# PRODUCT MONOGRAPH

**FLUOXETINE-10**

**FLUOXETINE-20**

**FLUOXETINE HYDROCHLORIDE CAPSULES USP**

**10 mg and 20 mg**

**Antidepressant/Antiobsessional/**
**Antibulimic Agent**

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# PRODUCT MONOGRAPH

FLUOXETINE-10 and FLUOXETINE-20
Fluoxetine Hydrochloride Capsules USP
10 mg and 20 mg

## THERAPEUTIC CLASSIFICATION

Antidepressant/Antiobsessional/Antibulimic Agent

## ACTIONS AND CLINICAL PHARMACOLOGY

The antidepressant, antiobsessional and antibulimic actions of fluoxetine are presumed to be linked to its ability to selectively inhibit the neuronal reuptake of serotonin. At clinically relevant doses fluoxetine blocks the uptake of serotonin into human platelets. Antagonism of muscarinic, histaminergic and $\alpha_1$-adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative and cardiovascular effects of classical tricyclic antidepressant drugs. *In vitro* receptor binding studies have demonstrated that fluoxetine binds to these and other membrane receptors [opiate, serotonergic (5-$HT_1$, 5-$HT_2$), adrenergic ($\alpha_1$, $\alpha_2$, $\beta$) and dopaminergic] much less potently than do the tricyclic drugs.

Pharmacokinetics:

Fluoxetine is well absorbed after oral administration. In man, following a single 40 mg dose, peak plasma concentrations of fluoxetine from 15 to 55 ng/mL are observed after 6 to 8 hours. 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.

Fluoxetine is extensively metabolized in the liver to norfluoxetine, and other unidentified metabolites. The pharmacological activity of norfluoxetine, which is formed by demethylation of fluoxetine appears to be similar to that of the parent drug. Norfluoxetine contributes to the long

duration of action of fluoxetine. The primary route of elimination appears to be hepatic metabolism to inactive metabolites excreted by the kidney. The elimination half-life of fluoxetine is 4 to 6 days and that of its active metabolite is 4 to 16 days.

Comparative Bioavailability

A two-way, single-dose, randomized, crossover bioavailability study using 18 normal male volunteers was conducted to evaluate the relative bioavailability of FLUOXETINE-20 mg Capsules and Prozac® 20 mg Capsules (manufactured by Eli Lilly Inc.). The mean pharmacokinetic parameters obtained are listed below.

| Summary of Results Based on Fluoxetine Plasma Levels | | | |
|---|---|---|---|
| Parameter | Mean* (C.V.) | | Relative Mean** |
| | FLUOXETINE-20 | PROZAC® | |
| $AUC_T$ (ng•hr/mL) | 2371.6 (64) | 2499.2 (68) | 96.1 |
| $AUC_{0-72}$ (ng•hr/mL) | 1440.8 (31) | 1503.5 (32) | 96.1 |
| $AUC_I$ (ng•hr/mL) | 2706.5 (60) | 2820.4 (63) | 96.8 |
| $C_{max}$ (ng/mL) | 37.7 (21) | 41.0 (21) | 92.2 |
| $T_{max}$ (hr) | 6.50 (23) | 6.00 (34) | 100.9 |
| $\lambda$ ($hr^{-1}$) | 0.0138 (42) | 0.0142 (42) | 97.3 |
| $t_{1/2}$ (hr) | 60.97 (48) | 61.34 (58) | 99.8 |

* For raw data; for $T_{max}$ these are medians.
**Based on the geometric means for $AUC_{0-72}$, $AUC_T$, $AUC_I$ and $C_{max}$ and arithmetic means for $T_{max}$, $\lambda$ and $t_{1/2}$.

| Summary of Results Based on Norfluoxetine Plasma Levels |
|---|

| Parameter | Mean* (C.V.) | | Relative Mean** |
|---|---|---|---|
| | FLUOXETINE-20 | PROZAC® | |
| $AUC_T$ (ng·hr/mL) | 5641.0 (30) | 6141.2 (30) | 92.2 |
| $AUC_{0-72}$ (ng·hr/mL) | 1072.2 (42) | 1129.2 (38) | 93.7 |
| $AUC_I$ (ng·hr/mL) | 7701.7 (19) | 8215.4 (19) | 94.2 |
| $C_{max}$ (ng/mL) | 20.9 (33) | 22.5 (36) | 93.7 |
| $T_{max}$ (hr) | 96.00 (24) | 96.00 (36) | 86.8 |
| $\lambda$ ($hr^{-1}$) | 0.0038 (29) | 0.0041 (42) | 91.6 |
| $t_{1/2}$ (hr) | 199.34 (38) | 199.16 (51) | 101.1 |

* For raw data; for $T_{max}$ these are medians.
**Based on the geometric means for $AUC_{0-72}$, $AUC_T$, $AUC_I$ and $C_{max}$ and arithmetic means for $T_{max}$, $\lambda$ and $t_{1/2}$.

## Clinical Issues Related To Metabolism/Elimination

### Variability in Metabolism

The metabolism of fluoxetine, like that of a number of other compounds, including tricyclic antidepressants and some selective serotonin reuptake inhibitors, involves the P450IID6 system. Concomitant therapy with fluoxetine and the aforementioned drugs may lead to clinically significant drug interactions (see Drug Interactions under PRECAUTIONS).

### Accumulation and Slow Elimination

The relatively slow elimination of fluoxetine and its active metabolite, norfluoxetine, results in significant accumulation of these active moieties in chronic use. Therefore, it may take up to 1 to 2 months for the active drug substance(s) to disappear from the body. This persistence of active moieties is important to keep in mind when FLUOXETINE is discontinued, or when drugs that are predicted to interact with FLUOXETINE are to be administered soon after its discontinuation (see Implications of the Long Elimination Half-Life of Fluoxetine under WARNINGS and Drug Interactions under PRECAUTIONS).

Kinetic Data

After 30 days of dosing at 20 mg/day, mean plasma concentrations of fluoxetine 79.1 ± 33.4 ng/mL and of norfluoxetine 129 ± 42.0 ng/mL have been observed. Plasma concentrations of fluoxetine (elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration) were higher than those predicted by single dose studies. Norfluoxetine appears to have linear pharmacokinetics. Its mean terminal half-lives after a single dose and multiple doses were 8.6 days and 9.3 days, respectively.

Steady state plasma levels are attained after 4 to 5 weeks of continuous drug administration. Patients receiving fluoxetine at doses of 40 to 80 mg/day over periods as long as 3 years exhibited, on average, plasma concentrations similar to those seen among patients treated for 4 to 5 weeks at the same dose.

Age

The effects of age upon the metabolism of fluoxetine have been investigated in a subset of 260 elderly, but otherwise healthy, depressed patients (mean age: 67.4 years, range 60 to 85 years) who received 20 mg fluoxetine for 6 weeks. The mean plasma concentrations were found to be 89.5 ± 53.6 ng/mL for fluoxetine and 119 ± 51.3 ng/mL for norfluoxetine. However, the effects of concomitant illness and/or concomitant drugs have not been evaluated.

Protein Binding

Approximately 94% of fluoxetine is protein bound. The interaction between fluoxetine and other highly protein bound drugs has not been fully evaluated, but may be important (see PRECAUTIONS).

