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56
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PHYSICIANS' DESK REFERENCE®

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FOREWORD TO THE FIFTY-SIXTH EDITION

Welcome to the 2002 edition of *PDR*. With over 3,000 pages of detailed prescribing information approved by the FDA, this volume is unquestionably the healthcare community's most fundamental pharmaceutical reference—an indispensable source of in-depth data on the efficacy, potential adverse effects, clinical pharmacology, and proper use of thousands of prescription medications.

For complicated cases and special patient problems, there is certainly no better resource to turn to. In routine situations, however, a synopsis of the most important facts will often suffice. For just such occasions, *PDR* now offers the *PDR Pharmacopoeia™ Pocket Dosing Guide*. This handy little book can accompany you wherever you need to go, around the office or on rounds. Only slightly larger than an index card and a half-inch thick, it fits easily into any pocket, while providing you with FDA-approved dosing recommendations for over 1,500 drugs. Unlike other condensed drug references, it's drawn almost exclusively from the FDA-approved drug labeling published in *Physicians' Desk Reference*. And its tabular presentation makes lookups a breeze. At $9.95 a copy, it's a tool you really can't afford to be without.

Recently, the use of over-the-counter nutritional supplements has sky-rocketed, and *PDR* has responded with a brand new medical reference covering this unfamiliar—even exotic—set of agents. Entitled *PDR® for Nutritional Supplements™*, it offers the latest scientific consensus on hundreds of popular supplement products, including an array of amino acids, co-factors, fatty acids, probiotics, phytoestrogens, phytosterols, over-the-counter hormones, hormonal precursors, and much more. Focused on the scientific evidence for each supplement's claims, this unique new reference offers you today's most detailed, informed, and objective overview of a burgeoning new area in the field of self-treatment. To protect your patients from bogus remedies and steer them towards truly beneficial products, this book is a must.

For counseling patients who favor herbal remedies, another *PDR* reference may prove equally valuable. Now in its second edition, *PDR® for Herbal Medicines™* provides you with the latest science-based assessment of some 700 botanicals. Indexed by scientific, common, and brand names (as well as Western, Asian, and homeopathic indications) this volume also includes a Side Effects Index, a Drug/Herb Interactions Guide, an Herb Identification Guide with nearly 400 color photos, and a Safety Guide that lists herbs to be avoided during pregnancy and nursing and herbs to be used only under professional supervision. Although botanical products are not officially regulated or monitored in the United States, *PDR for Herbal Medicines* provides you the closest analog to FDA-approved labeling—the findings of the German Regulatory Authority's herbal watchdog agency, Commission E.

To maximize the value of *PDR* itself, you'll also need a copy of the 2002 edition of the *PDR Companion Guide™*, an 1,800-page reference that augments *PDR* with a total of 10 unique decision-making tools:

- **Interactions Index** identifies all pharmaceuticals and foods capable of interacting with a chosen medication.
- **Food Interactions Cross-Reference** lists the drugs that may interact with a given dietary item.
- **Side Effects Index** pinpoints the pharmaceuticals associated with each of 3,600 distinct adverse reactions.
- **Indications Index** presents the full range of therapeutic options for any given diagnosis.
- **Off-Label Treatment Guide** lists medications routinely used—but never officially approved—for treatment of nearly 1,000 specific disorders.
- **Contraindications Index** lists all drugs to avoid in the presence of any given medical condition.
- **International Drug Index** names the U.S. equivalents of some 15,000 foreign medications.
- **Generic Availability Guide** shows which forms and strengths of a brand-name drug are also available generically.
- **Cost of Therapy Guide** provides a quick overview of the relative expense of the leading therapeutic options for a variety of common indications.
- **Imprint Identification Guide** enables you to establish the nature of any unknown tablet or capsule by matching its imprint against an exhaustive catalog of identifying codes.

The *PDR Companion Guide* includes all drugs described in *PDR, PDR For Nonprescription Drugs and Dietary Supplements™*, and *PDR For Ophthalmic Medicines™*. We're certain that you'll find it makes safe, appropriate selection of drugs faster and easier than ever before.

