CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18-936/S-054

FINAL PRINTED LABEL

PROZAC®
FLUOXETINE HYDROCHLORIDE
PV 3311 DPP

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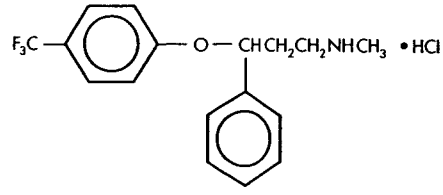
FLUOXETINE HYDROCHLORIDE

DESCRIPTION

Prozac® (Fluoxetine Hydrochloride) is an antidepressant for oral administration, it is chemically unrelated to tricyclic, tetracyclic, or other available antidepressant agents It is designated (±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-*p*-tolyl)oxy]propylamine hydrochloride and has the empirical formula of $C_{17}H_{18}F_3NO•HCl$ 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

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 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, and oral solution dosage forms of fluoxetine are bioequivalent. Food does not appear to affect the systemic bioavailability of fluoxetine, although it may delay its absorption inconsequentially. Thus, fluoxetine may be administered with or without food.

Protein Binding—Over the concentration range from 200 to 1,000 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 tricyclic antidepressants. 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 4 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 tricyclic and other selective serotonin antidepressants, involves the P450IID6 system, concomitant therapy with drugs also metabolized by this enzyme system (such as the tricyclic antidepressants) 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 4-5 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

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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.

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 two 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—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

Clinical Trials

Depression—The efficacy of Prozac for the treatment of patients with depression (≥ 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 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 depression 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 ≤ 7 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 depression 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 depression 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

Obsessive Compulsive Disorder—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 2 higher dose groups The following table provides the outcome classification by treatment group on the Clinical Global Impression (CGI) improvement scale for studies 1 and 2 combined

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

		Prozac		
Outcome Classification	Placebo	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.

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 mg/day or 60 mg/day of Prozac or placebo in the morning. Patients in the 16-week study received a fixed Prozac dose of 60 mg/day (once a day) or placebo. Patients in these 3 studies had moderate to severe bulimia with median binge-eating and vomiting frequencies ranging from 7 to 10 per week and 5 to 9 per week, respectively In these 3 studies, Prozac, 60 mg, but not 20 mg, was statistically significantly superior to placebo in reducing the number of binge-eating and vomiting episodes per week. The statistically significantly superior effect of 60 mg 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

INDICATIONS AND USAGE

Depression—Prozac is indicated for the treatment of depression The efficacy of Prozac was established in 5- and 6-week trials with depressed 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 5 of the following 9 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 antidepressant action of Prozac in hospitalized depressed patients has not been adequately studied.

The efficacy of Prozac in maintaining an antidepressant response 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)

Obsessive-Compulsive Disorder—Prozac is indicated for the treatment of obsessions and compulsions in patients with obsessive-compulsive disorder (OCD), as defined in the DSM-III-R, ie, 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)

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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, ie, 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)

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, ie, at least 3 bulimic episodes per week for 6 months (*see* Clinical Trials *under* Clinical Pharmacology)

The effectiveness of Prozac in long-term use, ie, for more than 16 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).

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

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and/or at higher doses [*see* Accumulation and Slow Elimination *under* Clinical Pharmacology]) should be allowed after stopping Prozac before starting an MAOI

WARNINGS

Rash and Possibly Allergic Events—In US fluoxetine clinical trials, 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, 2 patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but 1 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, 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, 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.

PRECAUTIONS

General

Anxiety and Insomnia—In US placebo-controlled clinical trials for depression, 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 obsessive-compulsive disorder, 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 depression) (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 depression, 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.

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.

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 depression, 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 antidepressants.

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, 0.7% of 10,782 patients reported mania/hypomania.

Seizures—In US placebo-controlled clinical trials for depression, 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, 0.2% of 10,782 patients reported convulsions. The percentage appears to be similar to that associated with other marketed antidepressants. Prozac should be introduced with care in patients with a history of seizures.

