CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75465

DRAFT FINAL PRINTED LABELING

75-755

AP 8/2/01

For dosage and other prescribing information, see accompanying product literature.

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

Dispense in a tight light-resistant container.

Keep tightly closed.

NDC 57315-052-02

FLUOXETINE HYDROCHLORIDE
TABLETS 20 mg
100 Tablets
Each tablet contains 20 mg of fluoxetine as fluoxetine hydrochloride.
R only

alphapharm

Lot No.:
Exp. Date:
1018/2
Manufactured by:
ALPHAPHARM PTY. LTD.
15 Garnet St.,
Carole Park, Qld. 4300
Australia
Call 1-800-661 3429

APPROVED
AUG - 2 2001

For dosage and other prescribing information, see accompanying product literature.

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

Dispense in a tight light-resistant container.

Keep tightly closed.

NDC 57315-051-02

FLUOXETINE HYDROCHLORIDE
TABLETS 10 mg
100 Tablets
Each tablet contains 10 mg of fluoxetine as fluoxetine hydrochloride.
R only

alphapharm

Lot No.:
Exp. Date:
1015/2
Manufactured by:
ALPHAPHARM PTY. LTD.
15 Garnet St.,
Carole Park, Qld. 4300
Australia
Call 1-800-661 3429

APPROVED
AUG - 2 2001

NDC 57315-051-02

FLUOXETINE HYDROCHLORIDE
TABLETS 10 mg
100 Tablets
Each tablet contains 10 mg of fluoxetine as fluoxetine hydrochloride.
R only

alphapharm

Lot No.:
Exp. Date:
1015/2
Manufactured by:
ALPHAPHARM PTY. LTD.
15 Garnet St.,
Carole Park, Qld. 4300
Australia
Call 1-800-661 3429

APPROVED
AUG - 2 2001

NDC 57315-052-03

FLUOXETINE HYDROCHLORIDE
TABLETS 20 mg
2000 Tablets
Each tablet contains 20 mg of fluoxetine as fluoxetine hydrochloride.
R only

APPROVED
AUG - 2 2001

For dosage and other prescribing information, see accompanying product literature.

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

Dispense in a tight light-resistant container.

Keep tightly closed.

Lot No.:
Exp. Date:
1019/2
Manufactured by:
ALPHAPHARM PTY. LTD.
15 Garnet St.,
Carole Park, Qld. 4300
Australia
Call 1-800-661 3429

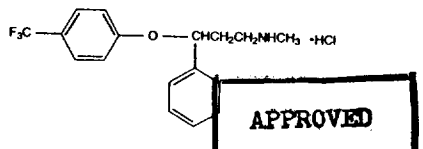
alphapharm

FLUOXETINE HYDROCHLORIDE TABLETS

℞ only

DESCRIPTION

Fluoxetine 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 molecular 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 tablet contains fluoxetine hydrochloride equivalent to 10 mg (32.3 μmol) or 20 mg (64.7 μmol) of fluoxetine. The tablets also contain colloidal anhydrous silica, crospovidone, hydroxypropyl methylcellulose, magnesium stearate, maize starch, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics:

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

Protein Binding–Over the concentration range from 200 to 1,000 ng/mL, approximately 94.5% of fluoxetine is bound *in vitro* to human serum proteins, including albumin and α_1-glycoprotein. The interaction between fluoxetine and other highly protein-bound drugs has not been fully evaluated, but may be important (*see* PRECAUTIONS).

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

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

Clinical Issues Related to Metabolism/Elimination–The complexity of the metabolism of fluoxetine has several consequences that may potentially affect fluoxetine's clinical use.

Variability in Metabolism–A subset (about 7%) of the population has reduced activity of the drug metabolizing enzyme cytochrome P450IID6. Such individuals are referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and the 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 4 active enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. Alternative, nonsaturable pathways (non-IID6) also contribute to the metabolism of fluoxetine. This explains how fluoxetine achieves a steady-state concentration rather than increasing without limit.