PDR and its major companion volumes are also found in the *PDR® Electronic Library™* on CD-ROM, now used in over 100,000 practices. This Windows-compatible disc provides users with a complete database of *PDR* prescribing information, electronically searchable for instant retrieval. A standard subscription includes *PDR's* sophisticated search software and an extensive file of chemical structures, illustrations, and full-color product photographs. Optional enhancements include the complete contents of *The Merck Manual Seventeenth Edition, Stedman's Medical Dictionary,* and *Stedman's Spellchecker*. For anyone who wants to run a fast double check on a proposed prescription, there's also the *PDR® Drug Interactions and Side Effects System™* — sophisticated software capable of automatically screening a 20-drug regimen for conflicts, then proposing alternatives for any problematic medication. This unique decision-making tool now comes free with the *PDR Electronic Library*.

For more information on these or any other members of the growing family of *PDR* products, please call, toll-free, 1-800-232-7379 or fax 201-573-4956.

Physicians' Desk Reference is published by Medical Economics Company in cooperation with participating manufacturers. Each full-length entry provides you with an exact copy of the product's FDA-approved labeling. Under the federal Food, Drug and Cosmetics (FD&C) Act, a drug approved for marketing may be labeled, promoted, and advertised by the manufacturer for only those uses for which the drug's safety and effectiveness have been established. The Code of Federal Regulations 201.100(d)(1) pertaining to labeling for prescription products requires that for *PDR* content "indications, effects, dosages, routes, methods, and frequency and duration of administration and any relevant warnings, hazards, contraindications, side effects, and precautions" must be *"same in language and emphasis"* as the approved labeling for the products. The Food and Drug Administration (FDA) regards the words *same in language and emphasis* as requiring VERBATIM use of the approved labeling providing such information. Furthermore, information that is emphasized in the approved labeling by the use of type set in a box, or in capitals, boldface, or italics, must be given the same emphasis in *PDR*.

The FDA has also recognized that the FD&C Act does not, however, limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may choose to prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. The FDA also observes that accepted medical practice includes drug use that is not reflected in approved drug labeling. For products that do not have official package circulars, the publisher has emphasized the necessity of describing such products comprehensively, so that physicians can have access to all information essential for intelligent and informed decision-making. Particularly in the case of over-the-counter dietary supplements, it should be remembered that this information has not been evaluated by the Food and Drug Administration, and that such products are not intended to diagnose, treat, cure, or prevent any disease.

The function of the publisher is the compilation, organization, and distribution of this information. Each product description has been prepared by the manufacturer, and edited and approved by the manufacturer's medical department, medical director, and/or medical consultant. In organizing and presenting the material in *Physicians' Desk Reference*, the publisher does not warrant or guarantee any of the products described, or perform any independent analysis in connection with any of the product information contained herein. *Physicians' Desk Reference* does not assume, and expressly disclaims, any obligation to obtain and include any information other than that provided to it by the manufacturer. It should be understood that by making this material available, the publisher is not advocating the use of any product described herein, nor is the publisher responsible for misuse of a product due to typographical error. Additional information on any product may be obtained from the manufacturer.

