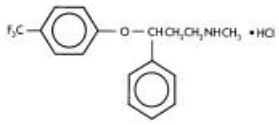
FINAL LABELING

SARAFEM^{Ô}
FLUOXETINE HYDROCHLORIDE

DESCRIPTION

SARAFEM™ (Fluoxetine Hydrochloride) is a selective serotonin reuptake inhibitor (SSRI) for oral administration; fluoxetine was initially developed and marketed as an antidepressant (Prozac®, fluoxetine hydrochloride). It is designated (±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-*p*-tolyl)oxy]propylamine hydrochloride and has the empirical formula of $C_{17}H_{18}F_3NO$•HCl. Its molecular weight is 345.79. The structural formula is:



Fluoxetine hydrochloride is a white to off-white crystalline solid with a solubility of 14 mg/mL in water.

Each Pulvule® contains fluoxetine hydrochloride equivalent to 10 mg (32.3 μmol) or 20 mg (64.7 μmol) of fluoxetine. The Pulvules also contain dimethicone, FD&C Blue No. 1, FD&C Red No. 3, FD&C Yellow No. 6, gelatin, sodium lauryl sulfate, starch, and titanium dioxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics:

The mechanism of action of fluoxetine in premenstrual dysphoric disorder (PMDD) is unknown, but is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin. Studies at clinically relevant doses in humans 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 certain psychoactive drugs. Fluoxetine has little affinity for these receptors.

Absorption, Distribution, Metabolism, and Excretion:

Systemic Bioavailability--In humans, 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.

Food does not appear to affect the systemic bioavailability of fluoxetine, although it may delay its absorption inconsequentially. Thus, fluoxetine may be administered with or without food.

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

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

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

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

Variability in Metabolism--A subset (about 7%) of the population has reduced activity of the drug metabolizing enzyme cytochrome P450IID6. Such individuals are referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and the tricyclic antidepressants. In a study involving labeled and unlabeled enantiomers administered as a racemate, these individuals metabolized *S*-fluoxetine at a slower rate and thus achieved higher concentrations of *S*-fluoxetine. Consequently, concentrations of *S*-norfluoxetine at steady state were lower. The metabolism of *R*-fluoxetine in these poor metabolizers appears normal. When compared with normal metabolizers, the total sum at steady state of the plasma concentrations of the 4 active enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. Alternative, nonsaturable pathways (non-IID6) also contribute to the metabolism of fluoxetine. This explains how fluoxetine achieves a steady-state concentration rather than increasing without limit.

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

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

dose was 8.6 days and after multiple dosing was 9.3 days. Steady state levels after prolonged dosing are similar to levels seen at 4-5 weeks.

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

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* Use in Patients with Concomitant Illness *under* 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).

Clinical Trials:

Premenstrual Dysphoric Disorder (PMDD)-- The effectiveness of SARAFEM for the treatment of PMDD was established in two placebo-controlled trials. Patients in these trials met DSM-IIIR criteria for Late Luteal Phase Dysphoric Disorder (LLPDD), the clinical entity now referred to as Premenstrual Dysphoric Disorder (PMDD) in DSM-IV. Patients on oral contraceptives were excluded from these trials; therefore, the efficacy of fluoxetine in combination with oral contraceptives for the treatment of PMDD is unknown.

In the first double-blind, parallel group study of 6 months duration involving n=320 patients, fixed doses of fluoxetine 20 mg and 60 mg/day given continuously throughout the menstrual cycle were shown to be significantly more effective than placebo as measured by a Visual Analogue Scale (VAS) total score (including mood and physical symptoms). The average total VAS score decreased 7% on placebo treatment, 36% on 20 mg and 39% on 60 mg fluoxetine. The difference between the 20 mg and 60 mg doses was not statistically significant. The following table shows the percentage of patients meeting criteria for either moderate or marked improvement on the VAS total score:

Percentage of Patients Moderately and Markedly Improved (> 50% and 75% reduction, respectively, from baseline Luteal Phase VAS total score)									
Improvement	N	**Placebo**	N	**Fluox 20mg**	N	**Fluox 60 mg**			
Moderate	94	**11%**	95	**37%**	85	**38%**			
Marked	94	**4%**	95	**6%**	85	**18%**			

In a second double-blind, cross-over study, patients (n=19) were treated with fluoxetine 20 mg to 60 mg/day (mean dose=27 mg/day) and placebo continuously throughout the menstrual cycle for a period of three months each. Fluoxetine was significantly more effective than placebo as measured by within cycle follicular to luteal phase changes in the VAS total score (mood, physical, and social impairment symptoms). The average VAS total score (follicular to luteal phase increase) was 3.8 times higher during placebo treatment than what was observed during fluoxetine treatment.

In a third double-blind, parallel group study, patients with LLPDD (n=42) were treated with fluoxetine 20 mg/day, bupropion 300 mg/day, or placebo for two months. Neither fluoxetine nor bupropion was shown to be superior to placebo on the primary endpoint, i.e., response rate [defined as a rating of 1 (very much improved) or 2 (much improved) on the CGI], possibly due to sample size.

INDICATIONS AND USAGE

SARAFEM is indicated for the treatment of premenstrual dysphoric disorder (PMDD).

The efficacy of fluoxetine in the treatment of PMDD was established in 2 placebo-controlled trials (*see* Clinical Trials *under* Clinical Pharmacology).

The essential features of PMDD, according to the Diagnostic and Statistical Manual-4th edition (DSM-IV) include markedly depressed mood, anxiety or tension, affective lability, and persistent anger or irritability. Other features include decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite or sleep, and feeling out of control. Physical symptoms associated with PMDD include breast tenderness, headache, joint and muscle pain, bloating, and weight gain. These symptoms occur regularly during the luteal phase and remit within a few days following onset of menses; the disturbance markedly interferes with work or school or with usual social activities and relationships with others. In making the diagnosis, care should be taken to rule out other cyclical mood disorders that may be exacerbated by treatment with an antidepressant.

The effectiveness of SARAFEM in long-term use, that is, for more than 6 months, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use SARAFEM for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

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

Monoamine Oxidase Inhibitors--There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) in patients receiving fluoxetine in combination with a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued fluoxetine and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, fluoxetine should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI. Since fluoxetine and its major metabolite have very long elimination half-lives,

at least 5 weeks (perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses [*see* Accumulation and Slow Elimination *under* Clinical Pharmacology]) should be allowed after stopping fluoxetine before starting an MAOI.

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

WARNINGS

Rash and Possibly Allergic Events—In three premarketing clinical trials for PMDD, 5% of 243 patients treated with SARAFEM reported rash and/or urticaria. None of these cases were classified as serious and 2 of 243 patients (both receiving 60 mg) were withdrawn from treatment because of rash and/or urticaria.

In US fluoxetine clinical trials for conditions other than PMDD, 7% of 10,782 patients developed various types of rashes and/or urticaria. Among the cases of rash and/or urticaria reported in premarketing clinical trials, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

In premarketing clinical trials of fluoxetine for conditions other than PMDD, 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 for other indications, systemic events, possibly related to vasculitis, have developed in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic events.

Anaphylactoid events, including bronchospasm, angioedema, and urticaria alone and in combination, have been reported.

Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These events have occurred with dyspnea as the only preceding symptom.

Whether these systemic events and rash have a common underlying cause or are due to different etiologies or pathogenic processes is not known. Furthermore, a specific underlying immunologic basis for these events has not been identified. Upon the appearance of rash or of other possibly allergic phenomena for which an alternative etiology cannot be identified, SARAFEM 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 a placebo-controlled trial of fluoxetine in premenstrual dysphoric disorder (PMDD), treatment-emergent adverse events were assessed. Rates were as follows for SARAFEM 20 mg (the recommended dose), SARAFEM 60 mg and placebo, respectively: anxiety (5%, 9%, and 6%), nervousness (7%, 9%, and 4%), and insomnia (9%, 26%, and 7%). Events associated with discontinuation for SARAFEM 20 mg, 60 mg, and placebo, respectively were: anxiety (0%, 6%, and 2%), nervousness (2%, 0%, and 1%), and insomnia (1%, 4%, and 1%). In US placebo-controlled clinical trials of fluoxetine for other approved indications, anxiety, nervousness, and insomnia have been among the most commonly reported adverse events (see Table 2 under Adverse Reactions).