Liver Disease

In patients with cirrhosis, the elimination half-life of fluoxetine was prolonged, with a mean of 7.6 days compared to the range of 2 to 3 days seen in healthy subjects; norfluoxetine half-life was also prolonged, with a mean of 12 days compared to a range of 7 to 9 days in healthy subjects. Fluoxetine should therefore be used with caution in patients with liver disease (see PRE-CAUTIONS and DOSAGE AND ADMINISTRATION).

Renal Disease

In single dose studies, the pharmacokinetics of fluoxetine and norfluoxetine were similar among subjects with all levels of impaired renal function including anephric patients on chronic hemo-dialysis. However, with chronic administration, additional accumulation of fluoxetine or its metabolites (possibly including some not yet identified) may occur in patients with severely impaired renal function and use of a lower or less frequent dose is advised (see PRECAUTIONS).

Clinical Trials

The efficacy of fluoxetine was established in 5 and 6-week placebo-controlled clinical trials in depressed outpatients (≥18 years of age), who met the DSM-III-R criteria for major depressive disorder.

Two, 6-week placebo-controlled clinical trials in depressed elderly patients, who met the DSM-III-R criteria for major depressive disorder (mean age 67.4 years, range 60 to 85 years) have shown fluoxetine, 20 mg/day, to be effective.

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 fluoxetine 20 mg/day. These patients (N=298) were randomized to continuation on double-blind fluoxetine 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 $\geq$14 for 3 weeks) was observed for patients taking fluoxetine compared to those on placebo.

## INDICATIONS

### Depression

FLUOXETINE (fluoxetine hydrochloride) may be indicated for the symptomatic relief of depressive illness.

### Bulimia Nervosa

Fluoxetine hydrochloride has been shown to significantly decrease binge-eating and purging activity when compared with placebo treatment.

### Obsessive-Compulsive Disorder

Fluoxetine hydrochloride has been shown to significantly reduce the symptoms of obsessive-compulsive disorder in double-blind, placebo-controlled clinical trials.

The obsessions or compulsions must be experienced as intrusive, markedly distressing, time consuming, or interfering significantly with the person's social or occupational functioning.

The efficacy of fluoxetine hydrochloride in hospitalized patients has not been adequately studied.

The long-term effectiveness of fluoxetine (i.e. for more than 5 to 6 weeks in depression, for more than 16 weeks in bulimia nervosa, or for more than 13 weeks in obsessive compulsive disorder), has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use FLUOXETINE in these indications for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

## CONTRAINDICATIONS

FLUOXETINE (fluoxetine hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.

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 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 14 days of discontinuing therapy with an MAOI.** Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks should be allowed after stopping FLUOXETINE before starting an MAOI. Limited reports

suggest that intravenously administered dantrolene (Dantrium®) or orally administered cyproheptadine (Periactin®) may benefit patients experiencing such reactions.

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

## WARNINGS

### POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM

**Pediatrics: Placebo-Controlled Clinical Trial Data**

- **Recent analyses of placebo-controlled clinical trial safety databases from SSRIs and other newer anti-depressants suggests that use of these drugs in patients under the age of 18 may be associated with behavioural and emotional changes, including an increased risk of suicidal ideation and behaviour over that of placebo.**

- **The small denominators in the clinical trial database, as well as the variability in placebo rates, preclude reliable conclusions on the relative safety profiles among these drugs.**

**Adults and Pediatrics: Additional data**

- **there are clinical trial and post-marketing reports with SSRIs and other newer anti-depressants, in both pediatrics and adults, of severe agitation-type adverse events coupled with self-harm or harm to others. The agitation-type events include: akathisia, agitation, disinhibition, emotional lability, hostility, aggression, depersonalization. In some cases, the events occurred within several weeks of starting treatment.**

**Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages. This includes monitoring for agitation-type emotional and behavioural changes.**

**Discontinuation Symptoms**

**Patients currently taking SSRIs or a newer anti-depressant should NOT be discontinued abruptly, due to risk of discontinuation symptoms. At the time that a medical decision is made to discontinue an SSRI or other newer anti-depressant drug, a gradual reduction in the dose rather than an abrupt cessation, except for fluoxetine, is recommended. Plasma fluoxetine and norfluoxetine concentrations decrease gradually at the conclusion of therapy which makes dose tapering unnecessary in most patients taking this drug (see PRECAUTIONS: DISCONTINUATION OF TREATMENT WITH FLUOXETINE (POST-MARKETING AND CLINICAL TRIALS); ADVERSE REACTIONS: Discontinuation of Treatment with Fluoxetine (Post-Marketing and Clinical Trials); DOSAGE AND ADMINISTRATION: DISCONTINUATION OF TREATMENT WITH FLUOXETINE).**

Allergic Reactions (Rash and Accompanying Events)

During premarketing testing, 7% of 10,782 patients developed various types of a rash and/or urticaria. Among these cases, almost a third were withdrawn from the treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with these allergic reactions include rash, 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 severe desquamation that was considered variously to be a vasculitis or erythema multiforme. Other patients have had systemic manifestations 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 (fluoxetine hydrochloride) should be discontinued. Particular caution should be exercised in patients with a history of allergic reactions.

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 P4502D6 isozyme activity. Thus, this study suggests that drugs which inhibit P4502D6, 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**).

Implications of the Long Elimination Half-Life of Fluoxetine

Because of the long elimination half-lives of fluoxetine and its major active metabolite norfluoxetine, 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 ACTIONS AND CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). Even when dosing is stopped, active drug substance will persist in the body for weeks due to the long elimination half-lives of fluoxetine and norfluoxetine. This is of potential consequence when drug discontinuation is required or when drugs are prescribed that might interact with fluoxetine and norfluoxetine following discontinuation of FLUOXETINE.

## PRECAUTIONS

### Anxiety and Insomnia

During premarketing clinical trials anxiety, nervousness and insomnia were reported by 10 to 15% of patients treated with fluoxetine. These symptoms led to discontinuation of the drug in 5% of the patients.

### Weight Change

Significant weight loss, especially in underweight depressed patients and the elderly, may be an undesirable result of treatment with FLUOXETINE (fluoxetine hydrochloride).

### Mania/Hypomania

During pre-marketing clinical trials in a patient population comprised primarily of unipolar depressives, hypomania or mania occurred in approximately 1% of fluoxetine treated patients. The incidence in a general patient population which might also include bipolar depressives is unknown. The likelihood of hypomanic or manic episodes may be increased at the higher dosage levels. Such reactions require a reduction in dosage or discontinuation of the drug.

### Seizures

FLUOXETINE should be used with caution in patients with a history of convulsive disorders. The incidence of seizures associated with fluoxetine during clinical trials did not appear to differ from that reported with other marketed antidepressants; however, patients with a history of convulsive disorders were excluded from these trials.

Concurrent administration with electroshock therapy should be avoided because of the absence of experience in this area. There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment.

DISCONTINUATION OF TREATMENT WITH FLUOXETINE (POST–MARKETING AND CLINICAL TRIALS):

When discontinuing treatment, patients should be monitored for symptoms which may be associated with discontinuation (e.g. headache, insomnia, paresthesias, nervousness, anxiety, nausea, sweating, numbness, dizziness, jitteriness, asthenia or other symptoms which may be of clinical significance).