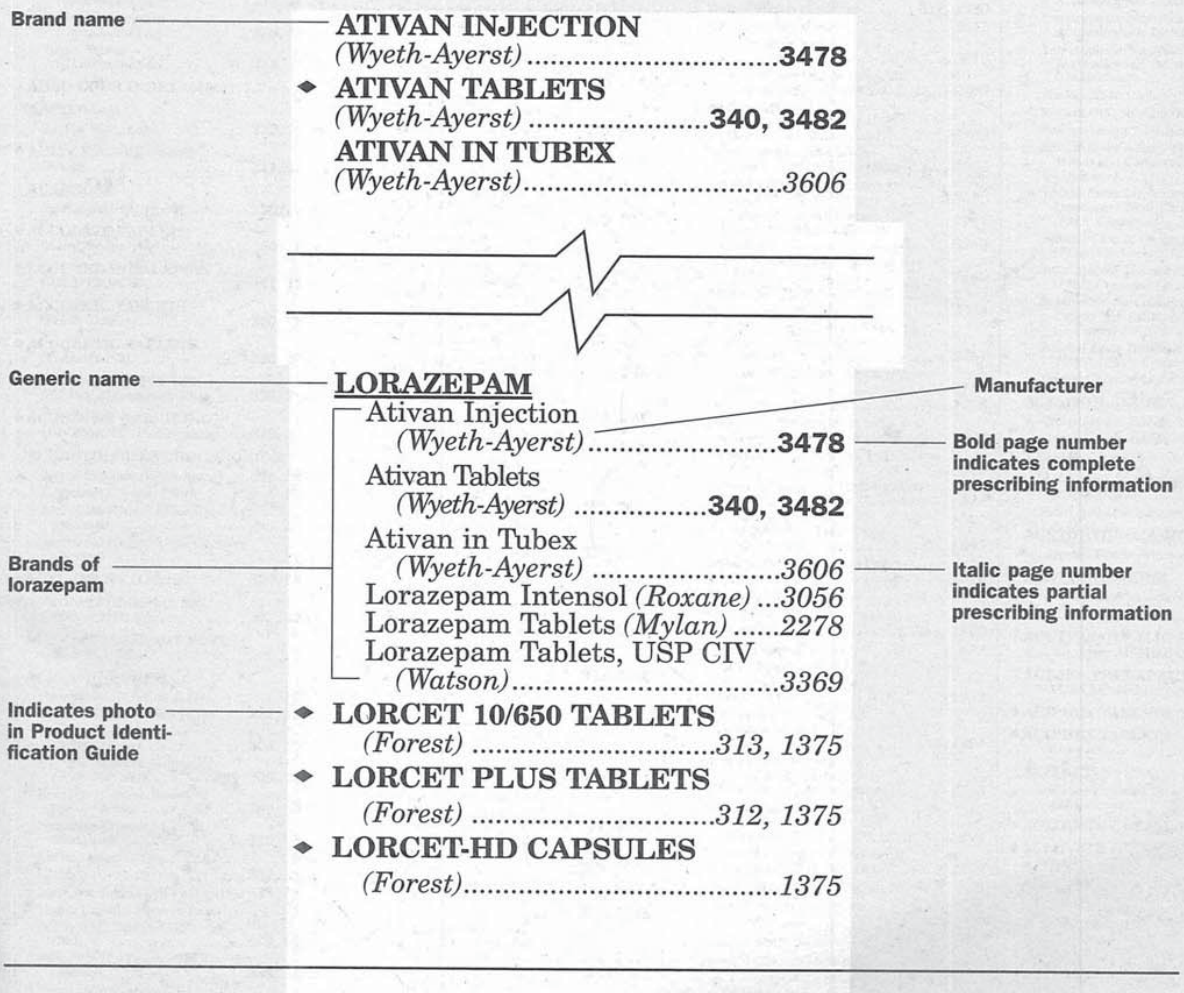
CONTENTS

HOW TO USE THE BRAND AND GENERIC NAME INDEX

This index lists every product alphabetically by both brand and generic name. Generic names are underlined; brand names are not.

Under each generic name, you will find a list of the brands that contain it. This enables you to find a particular product by either of its names. For example, "Ativan Injection" is listed once alphabetically and again under its generic name, lorazepam.

Each time a brand name appears, it is followed by the manufacturer's name and the page to consult for further information. Under a generic heading, all fully described brands are listed first, followed by those with only partial information. In each case, the brands are listed alphabetically.



SECTION 2

BRAND AND GENERIC NAME INDEX

This index includes all entries in the Product Information and Diagnostic Product Information sections. Products are listed alphabetically by both brand and generic name. Generic names are underlined; brand names are not. Under each generic name, you will find a list of the brands that contain it. This enables you to find a product by either of its names. For example, the brand Ativan appears once in the A's, and again under its generic name, lorazepam.

Each time a brand name appears, it is followed by the manufacturer's name and the page number to consult for further information. If multiple page numbers appear, the first ones refer to photos of the product, the last one to its prescribing information. Under a generic heading, all fully described brands are listed first, followed by those with only partial information.

- **Bold page numbers** indicate full prescribing information.
- *Italic page numbers* signify partial information.
- The ◆ symbol marks drugs shown in the Product Identification Guide.
- The ▣ symbol means product information is located in *PDR For Nonprescription Drugs and Dietary Supplements*™.
- The ⊙ symbol means product information is located in *PDR For Ophthalmic Medicines*™.

