

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

18-936/SE5-064

APPROVAL LETTER

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

18-936/SE5-064

APPROVED LABELING



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 18-936/S-064

Eli Lilly and Company
Attention: Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285-2643

Dear Dr. Brophy:

Please refer to your supplemental new drug application dated September 14, and received September 15, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prozac (fluoxetine hydrochloride) pulvules.

We additionally reference Agency action letters dated July 12, 2001, and March 19, 2002 as well as a conference call between representatives of the Agency and Lilly dated January 2, 2003.

We acknowledge receipt of your submission dated July 2, 2002. Your submission of July 2, 2002 constituted a complete response to our March 19, 2002 action letter.

We additionally acknowledge receipt of your correspondences dated July 23, August 22 and 28, September 5, October 4, and December 11 and 17, 2002.

This supplemental new drug application provides for the use of Prozac in the treatment of major depressive disorder (MDD) and obsessive compulsive disorder (OCD) in the pediatric population.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, this supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the agreed upon enclosed labeling (text for the package insert).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 18-936/S-064." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 postmarketing study commitments in your submissions dated July 2, and December 11, 2002 as well as those agreed upon in our conference call dated January 2, 2003. These commitments are listed below.

1. Juvenile Animal Toxicology Studies

We acknowledge your agreement to conduct juvenile animal toxicology studies as a Phase 4 postmarketing commitment. We additionally acknowledge your commitment to submit these reports to the Agency within 2 years from the date of the approval action for this supplement.

We note that, in your correspondence dated July 2, 2002, you submitted two draft juvenile animal toxicology protocols. We have the following comments in regard to these studies.

The proposed dosing periods (postnatal days 21 through 65 or 84) should be justified in terms of their relationship to the age range of the pediatric patient population. Since the clinical population for this product may include very young children, it is suggested that treatment be initiated at an earlier age in rats (1-2 weeks postnatally) in order to ensure that the appropriate developmental events are covered. In order to better evaluate the potential for long-term changes and avoid potentially confounding acute pharmacological effects, it is recommended that neurobehavioral and reproductive testing be conducted after cessation of dosing (post-treatment). A more sensitive test of learning and memory, such as the Cincinnati (multiple-T) or Morris water maze, is recommended. A specific histopathological examination of the CNS that includes all major areas and cellular elements should be performed.

2. Clinical Pediatric Trial to Assess the Longer-Term Effects of Fluoxetine on Growth

We note your Phase 4 postmarketing commitment to conduct a prospective longer-term trial to assess the effect of fluoxetine treatment on growth in pediatric patients. We additionally note your commitment to submit the protocol design to the Agency for review prior to implementing the study, and your commitment to submit the final study report within 5 years of the date of this letter.

3. Analysis of Pediatric ECG Readings Using Different Leads

We note your Phase 4 postmarketing commitment, agreed upon in a conference call dated January 2, 2003, to conduct analyses of the study HCJE pediatric QTc intervals using additional ECG leads. These analyses would, at a minimum, include QTc interval measurements from leads AVF and V5. The types of analyses should be consistent with those included in your December 11, 2002 submission. We additionally note your commitment to submit this study report no later than 3 months from the date of this letter.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Mr. Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

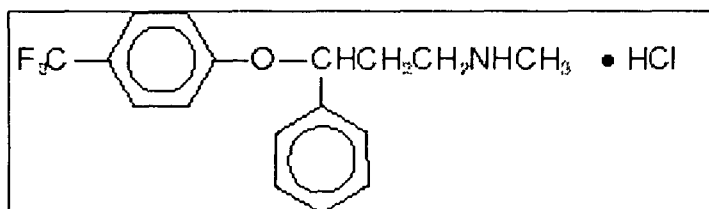
ENCLOSURE

[Note: Below is the Agency's final labeling for Prozac to incorporate the new pediatric major depressive disorder and obsessive compulsive disorder changes to the Prozac labeling.]

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 (Sarafem™, fluoxetine hydrochloride). It is designated (±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-*p*-tolyl)oxy]propylamine hydrochloride and has the empirical formula of C₁₇H₁₈F₃NO•HCl. Its molecular weight is 345.79. The structural formula is:



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, silicone, titanium dioxide, iron oxide, and other inactive ingredients. The 10 mg and 20 mg Pulvules also contain F D & C Blue No. 1, and the 40 mg Pulvule also contains F D & C Blue No. 1 and F D & 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, crospovidone, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, and yellow iron oxide. In addition to the above ingredients, the 10 mg tablet contains F D & C Blue No. 1 aluminum lake, and polysorbate 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 (291 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, antiobsessive-compulsive, and antibulimic actions of fluoxetine are presumed to be linked to its inhibition of CNS neuronal uptake of serotonin. Studies at 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 α_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 in vitro 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 α_1 -glycoprotein. 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 present in plasma at steady state.