Fluoxetine has been only rarely associated with such symptoms. Plasma fluoxetine and norfluoxetine concentrations decrease gradually at the conclusion of therapy, which makes dose tapering unnecessary in most patients (See ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

Hypokalemia

Self-induced vomiting often leads to hypokalemia which may lower seizure threshold and/or may lead to cardiac conduction abnormalities. Electrolyte levels of bulimic patients should be assessed prior to initiation of treatment.

Suicide

The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Therefore, high risk patients should be closely supervised throughout therapy

and consideration should be given to the possible need for hospitalization. In order to minimize the opportunity for overdosage, prescriptions for fluoxetine should be written for the smallest quantity of drug consistent with good patient management (see **WARNINGS: POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM)**.

Concomitant Illness

Clinical experience with fluoxetine in patients with concomitant systemic illness is limited and it should be used cautiously in such patients, especially those with diseases or conditions that could affect metabolism or hemodynamic responses.

Fluoxetine hydrochloride 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 premarketing clinical studies. Retrospective evaluation of EKG's in some of these studies showed no conduction abnormalities that resulted in heart block. The mean heart rate was reduced by approximately 3 beats/minute.

FLUOXETINE should be given with caution to patients suffering from anorexia nervosa and only if the expected benefits (e.g. co-morbid depression) markedly outweigh the potential weight reducing effect of the drug.

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.

Since fluoxetine is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. However, until an adequate number of patients with severe renal impairment have been evaluated in the course of chronic treatment, fluoxetine should be used with caution in such patients.

Since clearances of fluoxetine and norfluoxetine may be decreased in patients with impaired liver function including cirrhosis, a lower or less frequent dose should be used in such patients.

Hyponatremia

Several 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 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 of sodium in a fluoxetine treated patient 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.

Cognitive and Motor Performance

Patients should be cautioned against driving an automobile or performing hazardous tasks until they are reasonably certain that treatment with FLUOXETINE does not affect them adversely.

Electroconvulsive Therapy (ECT)

There are no clinical studies to support the safety and efficacy of combined use of ECT and fluoxetine. There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment.

Use in Pregnancy

Safe use of fluoxetine during pregnancy has not been established. Therefore it should not be administered to women of childbearing potential unless, in the opinion of the treating physician, the expected benefits to the patient markedly outweigh the possible hazards to the fetus or the child.

Post-marketing reports indicate that some neonates exposed to FLUOXETINE, other SSRIs (Selective Serotonin Reuptake Inhibitors), or other newer anti-depressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support,

and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and other newer anti-depressants, or possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see CONTRAINDICATIONS, Monoamine Oxidase Inhibitors). When treating a pregnant woman with FLUOXETINE during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION).

Use in Lactation

Fluoxetine and its metabolites are excreted in breast milk and have been observed to reach high plasma levels in nursing infants. Women who are taking FLUOXETINE should not breast feed unless in the opinion of the treating physician, breast feeding is necessary, in which case the infant should be closely monitored.

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, a 6-week infant, nursed by a mother on fluoxetine, developed crying, decreased sleep, vomiting and watery stools. The breast milk showed concentrations of 69 ng/mL for fluoxetine and 90 ng/mL for norfluoxetine. In the infant's plasma, the concentrations of fluoxetine and norfluoxetine on the second day of feeding were 340 and 208 ng/mL, respectively.

Use in Children

Safety and effectiveness in patients below the age of 18 have not been established.

Use in the Elderly

Evaluation of patients over the age of 60 who received fluoxetine 20 mg daily revealed no unusual pattern of adverse events relative to the clinical experience in younger patients. These data are, however, insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients who have concomitant systemic illnesses or who are receiving concomitant drugs.

DRUG INTERACTIONS

Monoamine Oxidase Inhibitors

Combined use of fluoxetine and MAO inhibitors is contraindicated (see CONTRAINDICATIONS).

Tricyclic Antidepressants

In two studies, previously stable plasma levels of imipramine and desipramine have increased greater than 2 to 10 fold when fluoxetine has been administered in combination. This influence may persist for three weeks or longer after fluoxetine is discontinued. Thus, the dose of tricyclic antidepressant (TCA) may need to be reduced and plasma TCA concentrations may need to be monitored temporarily when fluoxetine is coadministered or has been recently discontinued (see Accumulation and Slow Elimination under ACTIONS AND CLINICAL PHARMACOLOGY and P450 Isoenzyme [IID6] under PRECAUTIONS).

Lithium

There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with fluoxetine. Cases of lithium toxicity 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.

Benzodiazepines

The half-life of concurrently administered diazepam may be prolonged in some patients.

Coadministration of alprazolam and fluoxetine has resulted in increased alprazolam plasma concentrations and in further psychomotor performance decrement due to increased alprazolam levels. Consideration should be given to monitoring of clinical status. Experience with the use of fluoxetine in combination with other CNS-active drugs is limited and caution is advised if such concomitant medication is required (see WARNINGS).

Phenytoin

In patients on stable, maintenance doses of phenytoin, plasma phenytoin concentrations increased substantially and symptoms of phenytoin toxicity appeared (nystagmus, diplopia, ataxia and CNS depression) following initiation of concomitant fluoxetine treatment.

Carbamazepine

Patients on stable doses of phenytoin and carbamazepine have developed elevated plasma anticonvulsant concentrations and clinical anticonvulsant toxicity following initiation of concomitant fluoxetine treatment. Consideration should be given to monitoring of clinical status when fluoxetine treatment is initiated in these patients.

Antipsychotics

Elevation of blood levels of haloperidol and clozapine and in some cases, clinical manifestations of toxicity have been observed with coadministration of fluoxetine. Consideration should be given to monitoring of clinical status.

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.

Alcohol

The concomitant use of fluoxetine and alcohol on cognitive and psychomotor effects in depressed, panic disorder or OCD patients is not known and is not recommended.

St. John's Wort

In common with other SSRI's, pharmacodynamic interactions between fluoxetine and the herbal remedy St. John's Wort may occur and may result in an increase in undesirable effects.

Drugs Tightly Bound to Plasma Protein

Because fluoxetine is highly bound to plasma protein, the administration of fluoxetine to a patient taking another drug which 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.

Warfarin

Altered anti-coagulant effects, including increased bleeding, have been reported when fluoxetine is co-administered with warfarin. Serious bleeding events have been reported including five with outcome of death. However, a causal relationship to the bleeding events cannot be established. Therefore, patients receiving warfarin therapy should receive careful coagulation monitoring when fluoxetine is initiated or stopped.

Drugs Metabolized by P450 Isoenzyme (IID6)

Approximately 3 to 10% 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 debrisoquine, dextromethorphan, sparteine, tricyclic antidepressants (e.g. nortriptyline, amitriptyline, imipramine and desipramine), pheno-

thiazine neuroleptics (e.g. perphenazine and thioridazine) and Type 1C antiarrhythmics (e.g. propafenone and flecainide).

Conversely, approximately 90 to 97% of the normal population do not have this genetic defect, and are known as "extensive metabolizers". Fluoxetine, like other agents that are metabolized by the P450IID6 system, inhibits the activity of this isoenzyme, and thus may make normal "extensive" metabolizers resemble "poor metabolizers". Therapy with medications that are predominantly metabolized by the P450IID6 system and that have a relatively narrow therapeutic index (e.g. flecainide, encainide, vinblastine, carbamazepine and tricyclic antidepressants) 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.