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Keflex—Cont.

ually, and had disappeared 8 hours after administration. Caution should be exercised when Keflex is administered to a nursing woman.

ADVERSE REACTIONS

Gastrointestinal —Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely. The most frequent side effect has been diarrhea. It was very rarely severe enough to warrant cessation of therapy. Dyspepsia, gastritis, and abdominal pain have also occurred. As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.

Hypersensitivity —Allergic reactions in the form of rash, urticaria, angioedema, and, rarely, erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis have been observed. These reactions usually subsided upon discontinuation of the drug. In some of these reactions, supportive therapy may be necessary. Anaphylaxis has also been reported.

Other reactions have included genital and anal pruritus, genital moniliasis, vaginitis and vaginal discharge, dizziness, fatigue, headache, agitation, confusion, hallucinations, arthralgia, arthritis, and joint disorder. Reversible interstitial nephritis has been reported rarely. Eosinophilia, neutropenia, thrombocytopenia, and slight elevations in AST and ALT have been reported.

OVERDOSAGE

Signs and Symptoms —Symptoms of oral overdose may include nausea, vomiting, epigastric distress, diarrhea, and hematuria. If other symptoms are present, it is probably secondary to an underlying disease state, an allergic reaction, or toxicity due to ingestion of a second medication.

Treatment —To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*. In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

Unless 5 to 10 times the normal dose of cephalexin has been ingested, gastrointestinal decontamination should not be necessary.

Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

Forced diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion have not been established as beneficial for an overdose of cephalexin; however, it would be extremely unlikely that one of these procedures would be indicated.

The oral median lethal dose of cephalexin in rats is >5,000 mg/kg.

DOSAGE AND ADMINISTRATION

Keflex is administered orally.

Adults —The adult dosage ranges from 1 to 4 g daily in divided doses. The usual adult dose is 250 mg every 6 hours. For the following infections, a dosage of 500 mg may be administered every 12 hours: streptococcal pharyngitis, skin and skin structure infections, and uncomplicated cystitis in patients over 15 years of age. Cystitis therapy should be continued for 7 to 14 days. For more severe infections or those caused by less susceptible organisms, larger doses may be needed. If daily doses of Keflex greater than 4 g are required, parenteral cephalosporins, in appropriate doses, should be considered.

Pediatric Patients —The usual recommended daily dosage for pediatric patients is 25 to 50 mg/kg in divided doses. For streptococcal pharyngitis in patients over 1 year of age and for skin and skin structure infections, the total daily dose may be divided and administered every 12 hours.

Keflex Suspension

Weight	125 mg/5 mL
10 kg (22 lb)	1/2 to 1 tsp q.i.d.
20 kg (44 lb)	1 to 2 tsp q.i.d.
40 kg (88 lb)	2 to 4 tsp q.i.d
Weight	**250 mg/5 mL**
10 kg (22 lb)	1/4 to 1/2 tsp q.i.d.
20 kg (44 lb)	1/2 to 1 tsp q.i.d.
40 kg (88 lb)	1 to 2 tsp q.i.d.

or

Weight	125 mg/5 mL
10 kg (22 lb)	1 to 2 tsp b.i.d.
20 kg (44 lb)	2 to 4 tsp b.i.d.
40 kg (88 lb)	4 to 8 tsp b.i.d.
Weight	**250 mg/5 mL**
10 kg (22 lb)	1/2 to 1 tsp b.i.d.
20 kg (44 lb)	1 to 2 tsp b.i.d.
40 kg (88 lb)	2 to 4 tsp b.i.d.

In severe infections, the dosage may be doubled.

In the therapy of otitis media, clinical studies have shown that a dosage of 75 to 100 mg/kg/day in 4 divided doses is required.

In the treatment of β-hemolytic streptococcal infections, a therapeutic dosage of Keflex should be administered for at least 10 days.