Altered Appetite and Weight--In a placebo-controlled trial of fluoxetine in PMDD, 4% of patients on SARAFEM 20 mg (the recommended dose), 13% on SARAFEM 60 mg, and 3% of placebo patients reported anorexia. In two placebo-controlled trials, potentially clinically significant weight gain (≥7%) occurred in 8% of patients on SARAFEM 20 mg, 6% of patients on SARAFEM 60 mg, and 1% of patients on placebo. Potentially clinically significant weight loss (≥7%) occurred in 7% of patients on SARAFEM 20 mg, 12% of patients on SARAFEM 60 mg, and 3% of patients on placebo. In US placebo-controlled clinical trials of fluoxetine for other approved indications, changes in appetite and weight have also been reported (*see* Table 2 and Other Events Observed in US Clinical Trials *under* Adverse Reactions).

Activation of Mania/Hypomania--No patients treated with SARAFEM in three PMDD clinical trials (N=243) reported mania/hypomania. In all US fluoxetine clinical trials for conditions other than PMDD, 0.7% of 10,782 patients reported mania/hypomania. Activation of mania/hypomania may occur with medications used to treat depression, especially in patients predisposed to Bipolar Affective Disorder.

Seizures--No patients treated with SARAFEM in three PMDD clinical trials (N=243) reported seizures. In all US fluoxetine clinical trials for conditions other than PMDD, 0.2% of 10,782 patients reported seizures. Antidepressant medication should be introduced with care in patients with a history of seizures.

Suicide—No patients treated with SARAFEM in three PMDD clinical trials (N=243) attempted suicide. The possibility of a suicide attempt is inherent in mood disorders and may persist until significant remission occurs. In PMDD patients with a significant mood disturbance, close supervision should accompany drug therapy. In high-risk patients, prescriptions for antidepressant medication should be written for the smallest quantity of medication consistent with good patient management, in order to reduce the risk of overdose.

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 for a condition other than PMDD 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 (*see* Liver Disease *under* Clinical Pharmacology). A lower or less frequent dose should be used in patients with cirrhosis (*see* Dosage and Administration).

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—Patient information is printed at the end of this insert. To assure safe and effective use of SARAFEM, the information and instructions provided in the patient information section should be discussed with patients.

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

Drug Interactions—As with all drugs, the potential for interaction by a variety of mechanisms (eg, pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc) is a possibility (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

Drugs Metabolized by P450IID6--Approximately 7% of the normal population has a genetic defect that leads to reduced levels of activity of the cytochrome P450 isoenzyme P450IID6. Such individuals have been referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and tricyclic antidepressants. Many drugs, 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, her dosing requirements resemble those of "poor metabolizers." If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by P450IID6, the need for decreased dose of the original medication should be considered. Drugs with a narrow therapeutic index represent the greatest concern (eg, flecainide, vinblastine, and tricyclic antidepressants). Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, thioridazine should not be administered with fluoxetine or within a minimum of 5 weeks after fluoxetine has been discontinued (*see* Contraindications *and* Warnings).

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

CNS Active Drugs--The risk of using 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.

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

Sumatriptan—There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (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 (eg, 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 anti-coagulant effects, including increased bleeding, have been reported when fluoxetine is co-administered with warfarin. Patients receiving warfarin therapy should receive careful coagulation monitoring when fluoxetine is initiated or stopped.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility--There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with 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--The diagnosis of PMDD is not applicable to postmenopausal women.

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 a placebo-controlled, double-blind trial, 10 of 313 fluoxetine patients and 6 of 320 placebo recipients had a lowering of serum sodium below the reference range; this difference was not statistically significant. The lowest observed concentration was 129 mmol/L. The observed decreases were not clinically significant.