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. The aforementioned drugs with a narrow therapeutic index represent the greatest concern.

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 P4503A4

In an *in vivo* interaction study involving co-administration of fluoxetine with single doses of terfenadine (a cytochrome P4503A4 substrate), no increase in plasma terfenadine concentrations occurred with concomitant fluoxetine. In addition, *in vitro* studies have shown ketoconazole, a potent inhibitor of P4503A4 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 P4503A4 activity is not likely to be of clinical significance.

Dependence Liability

Fluoxetine has not been systematically studied, in animals or humans, for its potential for abuse, tolerance or physical dependence. 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.

## ADVERSE REACTIONS

Commonly Observed

In clinical trials, the most commonly observed adverse events associated with the use of fluoxetine and not seen at an equivalent incidence among placebo treated patients were: central nervous system complaints, including headache, nervousness, insomnia, drowsiness, fatigue or asthenia, anxiety, tremor, and dizziness or lightheadedness; gastrointestinal complaints, including nausea, diarrhea, dry mouth and anorexia; and excessive sweating.

Adverse events Leading to Discontinuation of Treatment

Fifteen percent of approximately 4,000 patients who received fluoxetine in North American clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation from depression trials in adults and elderly, included: psychiatric, primarily

nervousness, anxiety, and insomnia; digestive, primarily nausea; nervous system, primarily dizziness, asthenia and headaches; skin, primarily rash and pruritis.

In obsessive compulsive disorder studies, 12.1% of fluoxetine-treated patients discontinued treatment early because of adverse events. Anxiety and rash, at incidences of less than 2%, were the most frequently reported events. In bulimia nervosa studies, 10.2% of fluoxetine-treated patients discontinued treatment early because of adverse events. Insomnia, anxiety and rash, at incidences of less than 2%, were the most frequently-reported events.

Serious Adverse Reactions

Suicidal thoughts and acts are far more common among depressed patients than in the general population. It is estimated that suicide is 22 to 36 times more prevalent in depressed persons than in the general population. A comprehensive meta-analysis of pooled data from 17 double-blind clinical trials in patients with major depressive disorder compared fluoxetine (n=1765) with a tricyclic antidepressant (n=731) or placebo (n=569), or both. The pooled incidence of emergence of substantial suicidal ideation was 1.2% for fluoxetine, 2.6% for placebo, and 3.6% for tricyclic antidepressants.

In countries where the drug has already been marketed, the following potentially serious adverse reactions have been reported: interactions with MAO inhibitors and possibly other drugs, allergic reactions, cardiovascular reactions, syndrome of inappropriate ADH secretion, and grand mal seizure. Death and life-threatening events have been associated with some of these reactions, although causal relationship to fluoxetine has not necessarily been established.

Postmarketing experience also confirms the profile of adverse reactions commonly reported during clinical trials with fluoxetine hydrochloride including allergic skin reactions.

Adverse Experience Reports

Multiple doses of fluoxetine 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.

**TABLE 1**

| Percentage of Patients Reporting Event | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **DEPRESSION * (Adults)** | | **DEPRESSION (Elderly)** | | **OCD*** | | **BULIMIA*** | |
| Body System/ Adverse Event | Fluoxetine (N=1728) | Placebo (N=975) | Fluoxetine (N=335) | Placebo (N=336) | Fluoxetine (N=266) | Placebo (N=89) | Fluoxetine (N=450) | Placebo (N=267) |
| **Nervous System** | | | | | | | | |
| Headache | -- | -- | 28 | 24 | -- | -- | -- | -- |
| Nervousness | 14 | 9 | 12 | 7 | 14 | 15 | 11 | 5 |
| Insomnia | 16 | 9 | 18 | 12 | 28 | 22 | 33 | 13 |
| Somnolence | 13 | 6 | 9 | 6 | 17 | 7 | 13 | 5 |
| Anxiety | 12 | 7 | 13 | 8 | 14 | 7 | 15 | 9 |
| Tremor | 10 | 3 | 8 | 4 | 9 | 1 | 13 | 1 |
| Dizziness | -- | -- | 11 | 10 | -- | -- | -- | -- |
| Libido, decreased | 3 | 0 | -- | -- | 11 | 2 | 5 | 1 |
| Abnormal dreams | 1 | 1 | -- | -- | 5 | 2 | 5 | 3 |
| **Digestive System** | | | | | | | | |
| Nausea | 21 | 9 | 17 | 7 | 26 | 13 | 29 | 11 |
| Diarrhea | -- | -- | 14 | 9 | -- | -- | -- | -- |
| Dry mouth | 10 | 7 | 7 | 5 | 12 | 3 | 9 | 6 |
| Anorexia | 11 | 2 | 11 | 2 | 17 | 10 | 8 | 4 |
| Dyspepsia | 7 | 5 | 11 | 5 | 10 | 4 | 10 | 6 |
| Constipation | -- | -- | 7 | 6 | -- | -- | -- | -- |
| Flatulence | -- | -- | 7 | 2 | -- | -- | -- | -- |
| **Skin and Appendages** | | | | | | | | |
| Sweating | 8 | 3 | 7 | 3 | 7 | 0 | 8 | 3 |
| Rash | 4 | 3 | -- | -- | 6 | 3 | 4 | 4 |
| **Body as a Whole** | | | | | | | | |
| Asthenia | 9 | 5 | 13 | 10 | 15 | 11 | 21 | 9 |
| Flu syndrome | 3 | 4 | -- | -- | 10 | 7 | 8 | 3 |
| Back Pain | -- | -- | 7 | 9 | -- | -- | -- | -- |
| Abdominal Pain | -- | -- | 6 | 6 | -- | -- | -- | -- |
| Myalgia | -- | -- | 3 | 5 | -- | -- | -- | -- |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Respiratory System** | | | | | | | | |
| Rhinitis | -- | -- | 9 | 14 | -- | -- | -- | -- |
| Pharyngitis | 3 | 3 | -- | -- | 11 | 9 | 10 | 5 |
| Sinusitis | 1 | 4 | 3 | 7 | 5 | 2 | 6 | 4 |
| Yawn | -- | -- | -- | -- | 7 | -- | 11 | -- |
| **Cardiovascular System** | | | | | | | | |
| Vasodilatation | 3 | 2 | -- | -- | 5 | 0 | 2 | 1 |
| **Urogenital System** | | | | | | | | |
| Abnormal Ejaculation† | -- | -- | -- | -- | 7 | -- | 7 | -- |
| Impotence† | 2 | -- | -- | -- | -- | -- | 7 | -- |

† Denominator used was for males only (N= 690 FLUOXETINE depression; N=410 placebo depression; N=116 FLUOXETINE OCD; N=43 placebo OCD; N=14 FLUOXETINE bulimia; N=1 placebo bulimia).

-- Incidence less than 1%

* 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, OCD, and bulimia in US controlled clinical trials.