HOW SUPPLIED

Keflex® For Oral Suspension, (or cephalexin, USP), is available in:

The 125 mg per 5 mL oral suspension* is available as follows:

100-mL Bottles	NDC 0777-2321-48 (M-201)
200-mL Bottles	NDC 0777-2321-89 (M-201)

The 250 mg per 5 mL oral suspension* is available as follows:

100-mL Bottles	NDC 0777-2368-48 (M-202)
200-mL Bottles	NDC 0777-2368-89 (M-202)
ID†100	NDC 0777-2368-33 (M-202)

Keflex® Pulvules®, (or cephalexin, USP), are available in:

The 250 mg Pulvules are a white powder filled into size 2 Para-Posilok® Caps (opaque white and opaque dark green) that are imprinted with "Dista" and identity code "H69" on the green cap, and Keflex 250 on the white body in edible black ink. They are available as follows:

Bottles of 20	NDC 0777-0869-20 (PU402)
Bottles of 100	NDC 0777-0869-02 (PU402)

The 500 mg Pulvules are a white powder filled into an elongated, size 0 Para-Posilok Caps (opaque light green and opaque dark green) that are imprinted with "Dista" and identity code "H71" on the dark green cap, and Keflex 500 on the light green body in edible black ink. They are available as follows:

Bottles of 20	NDC 0777-0871-20 (PU403)
Bottles of 100	NDC 0777-0871-02 (PU403)

* After mixing, store in a refrigerator. May be kept for 14 days without significant loss of potency. Shake well before using. Keep tightly closed.

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

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

REFERENCES

1. National Committee for Clinical Laboratory Standards: Performance standards for antimicrobial disk susceptibility tests—5th ed. Approved Standard NCCLS Document M2-A5, Vol 13, No 24, NCCLS, Villanova, PA, 1993.
2. National Committee for Clinical Laboratory Standards: Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically—3rd ed. Approved Standard NCCLS Document M7-A3, Vol 13, No 25, NCCLS, Villanova, PA, 1993.

Literature revised December 15, 1998.

PV 0360 DPP [121598]

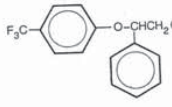
PROZAC®

[*prō 'zăk*]

(fluoxetine hydrochloride)

DESCRIPTION

Prozac® (fluoxetine hydrochloride) is an antidepressant for oral administration; it is also marketed for the treatment of premenstrual dysphoric disorder (Sarafem™, fluoxetine hydrochloride). 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 $C_{17}H_{18}F_3NO \cdot HCl$. 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 F D & C Yellow No. 10, F D & 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 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, desmethylmorphan, 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 tricyclic and other selective serotonin antidepressants, 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 propor-

tional 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—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—Daily Dosing: 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 (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 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 ≤ 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 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.

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 depression) 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—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

		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 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 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 one to two episodes per week for binge-eating and two to four 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 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 antidepressant action of Prozac in hospitalized depressed patients has not been adequately studied.

The efficacy of Prozac 20 mg once-daily 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 (*see* Clinical Trials *under* CLINICAL PHARMACOLOGY).

The efficacy of Prozac Weekly once-weekly in maintaining an antidepressant response 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 antidepressant 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.

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).

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, i.e., at least three bulimic episodes per week for 6 months (*see* Clinical Trials *under* CLINICAL PHARMACOLOGY).

The effectiveness of Prozac in long-term use, i.e., 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 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).

Continued on next page

This product information was prepared in June 2001. Current information on these and other products of Dista Products Company may be obtained by direct inquiry to Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, Indiana 46285, (800) 545-5979.

Prozac—Cont.

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, 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 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 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 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 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 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 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 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). 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 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* Accumulation and Slow Elimination un-

der 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 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 (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 coadministered 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 one breast milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng/mL. The concentration in the mother's plasma was 295.0 ng/mL.No adverse effects on the infant were reported. In another case, an infant nursed by a mother on Prozac developed crying, sleep disturbance, vomiting, and watery stools. The infant's plasma drug levels were 340 ng/mL of fluoxetine and 208 ng/mL of norfluoxetine on the second day of feeding.

Pediatric Use—Safety and effectiveness in pediatric patients have not been established.

Geriatric Use—US fluoxetine clinical trials (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. 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 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.

[See table 1 above]

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	—

Continued on next page

This product information was prepared in June 2001. Current information on these and other products of Dista Products Company may be obtained by direct inquiry to Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, Indiana 46285, (800) 545-5979.