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

ADVERSE REACTIONS

In one of 3 placebo-controlled trials of fluoxetine in PMDD, treatment-emergent adverse events reporting rates were assessed. The information from Table 1 included under Adverse Reactions is based on data from this trial at the recommended dose of SARAFEM (SARAFEM 20 mg, N=104; placebo, N=108). In addition, a broader set of information on

treatment-emergent adverse events in the population of female patients, 18-45 years of age, from the US placebo-controlled depression, OCD, and bulimia clinical trials is presented for comparison (Table 2).

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 a Placebo-Controlled PMDD Clinical Trial--Table 1 enumerates the most common treatment-emergent adverse events associated with the use of SARAFEM 20 mg (incidence of at least 5% for SARAFEM 20 mg and greater than placebo) for the treatment of PMDD.

TABLE 1
MOST COMMON TREATMENT-EMERGENT ADVERSE EVENTS: INCIDENCE IN A PMDD PLACEBO-CONTROLLED CLINICAL TRIAL

	Percentage of patients reporting event	
Body System/ Adverse Event *	SARAFEM 20 mg (N=104)	Placebo (N=108)
Body as a Whole		
Headache	13	9
Asthenia	12	3
Pain	9	7
Accidental injury	8	4
Infection	7	4
Digestive System		
Nausea	13	7
Nervous System		
Insomnia	9	7
Dizziness	7	4
Nervousness	7	4
Thinking abnormal†	6	--
Respiratory System		
Rhinitis	23	17
Pharyngitis	10	6

*Included are events reported by at least 5% of patients taking SARAFEM 20 mg, except the following events, which had an incidence on placebo > SARAFEM 20 mg: diarrhea and flu syndrome.

†Thinking abnormal is the COSTART term that captures concentration difficulties.

--Incidence less than 0.5%.

Incidence in US Depression, OCD, and Bulimia Placebo-Controlled Clinical Trials (excluding data from extensions of trials)--Table 2 enumerates the most common treatment-emergent adverse events associated with the use of fluoxetine up to 80 mg (incidence of at least 2% for fluoxetine and greater than placebo) in female patients ages 18-45 years from US placebo-controlled clinical trials in the treatment of depression, OCD, and bulimia.

TABLE 2
TREATMENT-EMERGENT ADVERSE EVENTS:
INCIDENCE IN FEMALE PATIENTS AGES 18-45 YEARS IN US DEPRESSION, OCD, AND BULIMIA PLACEBO-CONTROLLED CLINICAL TRIALS

	Percentage of patients reporting event	
Body System/Adverse Event*	Fluoxetine (N=1145)	Placebo (N=553)
Body as a Whole		
Headache	24	21
Asthenia	14	6
Flu syndrome	7	3
Abdominal pain	6	5
Accidental injury	4	3
Fever	3	2
Cardiovascular System		
Palpitation	3	2
Vasodilatation	3	1
Digestive System		
Nausea	27	11
Anorexia	11	4
Dry mouth	11	8
Diarrhea	10	7
Dyspepsia	7	5
Constipation	5	3
Vomiting	3	2
Metabolic and Nutritional Disorders		
Weight loss	3	1
Nervous System		
Insomnia	24	11
Nervousness	14	10
Anxiety	13	9
Somnolence	13	6
Tremor	12	1
Dizziness	11	5
Libido decreased	4	1
Abnormal dreams	3	2
Thinking abnormal†	3	2
Respiratory System		
Pharyngitis	6	5
Yawn	5	--

Skin and Appendages		
Sweating	8	3
Rash	5	3
Special Senses		
Abnormal vision	3	1
Urogenital System		
Urinary frequency	2	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): back pain, cough increased, depression (includes suicidal thoughts), dysmenorrhea, flatulence, infection, myalgia, pain, pruritus, rhinitis, sinusitis.

†Thinking abnormal is the COSTART term that captures concentration difficulties.

--Incidence less than 0.5%.