Suicide—The possibility of a suicide attempt is inherent in depression 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 depression and bulimia and depression, the same precautions observed when treating patients with depression 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 medications, [illegible]

controlled clinical trials for bulimia In all US Prozac clinical trials, 0 7% of 10,782 patients reported mania/hypomania

Seizures—In US placebo-controlled clinical trials for depression, 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, 0 2% of 10,782 patients reported convulsions The percentage appears to be similar to that associated with other marketed antidepressants. Prozac should be introduced with care in patients with a history of seizures

Suicide—The possibility of a suicide attempt is inherent in depression 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 depression and bulimia and depression, the same precautions observed when treating patients with depression 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)

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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 (eg, 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 tricyclic antidepressants Many drugs, such as most antidepressants, 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 4 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 (eg, flecainide, vinblastine, and tricyclic antidepressants)

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.
- Benzodiazepines—The half-life of concurrently administered diazepam may be prolonged in some patients (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology) Coadministration 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 Antidepressants—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 tricyclic antidepressant (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)

Potential Effects of Coadministration 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 (eg, 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/m^2 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/m^2 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/m^2 basis) throughout organogenesis However, in rat reproduction studies, an increase in stillborn pups, a decrease in pup weight, and an increase in pup deaths during the first 7 days postpartum occurred following maternal exposure to 12 mg/kg/day (1 5 times the MRHD on a mg/m^2 basis) during gestation or 7 5 mg/kg/day (0 9 times the MRHD on a mg/m^2 basis) during gestation and lactation There was no evidence of developmental neurotoxicity in the surviving offspring of rats treated with 12 mg/kg/day during gestation The no-effect dose for rat pup mortality was 5 mg/kg/day (0 6 times the MRHD on a mg/m^2 basis) Prozac should be used during pregnancy only if the

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 Antidepressants—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 tricyclic antidepressant (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).

Potential Effects of Coadministration 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 (eg, 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/m^2 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/m^2 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/m^2 basis) throughout organogenesis. However, in rat reproduction studies, an increase in stillborn pups, a decrease in pup weight, and an increase in pup deaths during the first 7 days postpartum occurred following maternal exposure to 12 mg/kg/day (1.5 times the MRHD on a mg/m^2 basis) during gestation or 7.5 mg/kg/day (0.9 times the MRHD on a mg/m^2 basis) during gestation and lactation. There was no evidence of developmental neurotoxicity in the surviving offspring of rats treated with 12 mg/kg/day during gestation. The no-effect dose for rat pup mortality was 5 mg/kg/day (0.6 times the MRHD on a mg/m^2 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.

Usage in the Elderly—Evaluation of patients over the age of 60 who received Prozac 20 mg daily revealed no unusual pattern of adverse events relative to the clinical experience in younger patients. However, these data are insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients who have concomitant systemic illnesses or who are receiving concomitant drugs (*see* Age *under* Clinical Pharmacology).

Hyponatremia—Several 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 a placebo-controlled, double-blind trial, 10 of 313 fluoxetine patients and 6 of 320 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. 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 (ie, 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 US 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 depression, OCD, and bulimia in US controlled clinical 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 controlled clinical trials comparing Prozac with placebo in the treatment of depression, 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 DEPRESSION, OCD, AND BULIMIA PLACEBO-CONTROLLED CLINICAL TRIALS

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

†Denominator used was for males only (N= 690 Prozac depression, N=410 placebo depression, N=116 Prozac OCD; N=43 placebo OCD, N=14 Prozac bulimia, N=1 placebo bulimia)
--Incidence less than 1%

TABLE 2
TREATMENT-EMERGENT ADVERSE EVENTS INCIDENCE IN US DEPRESSION, OCD, AND BULIMIA PLACEBO-CONTROLLED CLINICAL TRIALS

	Percentage of patients reporting event	
	Depression, OCD, and bulimia combined	
Body System/ Adverse Event*	Prozac (N=2444)	Placebo (N=1331)
Body as a Whole		
Headache	21	20
Asthenia	12	6
Flu syndrome	5	4
Fever	2	1
Cardiovascular System		
Vasodilatation	3	1
Palpitation	2	1
Digestive System		
Nausea	23	10
Diarrhea	12	8
Anorexia	11	3
Dry mouth	10	7
Dyspepsia	8	5
Flatulence	3	2
Vomiting	3	2
Metabolic and Nutritional Disorders		
Weight loss	2	1
Nervous System		
Insomnia	20	11
Anxiety	13	8
Nervousness	13	9
Somnolence	13	6
Dizziness	10	7
Tremor	10	3
Libido decreased	4	--
Respiratory System		
Pharyngitis	5	4
Yawn	3	--
Skin and Appendages		
Sweating	8	3
Rash	4	3
Pruritus	3	2
Special Senses		
Abnormal vision	3	1

*Included are events reported by at least 2% of patients taking Prozac, except the following events which had an incidence on placebo ≥ Prozac (depression, OCD, and bulimia combined): abdominal pain, abnormal dreams, accidental injury, back pain, chest pain, constipation, cough increased, depression (includes suicidal thoughts), dysmenorrhea, gastrointestinal disorder, infection, myalgia, pain, paresthesia, rhinitis, sinusitus, thinking abnormal.
--Incidence less than 1%.