Table 2 enumerates treatment-emergent adverse events that occurred in 2% or more patients treated with Fluoxetine and with incidence greater than placebo who participated in US controlled clinical trials comparing Fluoxetine with placebo in the treatment of depression, OCD, or bulimia. Table 2 provides combined data for the pool of studies that are provided separately by indication in Table 1.

TABLE 2

| Percentage of patients reporting event | | |
|---|---|---|
| | Depression, OCD, and bulimia combined | |
| Body System/Adverse Event* | Fluoxetine (N=2444) | Placebo (N=1331) |
| **Body as a Whole** | | |
| Headache | 21 | 20 |
| Asthenia | 12 | 6 |
| Flu syndrome | 5 | 4 |
| Fever | 2 | 1 |

| | | |
|---|---|---|
| **Cardiovascular System** | | |
| Vasodilatation | 3 | 1 |
| Palpitation | 2 | 1 |
| **Digestive System** | | |
| Nausea | 23 | 10 |
| Diarrhea | 12 | 8 |
| Anorexia | 11 | 3 |
| Dry mouth | 10 | 7 |
| Dyspepsia | 8 | 5 |
| Flatulence | 3 | 2 |
| Vomiting | 3 | 2 |
| **Metabolic and Nutritional Disorders** | | |
| Weight loss | 2 | 1 |
| **Nervous System** | | |
| Insomnia | 20 | 11 |
| Anxiety | 13 | 8 |
| Nervousness | 13 | 9 |
| Somnolence | 13 | 6 |
| Dizziness | 10 | 7 |
| Tremor | 10 | 3 |
| Libido decreased | 4 | -- |
| **Respiratory System** | | |
| Pharyngitis | 5 | 4 |
| Yawn | 3 | -- |
| **Skin and Appendages** | | |
| Sweating | 8 | 3 |
| Rash | 4 | 3 |
| Pruritus | 3 | 2 |
| **Special Senses** | | |
| Abnormal vision | 3 | 1 |

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

-- Incidence less than 1%.

Table 3 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, OCD, and bulimia.

**TABLE 3**

| 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%) | -- |

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 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.

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 labelling; (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 further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring on 1 or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 but at least 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† (characterized by the clustering of clinical features of changes in mental state and neuromuscular activity, in combination with autonomic nervous system dysfunction), photosensitivity reaction.

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

Cardiovascular

*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.

Respiratory

*Infrequent*: asthma, epistaxis, hiccup, hyperventilation

*Rare*: apnea, atelectasis, cough decreased, emphysema, hemoptysis, hypoventilation, hypoxia, larynx edema, lung edema, pneumothorax, stridor.

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

*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

*Infrequent*: arthritis, bone pain, bursitis, leg cramps, tenosynovitis

*Rare*: arthrosis, chondrodystrophy, myasthenia, myopathy, myositis, osteomyelitis, osteoporosis, rheumatoid arthritis.

Urogenital

*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*.

* Adjusted for gender

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.

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

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.

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 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 most severe cases, 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 behaviours.

Discontinuation of Treatment with Fluoxetine (Post–Marketing and Clinical Trials):

Symptoms associated with discontinuation of fluoxetine have been reported in clinical trials and post–marketing (e.g. headache, insomnia, paresthesias, nervousness, anxiety, nausea, sweating, numbness, dizziness, jitteriness, asthenia, or other symptoms which may be of clinical significance). The majority of these are mild and self–limiting. Fluoxetine has been only rarely associated with such symptoms. Plasma fluoxetine and norfluoxetine concentrations decrease gradually at the conclusion of therapy, which makes dose tapering unnecessary in most patients. (See ADVERSE REACTIONS and DOSAGE and ADMINISTRATION).

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

Cases of overdose of fluoxetine alone usually have a mild course. Symptoms of overdose included nausea, vomiting, seizures, cardiovascular dysfunction ranging from asymptomatic arrhythmias to cardiac arrest, pulmonary dysfunction, and signs of altered CNS status ranging from excitation to coma. Fatalities attributed to overdose of fluoxetine alone have been reported. (Please refer to Human Experience and Animal Experience sections below).

Symptoms: Nausea and vomiting were prominent in overdoses involving higher fluoxetine doses. Other prominent symptoms of overdose included agitation, restlessness, hypomania, and other signs of CNS excitation, including seizures.

Treatment:

There are no specific antidotes for fluoxetine.

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

Establish and maintain an airway; ensure adequate oxygenation and ventilation.

Cardiac and vital signs monitoring is recommended, along with general symptomatic and supportive measures.

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 considered in treating overdose.

Due to the large volume of distribution of fluoxetine, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit.

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.

Fluoxetine-induced seizures which fail to remit spontaneously may respond to diazepam. (see Product Monograph for diazepam).

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control centre on the treatment of any overdosage.

Human Experience:

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

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

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

Other important adverse events reported with fluoxetine overdose (single and 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 hyper-irritability 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.

## DOSAGE AND ADMINISTRATION

**FLUOXETINE (fluoxetine) is not indicated for use in children under 18 years of age (see WARNINGS: POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM).**

Since it may take up to four or five weeks to reach steady state plasma levels of FLUOXETINE (fluoxetine hydrochloride), sufficient time should be allowed to elapse before dosage is gradually increased. Higher dosages are usually associated with an increased incidence of adverse reactions.

Depression

Initial Adult Dosage: The usual initial dosage is 20 mg administered once daily in the morning. A gradual dose increase should be considered only after a trial period of several weeks if the expected clinical improvement does not occur. Dosage should not exceed a maximum of 80 mg per day since clinical experience with doses above 80 mg per day is very limited.

Long Term: The efficacy of fluoxetine in maintaining an antidepressant response for up to 38 weeks following 12 weeks of open-label acute treatment (50 weeks total) was demonstrated in a placebo-controlled trial. The usefulness of the drug in patients receiving fluoxetine for extended periods should be reevaluated periodically (see Clinical Trials).

Treatment of Pregnant Women During The Third Trimester: Post-marketing reports indicate that some neonates exposed to FLUOXETINE, SSRIs, or other newer anti-depressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube-feeding (see PRECAUTIONS). When treating pregnant women with

FLUOXETINE during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering FLUOXETINE in the third trimester.

Use in the Elderly: Fluoxetine was evaluated in depressed elderly patients only at a dosage of 20 mg/day. A lower or less frequent dosage may be effective and should be considered in elderly patients with concurrent disease or on multiple medications.

Use in Children: The safety and effectiveness of fluoxetine in patients below the age of 18 years have not been established **(see WARNINGS: POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM).**

Bulimia Nervosa

Adult Dosage: The recommended dosage is 60 mg per day, although studies show that lower doses may also be efficacious. Electrolyte levels should be assessed prior to initiation of treatment.

Obsessive-Compulsive Disorder

A dose range of 20 mg/day to 60 mg/day is recommended for the treatment of obsessive-compulsive disorder.

For any indication, the total fluoxetine dosage should not exceed a maximum of 80 mg per day since clinical experience with doses above 80 mg per day is very limited.

During maintenance therapy, the dosage should be kept at the lowest effective level.

**A lower or less frequent dosage should be used in patients with renal and/or hepatic impairment and in those on multiple medications.**

When dosing is stopped, active drug substances will persist in the body for weeks. This should be borne in mind when starting or stopping treatment. Dosage tapering is unnecessary in most patients.