Associated with Discontinuation in a Placebo-Controlled PMDD Clinical Trial--The most common adverse event (incidence at least 2% for SARAFEM 20 mg and greater than placebo) associated with discontinuation in a PMDD placebo-controlled trial was nausea (3% for SARAFEM 20 mg, N=104 and 1% for placebo, N=108). In this clinical trial, more than one event may have been recorded as the cause of discontinuation.

Associated with Discontinuation in US Depression, OCD, and Bulimia Placebo-Controlled Clinical Trials (excluding data from extensions of trials)--In female patients age 18-45 years in US depression, OCD, and bulimia placebo-controlled clinical trials combined, which collected a single primary event associated with discontinuation (incidence at least 1% for fluoxetine and at least twice that for placebo), insomnia (1%, N=561) was the only event reported**.**

Female Sexual Dysfunction with SSRIs—Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a mood-related disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that selective serotonin reuptake inhibitors (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. For example, in women (age 18-45) receiving fluoxetine for indications other than PMDD, decreased libido for at least one indication, showed an incidence for fluoxetine of 4% and at least twice that of placebo. There have been spontaneous reports in women (age 18-45) taking fluoxetine for indications other than PMDD of orgasmic dysfunction, including anorgasmia.

There are no adequate, controlled studies examining sexual dysfunction with fluoxetine treatment.

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 US Clinical Trials--Following is a list of all treatment-emergent adverse events reported at anytime by females and males taking fluoxetine in all

US clinical trials for conditions other than PMDD as of May 8, 1995 (10,782 patients) except (1) those listed in the body or footnotes of Tables 1 or 2 above or elsewhere in labeling; (2) those for which the COSTART terms were uninformative or misleading; (3) those events for which a causal relationship to fluoxetine use was considered remote; (4) events occurring in only 1 patient treated with fluoxetine and which did not have a substantial probability of being acutely life-threatening; and (5) events that could only occur in males.

Events are classified within body system categories using the following definitions: frequent adverse events are defined as those occurring on 1 or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Body as a Whole--*Frequent:* chest pain and chills; *Infrequent:* chills and fever, face edema, intentional overdose, malaise, pelvic pain, suicide attempt; *Rare:* abdominal syndrome acute, hypothermia, intentional injury, neuroleptic malignant syndrome, photosensitivity reaction.

Cardiovascular System--*Frequent:* hemorrhage, hypertension; *Infrequent:* angina pectoris, arrhythmia, congestive heart failure, hypotension, migraine, myocardial infarct, postural hypotension, syncope, tachycardia, vascular headache; *Rare:* atrial fibrillation, bradycardia, cerebral embolism, cerebral ischemia, cerebrovascular accident, extrasystoles, heart arrest, heart block, pallor, peripheral vascular disorder, phlebitis, shock, thrombophlebitis, thrombosis, vasospasm, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation.

Digestive System--*Frequent:* increased appetite, nausea and vomiting; *Infrequent:* aphthous stomatitis, cholelithiasis, colitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, glossitis, gum hemorrhage, hyperchlorhydria, increased salivation, liver function tests abnormal, melena, mouth ulceration, nausea/vomiting/diarrhea, stomach ulcer, stomatitis, thirst; *Rare:* biliary pain, bloody diarrhea, cholecystitis, duodenal ulcer, enteritis, esophageal ulcer, fecal incontinence, gastrointestinal hemorrhage, hematemesis, hemorrhage of colon, hepatitis, intestinal obstruction, liver fatty deposit, pancreatitis, peptic ulcer, rectal hemorrhage, salivary gland enlargement, stomach ulcer hemorrhage, tongue edema.

Endocrine System--*Infrequent:* hypothyroidism; *Rare:* diabetic acidosis, diabetes mellitus.

Hemic and Lymphatic System--*Infrequent:* anemia, ecchymosis; *Rare:* blood dyscrasia, hypochromic anemia, leukopenia, lymphedema, lymphocytosis, petechia, purpura, thrombocythemia, thrombocytopenia.