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

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

Depression—

Initial Treatment—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 antidepressant response 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 no clinical improvement is observed. Doses above 20 mg/day may be administered on a once a day (morning) or b.i.d. schedule (ie, morning and noon) and should not exceed a maximum dose of 80 mg/day.

As with other antidepressants, the full antidepressant 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* Usage in the Elderly *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 depression require several months or longer of sustained pharmacologic therapy. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Systematic evaluation of Prozac has shown that its antidepressant efficacy 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).

Obsessive-Compulsive Disorder—

Initial Treatment—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 (ie, morning) or b.i.d. schedule (ie, 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.

As with the use of Prozac in depression, 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* Usage in the Elderly *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 depression 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* Usage in the Elderly *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, bulimia is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of Prozac after 16 weeks has not been documented in controlled trials, some patients have been continued in therapy under double-blind conditions for up to an additional 6 months without loss of benefit. However, patients should be periodically reassessed to determine the need for continued 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 coadministered or has been recently discontinued (*see* Other Antidepressants *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).

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

*Fluoxetine base equivalent.
†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

[illegible]	3	2
Special Senses		
Abnormal vision	3	1

*Included are events reported by at least 2% of patients taking Prozac, except the following events, which had an incidence on placebo ≥ Prozac (depression, OCD, and bulimia combined) abdominal pain, abnormal dreams, accidental injury, back pain, chest pain, constipation, cough increased, depression (includes suicidal thoughts) dysmenorrhea, gastrointestinal disorder, infection, myalgia, pain paresthesia, rhinitis, sinusitis thinking abnormal

–Incidence less than 1%

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 depression, OCD, and bulimia.

TABLE 3
MOST COMMON ADVERSE EVENTS ASSOCIATED WITH DISCONTINUATION IN US DEPRESSION, OCD, AND BULIMIA PLACEBO-CONTROLLED CLINICAL TRIALS

Depression, OCD, and bulimia combined (N=1108)	Depression (N=392)	OCD (N=266)	Bulimia (N=450)
–	–	Anxiety (2%)	–
Insomnia (1%)	–	–	Insomnia (2%)
–	Nervousness (1%)	–	–
–	–	Rash (1%)	–

Other Events Observed In All US Clinical Trials—Following is a list of all treatment-emergent adverse events reported at anytime by individuals taking fluoxetine in US clinical trials (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 1 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:* 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, *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*

† 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, 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, 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, pancreatitis, pancytopenia, priapism, pulmonary embolism, QT prolongation, Stevens-Johnson syndrome, sudden unexpected death, suicidal ideation, thrombocytopenia, thrombocytopenic purpura, vaginal bleeding after drug withdrawal, 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 (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience—As of December 1987, there were 2 deaths among approximately 38 reports of acute overdose with fluoxetine, either alone or in combination with other drugs and/or alcohol One death involved a combined overdose with approximately 1,800 mg of fluoxetine and an undetermined amount of maprotiline Plasma concentrations of fluoxetine and maprotiline were 4 57 mg/L and 4 18 mg/L, respectively A second death involved 3 drugs yielding plasma concentrations as follows. fluoxetine, 1 93 mg/L, norfluoxetine, 1 10 mg/L, codeine, 1 80 mg/L; temazepam, 3 80 mg/L.

One other patient who reportedly took 3,000 mg of fluoxetine experienced 2 grand mal seizures that remitted spontaneously without specific anticonvulsant treatment (*see* Management of Overdose). The actual amount of drug absorbed may have been less due to vomiting.

Nausea and vomiting were prominent in overdoses involving higher fluoxetine doses. Other prominent symptoms of overdose included agitation, restlessness, hypomania, and other signs of CNS excitation Except for the 2 deaths noted above, all other overdose cases recovered without residua.

Since introduction, reports of death attributed to overdosage of fluoxetine alone have been extremely rare

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

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

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

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

Management of Overdose—Treatment should consist of those general measures employed in the management of overdosage with any antidepressant

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 [illegible]

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Indianapolis, IN 46285, USA

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iritis, parosmia, scleritis, strabismus, taste loss, visual field defect

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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 tricyclic antidepressant. 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 Antidepressants *under* Precautions).

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