Because fluoxetine's metabolism, like that of a number of other compounds including tricyclic and other selective serotonin antidepressants, involves the P450IID6 system, concomitant therapy with drugs also metabolized by this enzyme system (such as the TCAs) may lead to drug interactions (*see* Drug Interactions *under* PRECAUTIONS).

Accumulation and Slow Elimination–The relatively slow elimination of fluoxetine (elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration) and its active metabolite, norfluoxetine (elimination half-life of 4 to 16 days after acute and chronic administration), leads to significant accumulation of these active species in chronic use and delayed attainment of steady state, even when a fixed dose is used. After 30 days of dosing at 40 mg/day, plasma concentrations of fluoxetine in the range of 91 to 302 ng/mL and norfluoxetine in the range of 72 to 258 ng/mL have been observed. Plasma concentrations of fluoxetine were higher than those predicted by single-dose studies, because fluoxetine's metabolism is not proportional to dose. Norfluoxetine, however, appears to have linear pharmacokinetics. Its mean terminal half-life after a single dose was 8.6 days and after multiple dosing was 9.3 days. Steady-state levels after prolonged dosing are similar to levels seen at 4 to 5 weeks.

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

Liver Disease–As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of fluoxetine. The elimination half-life of fluoxetine was prolonged in a study of cirrhotic patients, with a mean of 7 6 days compared to the range of 2 to 3 days seen in subjects without liver disease; norfluoxetine elimination was also delayed, with a mean duration of 12 days for cirrhotic patients compared to the range of 7 to 9 days in normal subjects. This suggests that the use of fluoxetine in patients with liver disease must be approached with caution. If fluoxetine is administered to patients with liver disease, a lower or less frequent dose should be used (*see* PRECAUTIONS *and* DOSAGE AND ADMINISTRATION).

Renal Disease–In depressed patients on dialysis (N=12), fluoxetine administered as 20 mg once daily for two months produced steady-state fluoxetine and norfluoxetine plasma concentrations comparable to those seen in patients with normal renal function. While the possibility exists that renally excreted metabolites of fluoxetine may accumulate to higher levels in patients with severe renal dysfunction, use of a lower or less frequent dose is not routinely necessary in renally impaired patients (*see* Use in Patients with Concomitant Illness *under* PRECAUTIONS *and* DOSAGE AND ADMINISTRATION).

Age–The disposition of single doses of fluoxetine in healthy elderly subjects (greater than 65 years of age) did not differ significantly from that in younger normal subjects. However, given the long half-life and nonlinear disposition of the drug, a single-dose study is not adequate to rule out the possibility of altered pharmacokinetics in the elderly, particularly if they have systemic illness or are receiving multiple drugs for concomitant diseases. The effects of age upon the metabolism of fluoxetine have been investigated in 260 elderly, but otherwise healthy, depressed patients (≥60 years of age) who received 20 mg fluoxetine for 6 weeks. Combined fluoxetine plus norfluoxetine plasma concentrations were 209.3 ± 85.7 ng/mL at the end of 6 weeks. No unusual age-associated pattern of adverse events was observed in those elderly patients.

Clinical Trials:

Depression–The efficacy of fluoxetine for the treatment of patients with depression (≥18 years of age) has been studied in 5- and 6-week placebo-controlled trials. Fluoxetine was shown to be significantly more effective than placebo as measured by the Hamilton Depression Rating Scale (HAM-D). Fluoxetine 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 fluoxetine 20 mg, and placebo have sl
fluoxetine 20 mg daily, to be effective in the treatment of elderly patients (≥50 years of age) with depressio
these studies, fluoxetine produced a significantly higher rate of response and remission as defined respec
by a 50% decrease in the HAM-D score and a total endpoint HAM-D score of ≤8. Fluoxetine was well tole
and the rate of treatment discontinuations due to adverse events did not differ between fluoxetine (12%)
placebo (9%).

A study was conducted involving depressed outpatients who had responded (modified HAMD-17 score
during each of the last 3 weeks of open-label treatment and absence of major depression by DSM-III-R crit
by the end of an initial 12-week open treatment phase on fluoxetine 20 mg/day. These patients (N=298)
randomized to continuation on double-blind fluoxetine 20 mg/day or placebo. At 38 weeks (50 weeks tota
statistically significantly lower relapse rate (defined as symptoms sufficient to meet a diagnosis of m
depression for 2 weeks or a modified HAMD-17 score of ≥14 for 3 weeks) was observed for patients ta
fluoxetine compared to those on placebo.