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

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

Nervous System--*Frequent:* agitation, amnesia, confusion, emotional lability, paresthesia, and sleep disorder; *Infrequent:* abnormal gait, acute brain syndrome,

akathisia, apathy, ataxia, buccoglossal syndrome, CNS depression, CNS stimulation, depersonalization, euphoria, hallucinations, hostility, hyperkinesia, hypertonia, hypesthesia, incoordination, libido increased, myoclonus, neuralgia, neuropathy, neurosis, paranoid reaction, personality disorder†, psychosis, vertigo; *Rare:* abnormal electroencephalogram, antisocial reaction, circumoral paresthesia, coma, delusions, dysarthria, dystonia, extrapyramidal syndrome, foot drop, hyperesthesia, neuritis, paralysis, reflexes decreased, reflexes increased, stupor.

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

Skin and Appendages--*Infrequent:* acne, alopecia, contact dermatitis, eczema, maculopapular rash, skin discoloration, skin ulcer, vesiculobullous rash; *Rare:* furunculosis, herpes zoster, hirsutism, petechial rash, psoriasis, purpuric rash, pustular rash, seborrhea.

Special Senses--*Frequent:* ear pain, taste perversion, tinnitus; *Infrequent:* conjunctivitis, dry eyes, mydriasis, photophobia; *Rare:* blepharitis, deafness, diplopia, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, iritis, parosmia, scleritis, strabismus, taste loss, visual field defect.

Urogenital System--*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, uterine hemorrhage*, uterine fibroids enlarged*.

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

* Adjusted for gender

Postintroduction Reports--Voluntary reports of adverse events temporally associated with fluoxetine that have been received since market introduction of fluoxetine and that may have no causal relationship with the drug include the following: aplastic anemia, atrial fibrillation, cerebral vascular accident, cholestatic jaundice, confusion, dyskinesia (including, for example, a case of buccal-lingual-masticatory syndrome with involuntary tongue protrusion reported to develop in a 77-year-old female after 5 weeks of fluoxetine therapy and which completely resolved over the next few months following drug discontinuation), eosinophilic pneumonia, epidermal necrolysis, erythema nodosum, exfoliative dermatitis, gynecomastia, heart arrest, hepatic failure/necrosis, hyperprolactinemia, immune-related hemolytic anemia, kidney failure, misuse/abuse, movement disorders developing in patients with risk factors including drugs associated with such events and worsening of preexisting movement disorders, neuroleptic malignant syndrome-like events, pancreatitis, pancytopenia, priapism, pulmonary embolism, pulmonary hypertension, QT prolongation, Stevens-Johnson syndrome, sudden unexpected death, suicidal ideation, thrombocytopenia, thrombocytopenic purpura, vaginal bleeding after drug withdrawal, ventricular tachycardia (including torsades de pointes-type arrhythmias), and violent behaviors.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class--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 (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience--As of December 1987, there were 2 deaths among approximately 38 reports of acute overdose with fluoxetine, either alone or in combination with other drugs and/or alcohol. One death involved a combined overdose with approximately 1,800 mg of fluoxetine and an undetermined amount of maprotiline. Plasma concentrations of fluoxetine and maprotiline were 4.57 mg/L and 4.18 mg/L, respectively. A second death involved 3 drugs yielding plasma concentrations as follows: fluoxetine, 1.93 mg/L; norfluoxetine, 1.10 mg/L; codeine, 1.80 mg/L; temazepam, 3.80 mg/L.

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

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

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

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

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

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

In a separate single-dose study, the ECG of dogs given high doses did not reveal prolongation of the PR, QRS, or QT intervals. Tachycardia and an increase in blood pressure were observed. Consequently, the value of the ECG in predicting cardiac toxicity

is unknown. Nonetheless, the ECG should ordinarily be monitored in cases of human overdose (*see* Management of Overdose).