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 Tricyclic Antidepressants under DRUG INTERACTIONS).

Switching Patients To or From a Monoamine Oxidase Inhibitor (MAOI)

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 MAOI (see CONTRAINDICATIONS).

DISCONTINUATION OF TREATMENT WITH FLUOXETINE:

Symptoms associated with the discontinuation of fluoxetine have been reported in clinical trials and post–marketing. Patients should be monitored for these and other symptoms when discontinuing treatment, regardless of the indication for which fluoxetine is being prescribed. Fluoxetine has been only rarely associated with such symptoms. Plasma fluoxetine and norfluoxetine concentrations decrease gradually at the conclusion of therapy, which makes dose

tapering unnecessary in most patients (See ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

Information for the Patient: See **INFORMATION ABOUT YOUR FLUOXETINE PRESCRIPTION**

## PHARMACEUTICAL INFORMATION

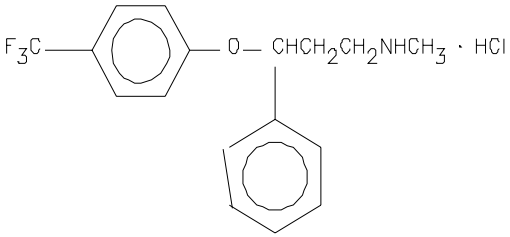
Drug Substance

Proper/Common Name: Fluoxetine Hydrochloride

Chemical Name(s): 1) Benzenepropanamine, *N*-methyl-γ-[4-(trifluoromethyl)phenoxy]-, hydrochloride,(±)-;

2) (±)-*N*-Methyl-3-phenyl-3-[(α,α,α-trifluoro-*p*-tolyl)-oxy]propylamine, hydrochloride

Structural Formula:




Molecular Formula: $C_{17}H_{18}F_3NO \cdot HCl$

Molecular Weight: 345.79

Description: An almost white, almost odourless, crystalline powder with a melting point of 153 to 155°C. Soluble in ethanol, methanol, ethyl acetate, water and acetone; insoluble in ether, benzene and ethyl acetate.

Composition

Each capsule of FLUOXETINE (fluoxetine hydrochloride) contains the following non-medicinal ingredients: gelatin, lactose, silicon dioxide, sodium lauryl sulphate, starch, stearic acid, titanium dioxide, talc, FD&C Yellow #6, D&C Yellow #10 and FD&C Blue #1. The 10 mg capsules also contain Sicomet black oxide.

Stability and Storage Recommendations

Store at room temperature (15° - 30°C) in tightly closed containers. Protect capsules from light.

## AVAILABILITY OF DOSAGE FORMS

FLUOXETINE-10 mg Capsules: Each green/grey, opaque, size #4 capsule imprinted 'PRO 10' contains fluoxetine hydrochloride equivalent to 10 mg fluoxetine. Available in bottles of 30,100, 250, 500 and 1000, and blisters of 100.

FLUOXETINE-20 mg Capsules: Each green/ivory, opaque size #3 capsule imprinted 'PRO 20' contains fluoxetine hydrochloride equivalent to 20 mg fluoxetine. Available in bottles of 100, 250, 500 and 1000 capsules, and blisters of 100.

## INFORMATION FOR THE PATIENT

## INFORMATION ABOUT YOUR FLUOXETINE PRESCRIPTION

Please read this information before you start to take your medicine, even if you have taken this drug before. Keep this leaflet until you have finished all your tablets as you may need to read it

again. FOR FURTHER INFORMATION OR ADVICE, PLEASE SEE YOUR DOCTOR OR PHARMACIST.

**WHAT YOU SHOULD KNOW ABOUT FLUOXETINE**

- FLUOXETINE hydrochloride belongs to a group of medications called selective serotonin reuptake inhibitors (SSRIs).

- FLUOXETINE has been prescribed by your doctor to relieve your symptoms of depression, bulimia, or obsessive-compulsive disorder. **Treatment with these types of medications is most safe and effective when you and your doctor have good communication about how you are feeling.**

**WHAT YOU SHOULD TELL YOUR DOCTOR BEFORE TAKING FLUOXETINE**

- all your medical conditions, including a history of liver or kidney problems, seizures or blackouts, or diabetes

- any medications (prescription or nonprescription) you are taking or have recently taken, especially monoamine oxidase inhibitors (e.g., phenelzine sulfate, tranylcypromine sulfate moclobemide or selegeline), any other antidepressants, drugs used to treat diabetes, drugs used to thin the blood (anticoagulants) or drugs containing tryptophan

- any natural or herbal products you are taking ( e.g. St. John’s Wort)

- if you are pregnant or thinking about becoming pregnant, or if you are breast feeding

- your habits of alcohol and /or street drug consumption

- if you have ever had an allergic reaction to medication used to treat your current condition

- if you drive a vehicle or perform hazardous tasks during your work

**HOW TO TAKE FLUOXETINE**

- It is important that you take FLUOXETINE exactly as your doctor has instructed. Generally people take between 20 mg to 80 mg per day for depression and obsessive-compulsive disorder and between 20 and 60 mg per day for bulimia. Your doctor may adjust the dose during the course of your treatment.

- Never increase the amount of FLUOXETINE you, or those in your care if you are a caregiver or guardian, are taking unless your doctor tells you to.

- You should continue to take your medicine even if you do not feel better, as it may take a number of weeks for your medicine to work. Improvement will be gradual.

- FLUOXETINE is usually taken once a day. It may be taken with or without food. You should swallow the capsules whole; do not chew them.

- Keep taking your FLUOXETINE until the doctor tells you to stop. The doctor may tell you to continue to take your medicine for several months. Continue to follow the doctor□s instructions.

- If you forget to take a dose of FLUOXETINE, don’t try to make up for it by taking a double dose the next time. Continue with the next scheduled dose.

- You should avoid taking St. John's Wort if you are taking FLUOXETINE.

**Remember: This medicine has been prescribed only for you. Do not give it to anybody else.**

**WHEN NOT TO USE FLUOXETINE**

- Do not use FLUOXETINE if you are allergic to it or any of the components of its formulation (see list of components at the end of this section)**.** Stop taking the drug and contact your doctor immediately if you experience an allergic reaction (e.g., skin rash, hives) or any severe or unusual side effects.

- Do not use FLUOXETINE if you are currently taking thioridazine

**PRECAUTIONS WHEN TAKING FLUOXETINE**

- Although FLUOXETINE seldom produces severe drowsiness, you should avoid driving a car, or operating hazardous machinery until you are reasonably certain your ability to do so is not affected.

- Contact your doctor before stopping your dosage of FLUOXETINE. Symptoms such as headache, insomnia, paresthesias, nervousness, anxiety, nausea, sweating, numbness, dizziness, jitteriness and weakness and other symptoms have been reported after stopping fluoxetine. These symptoms usually disappear without needing treatment. Tell your doctor immediately if you have these or any other symptoms. Your doctor may adjust the dosage of FLUOXETINE to alleviate the symptoms.