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

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

		Fluoxetine		
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 responsiven
on the basis of age or sex.

INDICATIONS AND USAGE

Depression–Fluoxetine is indicated for the treatment of depression. The efficacy of fluoxetine was establish
in 5- and 6-week trials with depressed adult and geriatric outpatients (≥18 years of age) whose diagnos
corresponded most closely to the DSM-III (currently DSM-IV) category of major depressive disorder (*s
Clinical Trials *under* CLINICAL PHARMACOLOGY).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for
least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at le
5 of the following 9 symptoms: depressed mood; loss of interest in usual activities; significant change in wei
and/or appetite; insomnia or hypersomnia; psychomotor agitation or retardation; increased fatigue; feelings
guilt or worthlessness; slowed thinking or impaired concentration; a suicide attempt or suicidal ideation.

The antidepressant action of fluoxetine in hospitalized depressed patients has not been adequately studie

The efficacy of fluoxetine in *maintaining* an antidepressant response for up to 38 weeks following 12 wee
of open-label acute treatment (50 weeks total) was demonstrated in a placebo-controlled trial. The usefulne
of the drug in patients receiving fluoxetine for extended periods should be reevaluated periodically (*see* Clinic
Trials *under* CLINICAL PHARMACOLOGY).

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

The efficacy of fluoxetine was established in 13-week trials with obsessive-compulsive outpatients who
diagnoses corresponded most closely to the DSM-III-R category of obsessive-compulsive disorder (*see* Clinic
Trials *under* CLINICAL PHARMACOLOGY).

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

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

CONTRAINDICATIONS

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

Monoamine Oxidase Inhibitors–There have been reports of serious, sometimes fatal, reactions (includin
hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and menta
status changes that include extreme agitation progressing to delirium and coma) in patients receiving fluoxetin
in combination with a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinue
fluoxetine and are then started on an MAOI. Some cases presented with features resembling neuroleptic
malignant syndrome. Therefore, fluoxetine should not be used in combination with an MAOI, or within
minimum of 14 days of discontinuing therapy with an MAOI. Since fluoxetine and its major metabolite have ver
long elimination half-lives, at least 5 weeks (perhaps longer, especially if fluoxetine has been prescribe
chronically and/or at higher doses (*see* Accumulation and Slow Elimination *under* CLINICAL
PHARMACOLOGY)) should be allowed after stopping fluoxetine before starting an MAOI.

Thioridazine - Thioridazine should not be administered with fluoxetine or within a minimum of 5 weeks afte
fluoxetine has been discontinued (*see* WARNINGS).

WARNINGS

Rash and Possibly Allergic Events–In U.S. 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 clinica
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 milc
transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive
treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover
completely.

In premarketing clinical trials, 2 patients are known to have developed a serious cutaneous systemic illness.
In neither patient was there an unequivocal diagnosis, but 1 was considered to have a leukocytoclastic
vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or
erythema multiforme. Other patients have had systemic syndromes suggestive of serum sickness.

Since the introduction of fluoxetine, 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, fluoxetine 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 U.S. placebo-controlled clinical trials for depression, 12% to 16% of patients treated with fluoxetine and 7% to 9% of patients treated with placebo reported anxiety, nervousness, or insomnia.

In U.S. placebo-controlled clinical trials for OCD, insomnia was reported in 28% of patients treated with fluoxetine and in 22% of patients treated with placebo. Anxiety was reported in 14% of patients treated with fluoxetine and in 7% 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 fluoxetine in clinical trials collecting only a primary event associated with discontinuation) in U.S. placebo-controlled fluoxetine clinical trials were anxiety (2% in OCD), insomnia, and nervousness (1% in depression) (*see* Table 2, below).

Altered Appetite and Weight–Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment with fluoxetine.