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 P450IID6. Such individuals are referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and the TCAs. In a study involving labeled and unlabeled enantiomers 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 four active enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. Alternative, nonsaturable pathways (non-IID6) also 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, involves the P450IID6 system, concomitant therapy with drugs also metabolized by this enzyme system (such as the TCAs) may lead to drug interactions (*see Drug Interactions under 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. After 30 days of dosing at 40 mg/day, plasma concentrations of fluoxetine in the range of 91 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 assure that, 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--Administration of Prozac Weekly once-weekly results in increased fluctuation between peak and trough concentrations of fluoxetine and norfluoxetine compared to 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 76% 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 to 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 contrast, when the first 90 mg once weekly dose and the last 20 mg once daily dose were separated by one 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 one week (see Dosage and Administration).

Liver Disease--As might be predicted from its primary site of metabolism, liver impairment can affect 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 to 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 to 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 to those seen in patients with normal renal function. While the possibility exists that renally excreted metabolites of fluoxetine may accumulate to higher levels in patients with severe renal dysfunction, use of a lower or less frequent dose is not routinely necessary in renally impaired patients (see Use in Patients with Concomitant Illness under PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Age—

Geriatric Pharmacokinetics--The disposition of single doses of fluoxetine in healthy elderly subjects (greater than 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 209.3 ± 85.7 ng/mL at the end of 6 weeks. No unusual age-associated pattern of adverse events was observed in those 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 ng/mL and 86 ng/mL, respectively). The average norfluoxetine steady-state concentrations in these children were 1.5-fold higher than in adolescents (195 ng/mL 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 8 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:

Adult--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 subfactor.

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 involving depressed outpatients who had responded (modified HAMD-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 HAMD-17 score of ≥ 14 for 3 weeks) was observed for patients taking Prozac compared to 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 8 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 HAMD-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 to placebo for a period of 25 weeks. However, the equivalence of these two treatments during continuation therapy has not been established.

Obsessive Compulsive Disorder—

Adult—The effectiveness of Prozac for the treatment for 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 to 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 to 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 two 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	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%

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 change from baseline to endpoint than did placebo as measured by the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS).

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 three 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 three 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 vs 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 judgement 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, 42% vs. 28%, 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 percent of Prozac-treated patients were free from panic attacks at endpoint than placebo-treated patients, 62% vs. 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 under CLINICAL PHARMACOLOGY*).

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 daily functioning, and includes at least five of the following nine symptoms: depressed mood; loss of interest in 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 12 weeks of open-label acute treatment (50 weeks total) was demonstrated in a placebo-controlled trial. ~~The usefulness of the drug in patients receiving Prozac for extended periods should be reevaluated periodically (*see Clinical Trials under CLINICAL PHARMACOLOGY*).~~

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 from relapse as that provided by Prozac 20 mg daily (*see Clinical Trials under CLINICAL PHARMACOLOGY*).

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

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 under CLINICAL PHARMACOLOGY).

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 obsessive-compulsive disorder (see Clinical Trials under CLINICAL PHARMACOLOGY).

Obsessive-compulsive disorder 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 under CLINICAL PHARMACOLOGY).

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 three bulimic episodes per week for 6 months (see Clinical Trials under CLINICAL PHARMACOLOGY).

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 under CLINICAL PHARMACOLOGY). 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 under CLINICAL PHARMACOLOGY*).

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 or shaking; 4) sensations of shortness of breath or smothering; 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, that is, 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 (DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

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

Monoamine 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 receiving fluoxetine in combination with a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued fluoxetine 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 (perhaps longer, 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

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/or urticaria. Among the cases of rash and/or urticaria reported in premarketing clinical trials, almost a third 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, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, 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 were reported to recover completely.

In premarketing clinical trials, two 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 and including lupus-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 to occur in association with these systemic events.

Anaphylactoid 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 debrisoquin, a single 25-mg oral dose of thioridazine produced a 2.4-fold higher C_{max} and a 4.5-fold higher AUC for thioridazine in the slow hydroxylators compared to the rapid hydroxylators. The rate of debrisoquin hydroxylation is felt to depend on the level of cytochrome P450IID6 isozyme activity. Thus, this study suggests that drugs which inhibit P450IID6, such as certain SSRIs, including fluoxetine, will produce elevated plasma levels of thioridazine (*see* PRECAUTIONS).