Management of Overdose—

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

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 tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and/or an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (*see* Precautions)

Based on experience in animals, which may not be relevant to humans, fluoxetine-induced seizures that fail to remit spontaneously may respond to diazepam.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference (PDR).*

DOSAGE AND ADMINISTRATION

Premenstrual Dysphoric Disorder--Initial Treatment—The recommended dose of SARAFEM for the treatment of PMDD is 20 mg/day. In a study comparing fluoxetine 20 and 60 mg/day to placebo, both doses were proven to be effective but there was no statistically significant added benefit for the 60 mg/day compared to the 20 mg/day dose. Fluoxetine doses above 60 mg/day have not been systematically studied in patients with PMDD. The maximum fluoxetine dose should not exceed 80 mg/day.

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

Maintenance/Continuation Treatment--Systematic evaluation of SARAFEM has shown that its efficacy in PMDD is maintained for periods of up to 6 months at a dose of 20 mg/day (*see* Clinical Trials *under* Clinical Pharmacology). Patients should be periodically reassessed to determine the need for continued treatment.

SARAFEM™ (Fluoxetine Hydrochloride)

HOW SUPPLIED

SARAFEM™ (Fluoxetine Hydrochloride) Pulvules® are available in 10 mg* and 20 mg* capsule strengths.

The 10 mg Pulvule has an opaque lavender body and cap, and is imprinted with "10 mg" on the body and "LILLY 3210" on the cap:

NDC 0002-3210-30 (PU3210) - Bottles of 30
NDC 0002-3210-02 (PU3210) - Bottles of 100
NDC 0002-3210-07 (PU3210) - Bottles of 2000
NDC 0002-3210-33 (PU3210) - Blisters of 100 (ID†100)
NDC 0002-3210-45 (PU3210) - Blisters of 28

The 20 mg Pulvule has an opaque pink body with opaque lavender cap, and is imprinted with "20 mg" on the body and "LILLY 3220" on the cap:

NDC 0002-3220-30 (PU3220) - Bottles of 30
NDC 0002-3220-02 (PU3220) - Bottles of 100
NDC 0002-3220-07 (PU3220) - Bottles of 2000
NDC 0002-3220-33 (PU3220) - Blisters of 100 (ID†100)
NDC 0002-3220-45 (PU3220) - Blisters of 28

---

* equivalent to fluoxetine base
† Identi-Dose (unit dose medication, Lilly)

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

Rx only

ANIMAL TOXICOLOGY

Phospholipids are increased in some tissues of mice, rats, and dogs given fluoxetine chronically. This effect is reversible after cessation of fluoxetine treatment. Phospholipid accumulation in animals has been observed with many cationic amphiphilic drugs, including fenfluramine, imipramine, and ranitidine. The significance of this effect in humans is unknown.

INFORMATION FOR THE PATIENT
SARAFEM™ (fluoxetine hydrochloride)

READ THIS INFORMATION COMPLETELY BEFORE USING SARAFEM (SAIR-a-fem). This leaflet provides a summary about SARAFEM and does not contain complete information about your medicine. This information is not meant to take the place of

discussions between you and your doctor. Talk with your doctor, pharmacist or other healthcare professional if there is something you do not understand or if you want to learn more about SARAFEM. Always follow your doctor's instructions on how to take SARAFEM.

What is SARAFEM?

SARAFEM is a prescription medicine used by women who have menstrual periods or cycles to treat the symptoms of premenstrual dysphoric disorder (PMDD).

What is PMDD?

PMDD is a medical condition that affects only women who have menstrual periods or cycles. Symptoms of PMDD are limited to the week or two before a woman's menstrual period and commonly include mood symptoms such as irritability, mood swings, and tension as well as physical symptoms of bloating and breast tenderness. When the symptoms of PMDD appear they cause interference in day to day activities and relationships.

What is the active ingredient in SARAFEM?

SARAFEM contains fluoxetine hydrochloride, the same active ingredient found in Prozac®.

How does SARAFEM work?

While it is unknown what causes PMDD, many doctors believe it may be related to an imbalance in a natural chemical in the body called serotonin. The actions of SARAFEM on serotonin may explain its effects in improving the symptoms of this condition.

Who should not take SARAFEM?