In U.S. placebo-controlled clinical trials for depression, 11% of patients treated with fluoxetine and 2% of patients treated with placebo reported anorexia (decreased appetite). Weight loss was reported in 1.4% of patients treated with fluoxetine and in 0.5% of patients treated with placebo. However, only rarely have patients discontinued treatment with fluoxetine because of anorexia or weight loss.

In U.S. placebo-controlled clinical trials for OCD, 17% of patients treated with fluoxetine and 10% of patients treated with placebo reported anorexia (decreased appetite). One patient discontinued treatment with fluoxetine because of anorexia.

Activation of Mania/Hypomania–In U.S. placebo-controlled clinical trials for depression, mania/hypomania was reported in 0.1% of patients treated with fluoxetine 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 U.S. placebo-controlled clinical trials for OCD, mania/hypomania was reported in 0.8% of patients treated with fluoxetine and no patients treated with placebo. In all U.S. fluoxetine clinical trials, 0.7% of 10,782 patients reported mania/hypomania.

Seizures–In U.S. placebo-controlled clinical trials for depression, convulsions (or events described as possibly having been seizures) were reported in 0.1% of patients treated with fluoxetine and 0.2% of patients treated with placebo. No patients reported convulsions in U.S. placebo-controlled clinical trials for OCD. In all U.S. fluoxetine clinical trials, 0.2% of 10,782 patients reported convulsions. The percentage appears to be similar to that associated with other marketed antidepressants. Fluoxetine 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 fluoxetine should be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose.

Because of well-established comorbidity between OCD and depression, the same precautions observed when treating patients with depression should be observed when treating patients with OCD.

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 fluoxetine in patients with concomitant systemic illness is limited. Caution is advisable in using fluoxetine 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 fluoxetine 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, fluoxetine may alter glycemic control. Hypoglycemia has occurred during therapy with fluoxetine, 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 fluoxetine 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 fluoxetine:

- Because fluoxetine 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 4 active enantiomers is comparable between poor and extensive metabolizers (*see* Variability in Metabolism *under* CLINICAL PHARMACOLOGY).

Fluoxetine, like other agents that are metabolized by P450IID6, inhibits the activity of this isoenzyme, and thus may make normal metabolizers resemble "poor metabolizers". Therapy with medications that are predominantly metabolized by the P450IID6 system and that have a relatively narrow therapeutic index (*see* list below), should be initiated at the low end of the dose range if a patient is receiving fluoxetine concurrently or has taken it in the previous 5 weeks. Thus, his/her dosing requirements resemble those of "poor metabolizers". If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by P450IID6, the need for decreased dose of the original medication should be considered. Drugs with a narrow therapeutic index represent the greatest concern (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 coadministration 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 fluoxetine in combination with other CNS active drugs has not been systematically evaluated. Nonetheless, caution is advised if the concomitant administration of fluoxetine 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 fluoxetine 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 coadministered or has been recently discontinued (*see* Accumulation and Slow Elimination *under* CLINICAL PHARMACOLOGY, *and* Drugs Metabolized by P450IID6 *under* Drug Interactions).

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

Potential Effects of 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., warfarin, 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 anticoagulant 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 fluoxetine.

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). Fluoxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery–The effect of fluoxetine 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 fluoxetine is excreted in human milk, nursing while on fluoxetine is not recommended. In 1 breast milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng/mL. The concentration in the mother's plasma was 295.0 ng/mL. No adverse effects on the infant were reported. In another case, an infant nursed by a mother on fluoxetine 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–U.S. 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 fluoxetine 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 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 fluoxetine had been administered to 10,782 patients with various diagnoses in U.S. 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 U.S. 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 fluoxetine (incidence of at least 5% for fluoxetine and at least twice that for placebo within at least one of the indications) for the treatment of depression and OCD in U.S. controlled clinical trials.

TABLE 1
MOST COMMON TREATMENT-EMERGENT ADVERSE EVENTS: INCIDENCE IN U.S. DEPRESSION AND OCD PLACEBO-CONTROLLED CLINICAL TRIALS

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

*Denominator used was for males only (N=690 fluoxetine depression; N=410 placebo depression; N=116 fluoxetine OCD; N=43 placebo OCD).
—Incidence less than 1%.