Thioridazine administration produces a dose-related prolongation of the QTc 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

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

Altered Appetite and Weight--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. However, only rarely have patients discontinued treatment with Prozac because of anorexia or weight loss (see also Pediatric Use under PRECAUTIONS).

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

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

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

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

Seizures--In US placebo-controlled clinical trials for major depressive disorder, convulsions (or events described as possibly having been seizures) were reported in 0.1% of patients treated with Prozac and 0.2% of patients treated with placebo. No patients reported convulsions 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 convulsions. The percentage appears to be similar to that associated with other marketed drugs effective in the treatment of major depressive disorder. Prozac should be introduced with care in patients with a history of seizures.

Suicide--The possibility of a suicide attempt is inherent in major depressive disorder and may persist until significant remission occurs. Close supervision of high risk patients should accompany initial drug therapy. 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.

Because of well-established comorbidity between both OCD and major depressive disorder and bulimia and major depressive disorder, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with OCD or bulimia.

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

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

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

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

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

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

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

Information for Patients--Physicians are advised to discuss the following issues with patients for whom they prescribe Prozac:

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

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

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

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

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

Laboratory Tests--There are no specific laboratory tests recommended.

Drug Interactions--As with all drugs, the potential for interaction by a variety of mechanisms (e.g., pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc) is a possibility (*see Accumulation and Slow Elimination under CLINICAL PHARMACOLOGY*).

Drugs Metabolized by P450IID6--Approximately 7% of the normal population has a genetic defect that leads to reduced levels of activity of the cytochrome P450 isoenzyme P450IID6. Such individuals have been referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and TCAs. Many drugs, such as most drugs effective in the treatment of major depressive disorder, including fluoxetine and other selective uptake inhibitors of serotonin, are metabolized by this isoenzyme; thus, both the pharmacokinetic properties and relative proportion of metabolites are altered in poor metabolizers. However, for fluoxetine and its metabolite the sum of the plasma concentrations of the four active enantiomers is comparable between poor and extensive metabolizers (*see Variability in Metabolism under CLINICAL PHARMACOLOGY*).

Fluoxetine, like other agents that are metabolized by P450IID6, inhibits the activity of this isoenzyme, and thus may make normal metabolizers resemble "poor metabolizers." Therapy with medications that are predominantly metabolized by the P450IID6 system and that have a relatively narrow therapeutic index (*see list below*), should be initiated at the low end of the dose range if a patient is receiving fluoxetine concurrently or has taken it in the previous 5 weeks. Thus, his/her dosing requirements resemble those of "poor metabolizers." If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by P450IID6, the need for decreased dose of the original medication should be considered. Drugs with a narrow therapeutic index represent the greatest concern (e.g., flecainide, vinblastine, and TCAs). Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, thioridazine should not be administered with fluoxetine or within a minimum of 5 weeks after fluoxetine has been discontinued (*see CONTRAINDICATIONS and WARNINGS*).

Drugs Metabolized by Cytochrome P450IIIA4--In an in vivo interaction study involving co-administration of fluoxetine with single doses of terfenadine (a cytochrome P450IIIA4 substrate), no increase in plasma terfenadine concentrations occurred with concomitant fluoxetine. In addition, in vitro studies have shown ketoconazole, a potent inhibitor of P450IIIA4 activity, to be at least 100 times more potent than fluoxetine or norfluoxetine as an inhibitor of the metabolism of several substrates for this enzyme, including astemizole, cisapride, and midazolam. These data indicate that fluoxetine's extent of inhibition of cytochrome P450IIIA4 activity is not likely to be of clinical significance.

CNS Active Drugs--The risk of using Prozac in combination with other CNS active drugs has not been systematically evaluated. Nonetheless, caution is advised if the concomitant administration of Prozac and such drugs is required. In evaluating individual cases, consideration

should be given to using lower initial doses of the concomitantly administered drugs, using conservative titration schedules, and monitoring of clinical status (*see* Accumulation and Slow Elimination *under* CLINICAL PHARMACOLOGY).

