placebo-controlled clinical trials for bulimia nervosa, insomnia was reported in 33% of patients treated with Prozac 60 mg, and 13% of patients treated with placebo. Nervousness was reported, respectively, in 15% and 11% of patients treated with Prozac 60 mg and in 9% and 5% of patients treated with placebo.  
Among the most common adverse events associated with discontinuation (incidence at least twice that for placebo and at least 1% for Prozac in clinical trials collecting only a primary event associated with discontinuation) in US placebo-controlled fluoxetine clinical trials were anxiety (2% in OCD), insomnia (1% in combined indications and 2% in bulimia), and nervousness (1% in major depressive disorder) (see Table 3).

**Weight gain and weight loss** — Significant weight loss, especially in underweight depressed or bulimic patients may be an undesirable result of treatment with Prozac.  
In US placebo-controlled clinical trials for major depressive disorder, 11% of patients treated with Prozac and 2% of patients treated with placebo reported anorexia (decreased appetite). Weight loss was reported in 1.4% of patients treated with Prozac and in 0.5% of patients treated with placebo. In placebo



Prozac® (fluoxetine hydrochloride)

Prozac® (fluoxetine hydrochloride)

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

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

**Neonatal/geriatric Effects** — Neonates exposed to Prozac and other SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypothermia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see Monoamine oxidase inhibitors under CONTRAINDICATIONS). When treating a pregnant woman with Prozac during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION).

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

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

**Pediatric Use**  
 The efficacy of Prozac for the treatment of major depressive disorder was demonstrated in two 8- to 9-week placebo-controlled clinical trials with 315 pediatric outpatients ages 8 to 18 (see CLINICAL TRIALS).  
 The efficacy of Prozac for the treatment of OCD was demonstrated in one 13-week placebo-controlled clinical trial with 103 pediatric outpatients ages 7 to <18 (see CLINICAL TRIALS).  
 The safety and effectiveness in pediatric patients <8 years of age with major depressive disorder and <7 years of age in OCD have not been established.

Fluoxetine pharmacokinetics were evaluated in 21 pediatric patients (ages 6 to ≤18) with major depressive disorder or OCD (see Pharmacokinetics under CLINICAL PHARMACOLOGY).  
 The acute adverse event profiles observed in the 3 studies (N=418 randomized; 228 fluoxetine-treated, 190 placebo-treated) were generally similar to that observed in adult studies with fluoxetine. The longer-term adverse event profile observed in the 19-week major depressive disorder study (N=219 randomized; 109 fluoxetine-treated, 110 placebo-treated) was also similar to that observed in adult trials with fluoxetine (see ADVERSE REACTIONS).

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

As with other SSRIs, decreased weight gain has been observed in association with the use of fluoxetine in children and adolescent patients. After 19 weeks of treatment in a clinical trial, pediatric subjects treated with fluoxetine gained an average of 1.1 cm less in height (p=0.004) and 1.1 kg less in weight (p=0.008) than subjects treated with placebo. In addition, fluoxetine treatment was associated with a decrease in alkaline phosphatase levels. The safety of fluoxetine treatment for pediatric patients has not been systematically assessed for chronic treatment longer than several months in duration. In particular, there are studies that directly evaluate the longer-term effects of fluoxetine on the growth, development, and maturation of children and adolescent patients. Therefore, height and weight should be monitored periodically in pediatric patients receiving fluoxetine.  
 (See WARNINGS, Clinical worsening and suicide risk.)

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

**ADVERSE REACTIONS**

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

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

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

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

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

| Body System/<br>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               |

<sup>1</sup> Includes US data for major depressive disorder, OCD, bulimia, and panic disorder clinical trials, plus non-US data for panic disorder clinical trials.  
<sup>2</sup> Denominator used for males only (N=690 Prozac; major depressive disorder; N=410 placebo major depressive disorder; N=116 Prozac OCD; N=43 placebo OCD; N=14 Prozac bulimia; N=1 placebo bulimia; N=162 Prozac panic; N=121 placebo panic).  
 --Incidence less than 1%.