Associated with Discontinuation in U.S. Placebo-Controlled Clinical Trials (excluding data from extensions of trials)–Table 2 lists the adverse events associated with discontinuation of fluoxetine treatment (incidence at least twice that for placebo and at least 1% for fluoxetine in clinical trials collecting only a primary event associated with discontinuation) in depression, and OCD.

TABLE 2
MOST COMMON ADVERSE EVENTS ASSOCIATED WITH DISCONTINUATION IN U.S. DEPRESSION AND OCD PLACEBO-CONTROLLED CLINICAL TRIALS

Depression (N=392)	OCD (N=266)
—	Anxiety (2%)
—	—
Nervousness (1%)	—
—	Rash (1%)

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 U.S. depression and OCD 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 U.S. Clinical Trials–Following is a list of all treatment-emergent adverse events reported at anytime by individuals taking fluoxetine in U.S. clinical trials (10,782 patients) except (1) those listed in the body or footnotes of Table 1 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 fluoxetine use was considered remote; and (4) events occurring in only 1 patient treated with fluoxetine 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 those defined as occurring on 1 or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Body as a Whole–*Frequent*: chills; *Infrequent*: chills and fever, face edema, intentional overdose, malaise, pelvic pain, suicide attempt; *Rare*: abdominal syndrome acute, hypothermia, intentional injury, neuroleptic malignant syndrome¶, pholosensitivity 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 anemi leukopenia, lymphedema, lymphocytosis, petechia, purpura, thrombocythemia, thrombocytopenia.

Metabolic and Nutritional–*Frequent*: weight gain; *Infrequent*: dehydration, generalized edema, gou hypercholesteremia, hyperlipemia, hypokalemia, peripheral edema; *Rare*: alcohol intolerance, alkalir phosphatase increased, BUN increased, creatine phosphokinase increased, hyperkalemia, hyperuricemi hypocalcemia, iron deficiency anemia, SGPT increased.

Musculoskeletal System–*Infrequent*: arthritis, bone pain, bursitis, leg cramps, tenosynovitis; *Rare*: arthrosi chondrodystrophy, myasthenia, myopathy, myositis, osteomyelitis, osteoporosis, rheumatoid arthritis.

Nervous System–*Frequent*: agitation, amnesia, confusion, emotional lability, sleep disorder; *Infrequen* abnormal gait, acute brain syndrome, akathisia, apathy, ataxia, buccoglossal syndrome, CNS depression, CN stimulation, depersonalization, euphoria, hallucinations, hostility, hyperkinesia, hypertonia, hypesthesi incoordination, libido increased, myoclonus, neuralgia, neuropathy, neurosis, paranoid reaction, personalit disorder*, psychosis, vertigo; *Rare*: abnormal electroencephalogram, antisocial reaction, circumor paresthesia, coma, delusions, dysarthria, dystonia, extrapyramidal syndrome, foot drop, hyperesthesi neuritis, paralysis, reflexes decreased, reflexes increased, stupor.

Respiratory System–*Infrequent*: asthma, epistaxis, hiccup, hyperventilation; *Rare*: apnea, atelectasis, coug decreased, emphysema, hemoptysis, hypoventilation, hypoxia, larynx edema, lung edema, pneumothora stridor.

Skin and Appendages–*Infrequent*: acne, alopecia, contact dermatitis, eczema, maculopapular rash, ski 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, urinar urgency, vaginal hemorrhage*; *Rare*: breast engorgement, glycosuria, hypomenorrhea*, kidney pain, oliguria priapism*, uterine hemorrhage*, uterine fibroids enlarged*.

¶Neuroleptic malignant syndrome is the COSTART term which best captures serotonin syndrome.
*Personality disorder is the COSTART term for designating non-aggressive objectionable behavior.
*Adjusted for gender.

Postintroduction Reports–Voluntary reports of adverse events temporally associated with fluoxetine 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 involuntar 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, ventricula tachycardia (including torsades de pointes-type arrhythmias), and violent behaviors.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class–Fluoxetine is not a controlled substance.