Prozac—Cont.

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, 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%)	—

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 depression, 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 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 one 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:* 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‡.

* Neuroleptic malignant syndrome is the COSTART term that 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 nonfatal 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 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 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 pos-

sibility of clinically significant sequelae and extend the time needed for close medical observation (*see* Other Antidepressants *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

Depression: Initial Treatment—In controlled trials used to support the efficacy of fluoxetine, patients were administered morning doses ranging from 20 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 (i.e., 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* 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 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.
Daily Dosing—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).
Weekly Dosing—Systematic evaluation of Prozac Weekly has shown that its antidepressant efficacy 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—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.
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* 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 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* 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, 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
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

*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.
Literature revised February 28, 2001
PV 3451 DPP [22801]

Dow Hickam Pharmaceuticals

for product information see Bertek Pharmaceuticals Inc.

DuPont Pharma

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Address all product-related inquiries to:
Medical Affairs Department

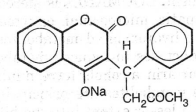
For Product Information/Adverse Drug Experience Reporting, call
Product Information
(℞) 992-4240 or 1-800-474-2762

COUMADIN® TABLETS ℞
(Warfarin Sodium Tablets, USP) Crystalline
Anticoagulant

COUMADIN® FOR INJECTION ℞
(Warfarin Sodium for Injection, USP)
Rx only

DESCRIPTION

COUMADIN (crystalline warfarin sodium), is an anticoagulant which acts by inhibiting vitamin K-dependent coagulation factors. Chemically, it is 3-(α-acetonylbenzyl)-4-hydroxycoumarin and is a racemic mixture of the R- and S-enantiomers. Crystalline warfarin sodium is an isopropanol clathrate. The crystallization of warfarin sodium virtually eliminates trace impurities present in amorphous warfarin. Its empirical formula is $C_{19}H_{15}NaO_4$ and its structural formula may be represented by the following:



Crystalline warfarin sodium occurs as a white, odorless, crystalline powder, is discolored by light and is very soluble in water; freely soluble in alcohol; very slightly soluble in chloroform and in ether.
COUMADIN Tablets for oral use also contain:

All strengths:	Lactose, starch and magnesium stearate
1 mg:	D&C Red No. 6 Barium Lake
2 mg:	FD&C Blue No. 2 Aluminum Lake and FD&C Red No. 40 Aluminum Lake
2-1/2 mg:	D&C Yellow No. 10 Aluminum Lake and FD&C Blue No. 1 Aluminum Lake
3 mg:	FD&C Yellow No. 6 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake and FD&C Red No. 40 Aluminum Lake
4 mg:	FD&C Blue No. 1 Aluminum Lake
5 mg:	FD&C Yellow No. 6 Aluminum Lake
6 mg:	FD&C Yellow No. 6 Aluminum Lake and FD&C Blue No. 1 Aluminum Lake
7-1/2 mg:	D&C Yellow No. 10 Aluminum Lake and FD&C Yellow No. 6 Aluminum Lake
10 mg:	Dye Free

COUMADIN for Injection is supplied as a sterile, lyophilized powder, which, after reconstitution with 2.7 mL sterile Water for Injection, contains:

Warfarin Sodium	2 mg/mL
Sodium Phosphate, Dibasic, Heptahydrate	4.98 mg/mL
Sodium Phosphate, Monobasic, Monohydrate	0.194 mg/mL
Sodium Chloride	0.1 mg/mL
Mannitol	38.0 mg/mL
Sodium Hydroxide, as needed for pH adjustment to	8.1 to 8.3

CLINICAL PHARMACOLOGY

COUMADIN and other coumarin anticoagulants act by inhibiting the synthesis of vitamin K dependent clotting factors, which include Factors II, VII, IX and X, and the anticoagulant proteins C and S. Half-lives of these clotting factors are as follows: Factor II — 60 hours, VII — 4–6 hours, IX — 24 hours, and X — 48–72 hours. The half-lives of proteins C and S are approximately 8 hours and 30 hours, respectively. The resultant *in vivo* effect is a sequential depression of Factors VII, IX, X and II activities. Vitamin K is an essential cofactor for the post ribosomal synthesis of the

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