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

Antipsychotics--Some clinical data suggests a possible pharmacodynamic and/or pharmacokinetic interaction between serotonin specific reuptake inhibitors (SSRIs) and antipsychotics. Elevation of blood levels of haloperidol and clozapine has been observed in patients receiving concomitant fluoxetine. A single case report has suggested possible additive effects of pimozide and fluoxetine leading to bradycardia. For thioridazine, see CONTRAINDICATIONS and WARNINGS.

Benzodiazepines--The half-life of concurrently administered diazepam may be prolonged in some patients (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology). Co-administration of alprazolam and fluoxetine has resulted in increased alprazolam plasma concentrations and in further psychomotor performance decrement due to increased alprazolam levels.

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

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

Monoamine Oxidase Inhibitors--*See* CONTRAINDICATIONS.

Other Drugs Effective in the Treatment of Major Depressive Disorder--In two studies, previously stable plasma levels of imipramine and desipramine have increased greater than 2 to 10-fold when fluoxetine has been administered in combination. This influence may persist for three weeks or longer after fluoxetine is discontinued. Thus, the dose of TCA may need to be reduced and plasma TCA concentrations may need to be monitored temporarily when fluoxetine is coadministered or has been recently discontinued (*see* Accumulation and Slow Elimination *under* CLINICAL PHARMACOLOGY, and Drugs Metabolized by P450IID6 *under* Drug Interactions).

Sumatriptan--There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of an SSRI and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, or citalopram) is clinically warranted, appropriate observation of the patient is advised.

Potential Effects of Co-administration of Drugs Tightly Bound to Plasma Proteins--Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (e.g., Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein bound fluoxetine by other tightly bound drugs (*see* Accumulation and Slow Elimination *under* CLINICAL PHARMACOLOGY).

Warfarin--Altered anti-coagulant effects, including increased bleeding, have been reported when fluoxetine is co-administered with warfarin. Patients receiving warfarin therapy should receive careful coagulation monitoring when fluoxetine is initiated or stopped.

Electroconvulsive Therapy--There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment.

Carcinogenesis, Mutagenesis, Impairment of Fertility--There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with Prozac.

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

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

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/m² 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 maximum recommended human dose [MRHD] of 80 mg on a mg/m² 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/m² basis) during gestation or 7.5 mg/kg/day (0.9 times the MRHD on a mg/m² 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/m² basis). Prozac should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 1 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--~~Safety and effectiveness in pediatric patients have not been established. 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 under CLINICAL PHARMACOLOGY).

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 under CLINICAL PHARMACOLOGY).

Safety and effectiveness in pediatric patients less than 8 years of age in major depressive disorder and less than 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 three 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 three 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 no 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.

Geriatric Use—U.S. 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 efficacy in geriatric patients has been established (see Clinical Trials under CLINICAL PHARMACOLOGY). 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).

Hyponatremia--Cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been reported. The hyponatremia appeared to be reversible when Prozac was discontinued. Although these cases were complex with varying possible etiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted. In two 6-week controlled studies in patients ≥ 60 years of age, 10 of 323 fluoxetine patients and 6 of 327 placebo recipients had a lowering of serum sodium below the reference range; this difference was not statistically significant. The lowest observed concentration was 129 mmol/L. The observed decreases were not clinically significant.

Platelet Function--There have been rare reports of altered platelet function and/or abnormal results from laboratory studies in patients taking fluoxetine. While there have been reports of abnormal bleeding in several patients taking fluoxetine, it is unclear whether fluoxetine had a causative role.

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 prescribing physician 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 within at least one of the indications) for the treatment of major depressive disorder, OCD, and bulimia in US controlled clinical trials and panic disorder in US ~~and~~ plus non-US controlled trials. Table 2 enumerates treatment-emergent adverse events that occurred in 2% or more patients treated with Prozac

and with 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, ~~US controlled clinical trials comparing Prozac with placebo in the treatment of major depressive disorder, OCD, or bulimia~~. 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 US-MAJOR DEPRESSIVE DISORDER,
OCD, BULIMIA AND PANIC DISORDER PLACEBO-CONTROLLED CLINICAL
TRIALS

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

Abnormal ejaculation†	--	--	7	--	7	--	2	1
-----------------------	----	----	---	----	---	----	---	---