Physical and Psychological Dependence–Fluoxetine has not been systematically studied, in animals or humans for its potential for abuse, tolerance, or physical dependence. While the premarketing clinical experience with fluoxetine 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 fluoxetine (e.g., development of tolerance, incrementation o dose, drug-seeking behavior).

OVERDOSAGE

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

Among 633 adult patients who overdosed on fluoxetine hydrochloride alone, 34 resulted in a fatal outcome 378 completely recovered, and 15 patients experienced sequelae after overdosage, including abnormal accommodation, abnormal gait, confusion, unresponsiveness, nervousness, pulmonary dysfunction, vertigo, tremor, elevated blood pressure, impotence, movement disorder, and hypomania. The remaining 206 patients had an unknown outcome. The most common signs and symptoms associated with non-fatal overdosage were seizures, somnolence, nausea, tachycardia, and vomiting. The largest known ingestion of fluoxetine hydrochloride in 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 6 dogs purposely overdosed with oral fluoxetine, 5 experienced grand mal seizures. Seizures stopped immediately upon the bolus intravenous administration of a standard veterinary dose of diazepam. In this short-term study, the lowest plasma concentration at which a seizure occurred was only twice the maximum plasma concentration seen in humans taking 80 mg/day, chronically.

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

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

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

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

A specific caution involves patients who are taking or have recently taken fluoxetine and might ingest excessive quantities of a TCA. In such a case, accumulation of the parent tricyclic and/or an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (*see* Other 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 centres 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, adminstered 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.

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

Obsessive-Compulsive Disorder–

Initial Treatment–In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of obsessive-compulsive disorder, patients were administered fixed daily doses of 20, 40, or 60 mg of fluoxetine or placebo (*see* Clinical Trials *under* CLINICAL PHARMACOLOGY). In one of these studies, no dose response-relationship for effectiveness was demonstrated. Consequently, a dose of 20 mg/day, administered in the morning, is recommended as the initial dose. Since there was a suggestion of a possible dose response relationship for effectiveness in the second study, a dose increase may be considered after several weeks if insufficient clinical improvement is observed. The full therapeutic effect may be delayed until 5 weeks of treatment or longer.

Doses above 20 mg/day may be administered on a once a day (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 fluoxetine 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 fluoxetine, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of fluoxetine 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.

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* PRECAUTIONS, 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 fluoxetine. In addition, at least 5 weeks, perhaps longer, should be allowed after stopping fluoxetine before starting an MAOI (*see* CONTRAINDICATIONS *and* PRECAUTIONS).

HOW SUPPLIED

Fluoxetine Hydrochloride Tablets are available as follows:

10 mg[1], oval, normal convex, film coated, scored white tablet, debossed "FL | 10" on one side and "G" on the other

Bottles of 30	NDC 57315-051-01
Bottles of 100	NDC 57315-051-02
Bottles of 2000	NDC 57315-051-03

20 mg[1], oval, normal convex, film coated, scored white tablet, debossed "FL | 20" on one side and "G" on the other

Bottles of 30	NDC 57315-052-01
Bottles of 100	NDC 57315-052-02
Bottles of 2000	NDC 57315-052-03

[1] Fluoxetine base equivalent.

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

Dispense in a light, light-resistant container. Protect from light.

Sarafem™ is a trademark of Eli Lilly.

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 lenfluramine, imipramine, and ranitidine. The significance of this effect in humans is unknown.

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For dosage and other prescribing information, see accompanying product literature.

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

Dispense in a tight light-resistant container.

Keep tightly closed.

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FLUOXETINE HYDROCHLORIDE TABLETS 20 mg

30 Tablets

Each tablet contains 20 mg of fluoxetine as fluoxetine hydrochloride.

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FLUOXETINE HYDROCHLORIDE TABLETS 10 mg

2000 Tablets

Each tablet contains 10 mg of fluoxetine as fluoxetine hydrochloride

℞ only

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For dosage and other prescribing information, see accompanying product literature.

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

Dispense in a tight light-resistant container.

Keep tightly closed.

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