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

| Body System/<br>Adverse Event <sup>2</sup> | Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Combined |                  |
|--|--|------------------|
|  | 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                |

<sup>1</sup> Includes US data for major depressive disorder, OCD, bulimia, and panic disorder clinical trials, plus non-US data for panic disorder clinical trials.  
<sup>2</sup> Includes adverse events reported by at least 2% of patients taking Prozac, except the following events, which had an incidence on placebo ≥ Prozac (major depressive disorder, OCD, bulimia, and panic disorder combined): abnormal pain, abnormal dreams, accidental injury, back pain, cough increased, major depressive disorder (includes suicidal thoughts), dysmenorrhea, infection, myalgia, pain, paresthesia, pharyngitis, rhinitis, sinusitis.  
 -- Incidence less than 1%.

Associated with discontinuation in major depressive disorder, OCD, bulimia, and panic disorder placebo-controlled clinical trials (excluding data from extensions of trials) — Table 3 lists the adverse events associated with discontinuation of Prozac treatment (incidence at least twice that for placebo and at least 1% for Prozac in clinical trials collecting only a primary event associated with discontinuation) in major depressive disorder, OCD, bulimia, and panic disorder clinical trials, plus non-US panic disorder clinical trials.

**Table 3: Most Common Adverse Events Associated with Discontinuation in Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Placebo-Controlled Clinical 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%)    | --              | --                     |

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

**Other adverse events in pediatric patients (children and adolescents)** — Treatment-emergent adverse events were collected in 322 pediatric patients (180 fluoxetine-treated, 142 placebo-treated). The overall profile of adverse events was generally similar to that seen in adult studies, as shown in Tables 1 and 2. However, the following adverse events (excluding those which appear in the body of footnotes of Tables 1 and 2 and those for which the COSTART terms were uninformative or misleading) were reported at an incidence of at least 2% for fluoxetine and greater than placebo: thirst, hyperkinesia, agitation, personality disorder, epistaxis, urinary frequency, and menorrhagia.

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

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

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

There are no adequate and well-controlled studies examining sexual dysfunction with fluoxetine treatment. Priapism has been reported with all SSRIs.  
 While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

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

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

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

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

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

**Endocrine System** — *Infrequent:* hypothyroidism; *Rare:* diabetic acidosis, diabetes mellitus.

**Hemic and Lymphatic System** — *Infrequent:* anemia, ecchymosis; *Rare:* blood dyscrasia, hypochromic anemia, leukopenia, lymphedema, lymphocytosis, petechia, purpura, thrombocytopenia, thrombocytopenia.

**Metabolic and Nutritional** — *Frequent:* weight gain; *Infrequent:* dehydration, generalized edema, gout, hypercholesterolemia, hyperlipemia, hypokalemia, peripheral edema; *Rare:* alcohol intolerance, alkaline phosphatase increased, BUN increased, creatine phosphokinase increased, hyperkalemia, hyperuricemia, hypocalcemia, iron deficiency anemia, SGPT increased.

**Musculoskeletal System** — *Infrequent:* arthritis, bone pain, bursitis, leg cramps, tenosynovitis; *Rare:* arthrosis, chondrodystrophy, myasthenia, myopathy, myositis, osteomyelitis, osteoporosis, osteoarthritis.

**Nervous System** — *Frequent:* agitation, amnesia, confusion, emotional lability, sleep disorder; *Infrequent:* abnormal gait, acute brain syndrome, akathisia, acute dystonia, buccal dyskinesia, CNS depression, CNS overstimulation, depersonalization, euphoria, hallucinations, hostility, hyperkinesia, hypertonía, hypethesia, incoordination, libido increased, myoclonus, neuralgia, neuropathy, neurosis, paranoid reaction, personality disorder<sup>2</sup>, psychosis, vertigo; *Rare:* abnormal electroencephalogram, antisocial reaction, circumoral paresthesia, coma, delusions, dysarthria, dystonia, extrapyramidal syndrome, foot drop, hyperesthesia, neuritis, paralysis, reflexes decreased, reflexes increased, stupor.