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

†Denominator used was 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*

Body System/ Adverse Event†	Percentage of patients reporting event Major Depressive Disorder, OCD, bulimia, and panic disorder combined	
	Prozac (N=2869)	Placebo (N=1673)
Body as a Whole		
Headache	21	19
Asthenia	11	6
Flu syndrome	5	4
Fever	2	1
Cardiovascular System		
Vasodilatation	2	1
Digestive System		
Nausea	22	9
Diarrhea	11	7
Anorexia	10	3
Dry mouth	9	6
Dyspepsia	8	4
Constipation	5	4
Flatulence	3	2
Vomiting	3	2
Metabolic and Nutritional Disorders		
Weight loss	2	1
Nervous System		
Insomnia	19	10
Nervousness	13	8
Anxiety	12	6
Somnolence	12	5
Dizziness	9	6
Tremor	9	2
Libido decreased	4	1

Thinking Abnormal	2	1
Respiratory System		
Yawn	3	--
Skin and Appendages		
Sweating	7	3
Rash	4	3
Pruritus	3	2
Special Senses		
Abnormal vision	2	1

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

†Included are 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): abdominal pain, abnormal dreams, accidental injury, back pain/cough increased, major depressive disorder (includes suicidal thoughts), dysmenorrhea, infection, myalgia, pain, paresthesia, pharyngitis, rhinitis, sinusitis.

--Incidence less than 1%.

Associated with discontinuation in major depressive disorder, OCD, bulimia, and panic disorder placebo-controlled clinical trials (excluding data from extensions of trials). ~~Associated with Discontinuation in US 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 US-MAJOR DEPRESSIVE DISORDER, OCD, BULIMIA
AND PANIC DISORDER PLACEBO-CONTROLLED CLINICAL TRIALS

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%)	--	--

*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 or 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 three 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% vs. 3%, respectively) or taking Prozac 20 mg daily (10% vs. 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 acutely 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 1/1,000 patients; rare events are those occurring in less than 1/1,000 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*, 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, hyperchlorhydria, 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, thrombocythemia, thrombocytopenia.

Metabolic and Nutritional--*Frequent*: weight gain; *Infrequent*: dehydration, generalized edema, gout, hypercholesteremia, 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, rheumatoid arthritis.

Nervous System--*Frequent*: agitation, amnesia, confusion, emotional lability, sleep disorder; *Infrequent*: abnormal gait, acute brain syndrome, akathisia, apathy, ataxia, buccoglossal syndrome, CNS depression, CNS stimulation, depersonalization, euphoria, hallucinations, hostility, hyperkinesia, hypertonia, hypesthesia, incoordination, libido increased, myoclonus, neuralgia, neuropathy, neurosis, paranoid reaction, personality disorder†, 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, hypoventilation, 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, deafness, diplopia, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, iritis, parosmia, scleritis, strabismus, taste loss, visual field defect.

Urogenital System--*Frequent*: urinary frequency; *Infrequent*: abortion†, albuminuria, amenorrhea†, anorgasmia, breast enlargement, breast pain, cystitis, dysuria, female lactation†, fibrocystic breast†, hematuria, leukorrhea†, menorrhagia†, metrorrhagia†, nocturia, polyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage†; *Rare*: breast engorgement, glycosuria, hypomenorrhea†, kidney pain, oliguria, priapism†, uterine hemorrhage†, uterine fibroids enlarged†.

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

† Personality disorder is the COSTART term for designating non-aggressive objectionable behavior.

‡ Adjusted for gender

Postintroduction Reports-- Voluntary reports of 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 a 77-year-old female after 5 weeks of fluoxetine therapy and which completely resolved over the next few months following drug discontinuation), eosinophilic pneumonia, epidermal necrolysis, erythema nodosum, exfoliative dermatitis, gynecomastia, heart arrest, hepatic failure/necrosis, hyperprolactinemia, 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, pulmonary embolism, pulmonary hypertension, QT prolongation, serotonin syndrome (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

Human Experience—Worldwide exposure to fluoxetine hydrochloride is estimated to be over 38 million 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, pulmonary 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 six overdoses in children that resulted in fatalities. The largest ingestion in pediatric patients was 3 grams which was non-lethal.

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 six dogs purposely overdosed with oral fluoxetine, five 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 certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*.

DOSAGE AND ADMINISTRATION

Major Depressive Disorder--

Initial Treatment—

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

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

Pediatric (Children and Adolescents)--In the, short-term (8 to 9 week) controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of major depressive disorder, patients were administered fluoxetine doses of 10 to 20 mg/day (see Clinical Trials under CLINICAL PHARMACOLOGY). Treatment should be initiated with a dose of 10 or 20 mg/day. After 1 week at 10 mg/day, the dose should be increased to 20 mg/day.