- Post-marketing reports indicate that some newborns whose mothers took an SSRI (Selective Serotonin Reuptake Inhibitor) or other newer anti-depressants, such as FLUOXETINE, during pregnancy have developed complications at birth requiring prolonged hospitalization, breathing support and tube feeding. Reported symptoms included feeding and / or breathing difficulties, seizures, tense or overly relaxed muscles, jitteriness and constant crying. In most cases, the newer anti-depressant was taken during the third trimester of pregnancy. These symptoms are consistent with either a direct adverse effect of the anti-depressant on the baby, or possibly a discontinuation syndrome caused by sudden withdrawal from the drug. These symptoms normally resolve over time. However, if your baby experiences any of these symptoms, contact your doctor as soon as you can.

If you are pregnant and taking an SSRI, or other newer anti-depressants, you should discuss the risks and benefits of the various treatment options with your doctor. It is very important that you do NOT stop taking these medications without first consulting your doctor.

**SIDE EFFECTS OF FLUOXETINE**

- Changes in sexual desire, performance, and satisfaction are often associated with psychiatric disorders. However, this medication can cause such undesired sexual experiences.

- You may experience other side effects such as nausea, dizziness, headache, anxiety, nervousness, drowsiness, or insomnia. Consult your doctor if you experience these or other side effects, as the dose may have to be adjusted.

- Particularly in the first few weeks or when doses are adjusted, a small number of patients taking drugs of this type may feel worse instead of better; for example, they may experience unusual feelings of agitation, hostility or anxiety, or have impulsive or disturbing thoughts such as

thoughts of self-harm or harm to others. Should this happen to you, or those in your care if you are a caregiver or guardian, consult your doctor immediately; do not discontinue your medication on your own.

**WHAT TO DO IN CASE OF OVERDOSE**

- If you have taken a large number of tablets all at once, contact your doctor or the nearest hospital emergency department immediately, even though you may not feel sick. Show the doctor your prescription bottle.

**HOW TO STORE FLUOXETINE**

- Keep out of reach of children
- Store in its original package at room temperature, in a dry place, and out of direct sunlight
- Do not use the medication after the expiry date, which is printed on the package label

**WHAT DOES FLUOXETINE CONTAIN**

- FLUOXETINE capsules contain the active ingredient fluoxetine hydrochloride.
- FLUOXETINE capsules contain the following inactive ingredients: gelatin, lactose, silicon dioxide, sodium lauryl sulphate, starch, stearic acid, titanium dioxide, talc, FD&C Yellow #6, D&C Yellow #10 and FD&C Blue #1. The 10 mg capsules also contain Sicomet black oxide.

## PHARMACOLOGY

*In vitro* and *in vivo* studies have shown fluoxetine and norfluoxetine (the major metabolite) to be potent and selective inhibitors of neuronal presynaptic reuptake of serotonin. Serotonin released into the synaptic cleft by a nerve impulse is inactivated principally by reuptake into the pre-synaptic nerve ending where it is metabolized or retained in storage granules. Fluoxetine specifically inhibits the reuptake process, thereby allowing serotonin to remain longer in the synaptic cleft and enhancing the action of the neurotransmitter on synaptic receptors. Fluoxetine has only weak affinity for various receptor systems in receptor binding studies.

A number of behavioral, neuroendocrinologic, and other pharmacologic effects of fluoxetine in experimental animals have been attributed to its enhancement of serotonergic function by inhibition of serotonin uptake. Fluoxetine restored the capacity for acquisition of passive avoidance task in olfactory bulbectomized rats, potentiated 5-hydroxytryptophan-induced head twitch in mice, potentiated 5-hydroxytryptophan-induced depression of operant behavior in pigeons, and potentiated the behavioral effect of 5-hydroxytryptophan in rats working on a milk reinforcement schedule. Fluoxetine suppressed REM sleep in rats and cats, and reduced the amount or altered the composition of dietary intake in rats. It also selectively reduced non-protein caloric intake in rats.

Few pharmacologic actions of fluoxetine other than inhibition of serotonin uptake and consequences of that inhibition have been found. For instance, fluoxetine does not antagonize reserpine or apomorphine-induced hypothermia in mice, and does not reduce immobility in the forced swimming test in rats.

Pharmacokinetics:

Fluoxetine was well absorbed orally and the oral bioavailability of fluoxetine in dogs was 72%. In dogs given oral doses of 1 to 10 mg/kg fluoxetine for one year, dose dependent increases in fluoxetine and norfluoxetine concentrations were observed in liver, adrenal, and lung.

Norfluoxetine concentrations exceeded fluoxetine concentrations in the tissues, and persisted for a longer period in plasma.

In rats, after a single i.p. dose of 10 mg/kg, the plasma half-life of fluoxetine was 26 hours and that of norfluoxetine, 40 hours. The plasma half-life in dogs dosed orally at 5 to 10 mg/kg for 15 days, was 1 day for fluoxetine and 2.1 to 5.4 days for norfluoxetine.

*In vitro*, fluoxetine was *N*-demethylated to norfluoxetine by rat, guinea pig, and rabbit liver microsomes. *In vivo*, fluoxetine was metabolized mainly by *N*-demethylation in mice, rats, guinea pigs, rabbits, and dogs. The other major metabolite was p-trifluoromethylphenol, formed by O-dealkylation, which was excreted as a sulphate or glucuronide conjugate by rats, guinea pigs, and dogs.

Fluoxetine and norfluoxetine were also excreted in the urine unchanged in guinea pigs, rabbits, and dogs. In rats, fluoxetine and norfluoxetine were both further metabolized, so that neither fluoxetine nor its *N*-demethylated metabolite was found in the urine. Rats eliminated 16 to 42 percent of the dose in urine as p-trifluoromethylphenol and 8 percent of the dose as hippuric acid in 24 hours.

# TOXICOLOGY

## Acute Toxicity

| Species | Route | Sex | Fluoxetine $LD_{50}$ (mg/kg) | Norfluoxetine $LD_{50}$ (mg/kg) |
|---|---|---|---|---|
| Mouse | Oral | F | 248 ± 14 | 361 ± 14 |
| | i.v. | F | 45 ± 1.5 | 42 ± 3 |
| Rat | Oral | M | 467 ± 33 | |
| | | F | 437 ± 40 | |
| | i.v. | M | 35 ± 1 | |
| | | F | 35 ± 1 | 37 ± 2 |
| Guinea Pig | Oral | M | >250 | |
| Cat | Oral | M/F | >50 | |
| Dog | Oral | M/F | >100 | |
| Monkey | Oral | M/F | >50 | |

Signs of toxicity included vomiting, anorexia, mydriasis, salivation, tremors, clonic convulsions, hyperirritability and cachexia.

## Subchronic Toxicity

Mice (5/sex/dose) were maintained on diets containing ca. 25, 59 and 204 mg/kg/day fluoxetine for 15 days. Thirty and 100% mortality were observed at the middle and high dose, respectively. Significant effects at the two highest doses included: hyperactivity and body weight loss, decrease in spleen weights and phospholipidosis.

Mice were maintained for three months on diets equivalent to ca. 2, 7 or 31 mg/kg/day. Significant effects were essentially limited to high dose mice and included 15% mortality; persistent hyperactivity and decreased body weight gain; slight and reversible increases in alkaline phosphatase

and alanine transaminase; decreases in testes, heart, and spleen weights; hypospermatogenesis; reversible pulmonary phospholipidosis.