**Respiratory System** — *Infrequent:* asthma, epistaxis, hiccup, hyperventilation; *Rare:* apnea, atelectasis, cough decreased, emphysema, hemoptysis, hyperventilation, hypoxia, larynx edema, lung edema, pneumothorax, stridor.

**Skin and Appendages** — *Infrequent:* acne, alopecia, contact dermatitis, eczema, maculopapular rash, skin discoloration, skin ulcer, vesiculobullous rash; *Rare:* furunculosis, herpes zoster, hirsutism, petechial rash, psoriasis, purpuric rash, pustular rash, seborrhea.

**Special Senses** — *Frequent:* ear pain, taste perversion, tinnitus; *Infrequent:* conjunctivitis, dry eyes, mydriasis, photophobia; *Rare:* blepharitis, diplopia, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, hiccups, strabismus, strabismic amblyopia, taste loss, visual field defect.

**Urogenital System** — *Frequent:* urinary frequency; *Infrequent:* abortion<sup>3</sup>, albuminuria, amenorrhea<sup>3</sup>, anorgasmia, breast enlargement, breast pain, cystitis, dysuria, female lactation<sup>3</sup>, fibrocystic breast<sup>3</sup>, hematuria, leukorrhea<sup>3</sup>, menorrhagia<sup>3</sup>, nocturia, polyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage<sup>3</sup>; *Rare:* breast engorgement, glycosuria, hypomenorrhea<sup>3</sup>, kidney pain, oliguria.

<sup>1</sup> Neuroleptic malignant syndrome is the COSTART term which best captures serotonin syndrome.  
<sup>2</sup> Personality disorder is the COSTART term for describing non-aggressive objectionable behavior.  
<sup>3</sup> Adjusted for gender.

**Postintrauterine Effects**  
 Adverse events temporally associated with Prozac that have been received since market introduction and that may have no causal relationship with the drug include the following: aplastic anemia, atrial fibrillation, cataract, cerebral vascular accident, cholestatic jaundice, confusion, dyskinesia (including, for example, a case of buccal-lingual-masticatory syndrome with involuntary tongue protrusion reported to develop in 17-year-old female after 5 weeks of fluoxetine therapy and which completely resolved over the next few months following drug discontinuation), eosinophilic pneumonia, eyelid necrosis, erythema nodosum, exfoliative dermatitis, gynecomastia, heart arrest, hepatic failure/necrosis, hyperproliferative, hypoglycemia, immune-related hemolytic anemia, kidney failure, misuse/abuse, movement disorders developing in patients with risk factors including drugs associated with such events and worsening of preexisting movement disorders, neuroleptic malignant syndrome-like events, optic neuritis, pancreatitis, pancytopenia, priapism in pediatric patients, prostatic hypertrophy, serotonin syndrome, QT prolongation, respiratory depression (a range of signs and symptoms that can rarely, in its most severe form, resemble neuroleptic malignant syndrome), Stevens-Johnson syndrome, sudden unexpected death, suicidal ideation, thrombocytopenia, thrombocytopenic purpura, vaginal bleeding after drug withdrawal, ventricular tachycardia (including torsades de pointes-type arrhythmias), and violent behaviors.

**DRUG ABUSE AND DEPENDENCE**

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

**OVERDOSAGE**

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

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

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

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

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

The oral median lethal dose in rats and mice was found to be 452 and 248 mg/kg, respectively. Acute high oral doses produced hyperirritability and convulsions in several animal species.  
 Among 6 dogs purposely overdosed with oral fluoxetine, 5 experienced grand mal seizures. Seizures stopped immediately upon the bolus intravenous administration of a standard veterinary dose of diazepam. In this short-term study, the lowest plasma concentration at which a seizure occurred was only twice the maximum plasma concentration seen in humans taking 80 mg/day, chronically.

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

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

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

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

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

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

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for