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

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

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

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

Daily Dosing--Systematic evaluation of Prozac has shown that its efficacy in major depressive disorder is maintained for periods of up to 38 weeks following 12 weeks of open-label acute treatment (50 weeks total) at a dose of 20 mg/day (see Clinical Trials under CLINICAL PHARMACOLOGY).

Weekly Dosing--Systematic evaluation of Prozac Weekly has shown that its efficacy in major depressive disorder is maintained for periods of up to 25 weeks with once-weekly dosing following 13 weeks of open-label treatment with Prozac 20 mg once-daily. However, therapeutic equivalence of Prozac Weekly given on a once-weekly basis with Prozac 20 mg given daily for delaying time to relapse has not been established. (see Clinical Trials under CLINICAL PHARMACOLOGY).

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

If satisfactory response is not maintained with Prozac Weekly, consider reestablishing a daily dosing regimen (see Clinical Trials under CLINICAL PHARMACOLOGY).

Obsessive-Compulsive Disorder--

Initial Treatment--

Adult--In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of obsessive-compulsive disorder, patients were administered fixed daily doses of 20, 40, or 60 mg of fluoxetine or placebo (see Clinical Trials under CLINICAL PHARMACOLOGY). In one of these studies, no dose response relationship for effectiveness was demonstrated. Consequently, a dose of 20 mg/day, administered in the morning, is recommended as the initial

dose. Since there was a suggestion of a possible dose response relationship for effectiveness in the second study, a dose increase may be considered after several weeks if insufficient clinical improvement is observed. The full therapeutic effect may be delayed until 5 weeks of treatment or longer.

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

Pediatric (Children and Adolescents)--In the controlled clinical trial of fluoxetine supporting its effectiveness in the treatment of OCD, patients were administered fluoxetine doses in the range of 10 to 60 mg/day (see Clinical Trials under CLINICAL PHARMACOLOGY). In adolescents and higher weight children, treatment should be initiated with a dose of 10 mg/day. After 2 weeks, the dose should be increased to 20 mg/day. Additional dose increases may be considered after several more weeks if insufficient clinical improvement is observed. A dose range of 20 to 60 mg/day is recommended.

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

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

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

Bulimia Nervosa--

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

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

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

Switching Patients to a Tricyclic Antidepressant (TCA):

Dosage of a TCA may need to be reduced, and plasma TCA concentrations may need to be monitored temporarily when fluoxetine is co-administered or has been recently discontinued (*see Other Drugs Effective in the Treatment of Major Depressive Disorder under Drug Interactions*).

Switching Patients to or from a Monoamine Oxidase Inhibitor:

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

Panic Disorder—

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

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

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

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

HOW SUPPLIED

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

Prozac® Pulvules®, USP, are available in:

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

- NDC 0777-3104-02 (PU3104**) - Bottles of 100
- NDC 0777-3104-07 (PU3104**) - Bottles of 2000
- NDC 0777-3104-82 (PU3104**) - 20 FlexPak™§ blister cards of 31

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

- NDC 0777-3105-30 (PU3105**) - Bottles of 30
- NDC 0777-3105-02 (PU3105**) - Bottles of 100
- NDC 0777-3105-07 (PU3105**) - Bottles of 2000
- NDC 0777-3105-33 (PU3105**) - (ID†100) Blisters
- NDC 0777-3105-82 (PU3105**) - 20 FlexPak™§ blister cards of 31

The 40 mg* 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**) – Bottles of 30

Liquid, Oral Solution is available in:
20 mg* per 5 mL with mint flavor:

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

The following products are manufactured and distributed by Eli Lilly and Company.

Prozac® Tablets are available in:

The 10 mg* tablet is green, elliptical shaped, and scored, with PROZAC 10 debossed on opposite side of score.

- NDC 0002-4006-30 (TA4006) - Bottles of 30
- NDC 0002-4006-02 (TA4006) - Bottles of 100

Prozac Weekly™ Capsules are available in:

The 90 mg* 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
NDC 0002-3004-99 (PU3004) – Blister package of 12

*Fluoxetine base equivalent

**Protect from light.

†Identi-Dose® (unit dose medication, Lilly).

‡Dispense in a tight, light-resistant container.

§FlexPak™ (flexible blister card, Lilly).

Store at controlled room temperature, 59° to 86°F (15° to 30°C).

ANIMAL TOXICOLOGY

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.

~~Rx only~~

Eli Lilly and Company
Indianapolis, IN 46285, USA

PRINTED IN USA

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Russell Katz
1/3/03 10:19:39 AM