Pulmonary histiocytosis (phospholipidosis) was the major pathological finding in rats maintained on diets providing average doses of approximately 9, 25 or 74 mg/kg/day for three months. All animals at ca. 74 mg/kg/day died by week 8. Decreased food consumption, weight loss, and hyperirritability were observed at ca. 25 and 74 mg/kg/day.

Dogs given 5 to 50 mg/kg/day orally for two weeks experienced anorexia, mydriasis and vomiting. Dogs receiving 50 mg/kg/day exhibited ataxia, tremors and a convulsion in one dog.

Dogs survived oral doses up to 20 mg/kg/day for three months with significant anorexia as the major treatment related effect. Significant accumulation of both fluoxetine and norfluoxetine occurred in the plasma and tissues. Mydriasis and tremors were observed during the first month.

Monkeys given 10 or 25 mg/kg/day p.o. for two weeks exhibited anorexia and weight loss. One monkey at 25 mg/kg/day exhibited clonic convulsions after six doses. Accumulation of fluoxetine and norfluoxetine was observed after multiple dosing and decreased erythrocyte and white blood cell counts were observed.

Chronic Toxicology

Fluoxetine was given daily to rats (25/sex/dose) for one year at dietary levels of ca. 0.5, 2.3 and 10.7 mg/kg/day. Physical signs of toxicity were limited to females at the high dose level and consisted of anorexia, chromodacryorrhea and an unusual behaviour first noted during the eighth month of treatment in which the animals walked on their toes with feet extended and backs arched after they had been handled.

Evidence of phospholipidosis was obtained in the lung, liver and adrenal cortex of 24/40 animals at the high dose level and in one rat at the mid dose level. Phospholipidosis was reversible after two months' withdrawal from treatment. Minimal to slight fat deposition in the liver was prevalent at the mid- and high-dose levels. Reversible, minimal reticuloendothelial cell hyperplasia was present in the lymph nodes of the high dose level animals.

Dogs (5/sex/dose) received daily oral doses of 1, 4.5, or 20 mg/kg (decreased to 10 mg/kg after 6 months as three females died) of fluoxetine for one year. The toxic effects observed in this study were similar to those of the subchronic study except that phospholipidosis was seen after chronic administration in the lung, liver, adrenals, the inner plexiform layer of the retina, lymph nodes, spleen, and peripheral leukocytes in the animals receiving the high dose. They also showed moderate bradycardia and a moderate decrease in adrenal weight.

Phospholipidosis was only observed in the lung and leukocytes in a few of the dogs at the lowest dose level of 1.0 mg/kg/day. No cardiovascular effects were seen apart from a slight decrease in basal heart rate. All treatment related effects were reversible during the recovery period in surviving animals.

Carcinogenicity

Rats were maintained for two years at dietary levels equivalent to a time weighted average dose of ca. 0.45, 2 and 9 mg/kg/day. Age related observations such as chromodacryorrhea, alopecia, and poor grooming increased at the high dose, especially in females. Weight gain and food consumption were depressed at the high dose and a handling-induced behaviour involving arching of the back and walking on toes was observed primarily in females in this group. Increased tissue levels of fluoxetine and norfluoxetine were observed at all doses, and

phospholipidosis was observed primarily at the high dose. There were no significant increases in tumor incidence or animal mortality.

Mice were fed dietary levels of fluoxetine equivalent to ca. 1.2, 4.8 and 12.1 mg/kg/day. The dietary levels were based on the results of the three month subchronic study. Unexpectedly, high mortality occurred in females receiving the high dose early in the two-year study, necessitating lowering the dose after 30 days. The survival rate of females receiving the high dose was reduced at two years. No major toxicological effects were seen in mice other than a moderate increase in alanine transaminase in males receiving the high dose and slight changes in organ weights. Hepatocellular degeneration, fat deposition in liver, and centrilobular hepatocellular degeneration were observed microscopically at the median and high dose. There was no evidence of phospholipid accumulation in the lung and no oncogenic response was observed.

A second two-year mouse study using similar doses gave similar results. Survival at two years was reduced in females receiving the high dose. Handling-induced clonic convulsions occurred at all levels in males, and in females, at the high-dose level it was accompanied by a slight increase in liver weight. Minimal-to-moderate fatty change in the liver and hepatocellular cytomegaly were seen in mice from the median- and high-dose levels. There was a dose-dependent increase in concentrations of fluoxetine and norfluoxetine in lung tissue. There was no evidence of phospholipid accumulation in the lung, and no oncogenic response was observed.

Mutagenicity

The mutagenicity of fluoxetine and its metabolite norfluoxetine was evaluated in a battery of *in vitro* and *in vivo* tests including Ames test, modified Ames test, DNA repair in rat hepatocytes, sister chromatid exchange in Chinese hamster bone marrow assays, and mouse lymphoma assay. Fluoxetine and norfluoxetine were negative in all 5 systems.

Teratology Studies

Virgin female Fischer 344 rats (25/dose) were bred with untreated control males and were given daily oral (gavage) doses of 2, 5, or 12.5 mg/kg/day fluoxetine on gestation days 6-15; animals were evaluated on gestation day 20. Body weight gains and food consumption were depressed at 12.5 mg/kg/day. Fluoxetine produced no teratogenic effects and no changes in reproductive parameters.

Virgin female Dutch Belted rabbits (15/dose) were artificially inseminated with semen from untreated control males and were given daily oral (gavage) doses of 2.5, 7.5, or 15 mg/kg/day fluoxetine on gestation days 6-18; animals were evaluated on gestation day 28. Maternal toxicity was demonstrated by depressed body weight gains and food consumption at all dose levels in a dose-dependent manner. At the 15 mg/kg/day dose, two rabbits died and three aborted. Resorptions were also increased in this group. There was no evidence of a teratogenic effect.

Reproductive Studies

Female Wistar rats (30/dose) were given daily oral doses of 2, 5, or 12.5 mg/kg from two weeks prior to mating through gestation or lactation. In a second study, male Wistar rats (40/dose) were maintained on diets approximately equivalent to 1.5, 3.9, or 9.7 mg/kg for 10 weeks prior to mating and through the breeding trial. These treated males were mated with female Wistar rats (40/dose) maintained at the same dietary levels for three weeks prior to mating and throughout lactation. In both studies, a depression in neonatal survival was obtained at the high dose level. No teratogenic effects or adverse effects on fertility or post-natal development were associated with fluoxetine administration.

Discussion of Phospholipidosis

Systemic phospholipidosis was associated with the subchronic and/or chronic administration of fluoxetine to mice, rats and dogs. This effect was associated with the accumulation of norfluoxetine, and to a lesser extent, fluoxetine, in affected tissues. Systemic phospholipidosis was not associated with any adverse effects and was shown to be reversible after the chronic administration of fluoxetine for one year in rats and dogs.

This effect has been demonstrated in animals with a number of other clinically useful cationic amphiphilic drugs including anti-depressants - imipramine, clomipramine, iprindole and other drugs - chlorphentermine, fenfluramine, clozapine, chloroquine, mepacocine, chlorcyclizine, tamoxifen, 4,4'diethylaminoethoxyhexestrol, amiodarone and perhexiline. The significance of this finding for man is not fully understood. It is anticipated that in the clinical use of fluoxetine, the properties of the drug which are associated with phospholipidosis will not result in any untoward effect.

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