You should not take SARAFEM if you:

- are allergic to fluoxetine hydrochloride, the active ingredient in SARAFEM.

- are taking a type of antidepressant medicine known as a monoamine oxidase inhibitor (MAOI), such as Nardil (phenelzine) or Parnate (tranylcypromine). Using an MAOI together with many prescription medicines including SARAFEM can cause serious or even life-threatening reactions. You must wait at least 14 days after you have stopped taking an MAOI before you can take SARAFEM. Also, you

need to wait at least 5 weeks after you stop taking SARAFEM before you take an MAOI.

- are taking a type of antipsychotic medicine known as Mellaril (thioridazine). You need to wait at least 5 weeks after you stop taking SARAFEM before you take Mellaril.

How should I take SARAFEM?

- Take SARAFEM exactly as directed by your doctor.
- SARAFEM comes as a 10 mg lavender capsule and a 20 mg pink and lavender capsule. The usual dose is 20 mg a day, but your doctor will prescribe the dose that is right for you.
- If you miss a dose, take it as soon as you remember. However, if it is time for your next dose, skip the missed dose and take only your regularly scheduled dose. Do not take more than the daily amount of SARAFEM that has been prescribed for you.
- SARAFEM can be taken with or without food.
- To help you remember to take SARAFEM, it may be best to take it at about the same time each day, such as every morning.
- Remember to get your refills before you run out of SARAFEM.
- Talk with your doctor about how long you should keep taking SARAFEM.
- Talk with your doctor before you stop taking SARAFEM.

What should I talk to my doctor about when taking SARAFEM?

- If you get a rash or hives while taking SARAFEM, call your doctor right away because this can be a sign of a serious medical condition.
- Be sure to tell your doctor if you are taking Prozac, since this contains fluoxetine, the same active ingredient found in SARAFEM.
- Be sure to tell your doctor if you are taking or plan to take any prescription or nonprescription medicines, vitamins, natural supplements, herbal remedies or

alcohol. As with most other prescription medications, SARAFEM may interact with some of these products.

- You should tell your doctor if you are pregnant, plan to become pregnant or are breast feeding while taking SARAFEM.

- Tell your doctor if you have diabetes. The dose of diabetes medicine you need may change when you start or stop taking SARAFEM.

- Tell your doctor about any other medical conditions you may have, especially liver disease, or a history of seizures or mania.

What are possible side effects of SARAFEM?

All prescription medicines may cause side effects in some patients.

- In medical studies of women taking SARAFEM for PMDD, the most common side effects likely caused by SARAFEM were tiredness, upset stomach, nervousness, dizziness, and difficulty concentrating. Other side effects were reported less frequently in those same studies. Side effects were generally mild, often disappeared after a few weeks and most did not cause women to stop taking SARAFEM.

- SARAFEM can cause changes in sexual desire or satisfaction.

- Do not drive a car or operate dangerous machinery until you know what effect SARAFEM may have on you.

- Contact your doctor or healthcare professional if you get a rash or hives, or if you get other side effects that concern you while taking SARAFEM.

What else can I do?

In addition to taking SARAFEM:

- eat a well-balanced diet (including fruits, vegetables and fiber) and get regular exercise.

- drink plenty of water daily and lower the amount of caffeine and salt in your diet, especially before your menstrual period.

Talk to your doctor before you begin any diet or exercise program.

How do I store SARAFEM?

- Store SARAFEM at room temperature.
- Keep all medicines, including SARAFEM, out of the reach of children.

General Information

This is a summary of information about SARAFEM. Medicines are sometimes prescribed for purposes other than those listed in a patient information summary. This medicine was prescribed for your use only. Do not let anyone else use your SARAFEM.

If you have any questions or concerns, want to report any problems with the use of SARAFEM or want more information about SARAFEM, contact your doctor, pharmacist or other healthcare professional.

This patient information summary has been approved by the US Food and Drug Administration.

www.sarafem.com

Literature issued

Eli Lilly and Company
Indianapolis, IN 46285, USA

PRINTED IN USA

Doc LABLAP8a.DOC