PV 5971 UCP

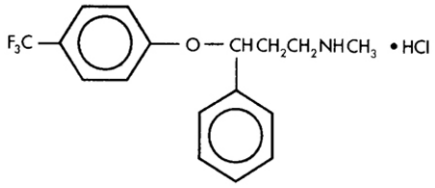
SARAFEM®
fluoxetine hydrochloride

WARNING

Suicidality and Antidepressant Drugs — Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of SARAFEM or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SARAFEM is not approved for use in pediatric patients with MDD and obsessive compulsive disorder (OCD). (*See* WARNINGS, PRECAUTIONS, Information for Patients, *and* PRECAUTIONS, Pediatric Use.)

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 capsules, USP). 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 1000 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 P450 2D6 (CYP2D6). Such individuals are referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and the tricyclic antidepressants (TCAs). In a study involving labeled and unlabeled enantiomers administered as a racemate, these individuals metabolized *S*-fluoxetine at a slower rate and thus achieved higher concentrations of *S*-fluoxetine. Consequently, concentrations of *S*-norfluoxetine at steady state were lower. The metabolism of *R*-fluoxetine in these poor metabolizers appears normal. When compared with normal metabolizers, the total sum at steady state of the plasma concentrations of the 4 active enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. Alternative, nonsaturable pathways (non-2D6) 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 TCAs and other SSRIs, involves the CYP2D6 system, concomitant therapy with drugs also metabolized by this enzyme system (such as the TCAs) may lead to drug interactions (*see* Drug Interactions *under* PRECAUTIONS).

Accumulation and slow elimination — The relatively slow elimination of fluoxetine (elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration) and its active metabolite, norfluoxetine (elimination half-life of 4 to 16 days after acute and chronic administration), leads to significant accumulation of these active species in chronic use and delayed attainment of steady state, even when a fixed dose is used. After 30 days

of dosing at 40 mg/day, plasma concentrations of fluoxetine in the range of 91 to 302 ng/mL and norfluoxetine in the range of 72 to 258 ng/mL have been observed. Plasma concentrations of fluoxetine were higher than those predicted by single-dose studies, because fluoxetine's metabolism is not proportional to dose. Norfluoxetine, however, appears to have linear pharmacokinetics. Its mean terminal half-life after a single dose was 8.6 days and after multiple dosing was 9.3 days. Steady-state levels after prolonged dosing are similar to levels seen at 4 to 5 weeks.

The long elimination half-lives of fluoxetine and norfluoxetine assure that, even when dosing is stopped, active drug substance will persist in the body for weeks (primarily depending on individual patient characteristics, previous dosing regimen, and length of previous therapy at discontinuation). This is of potential consequence when drug discontinuation is required or when drugs are prescribed that might interact with fluoxetine and norfluoxetine following the discontinuation of 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 with 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 with 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 2 months produced steady-state fluoxetine and norfluoxetine plasma concentrations comparable with 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 3 placebo-controlled trials (1 intermittent and 2 continuous dosing). In an intermittent dosing trial described below, patients met Diagnostic and Statistical Manual-4th edition (DSM-IV) criteria for PMDD. In the continuous dosing trials described below, patients met Diagnostic and Statistical Manual-3rd edition revised (DSM-IIIR) criteria for Late Luteal Phase Dysphoric Disorder (LLPDD), the clinical entity now referred to as PMDD in the 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 an intermittent dosing double-blind, parallel group study of 3 months duration, patients (N=260 randomized) were treated with fluoxetine 10 mg/day, fluoxetine 20 mg/day, or placebo. Fluoxetine or placebo was started 14 days prior to the anticipated onset of menstruation and was continued through the first full day of menses. Efficacy was assessed with the Daily Record of Severity of Problems (DRSP), a patient-rated instrument that mirrors the diagnostic criteria for PMDD as identified in the DSM-IV, and includes assessments for mood, physical symptoms, and other symptoms. Fluoxetine 20 mg/day was shown to be significantly more effective than

placebo as measured by the DRSP total score. Fluoxetine 10 mg/day was not shown to be significantly more effective than placebo on this outcome. The average DRSP total score decreased 38% on fluoxetine 20 mg/day, 35% on fluoxetine 10 mg/day, and 30% on placebo.

In the first continuous dosing double-blind, parallel group study of 6 months duration involving N=320 patients, fixed doses of fluoxetine 20 and 60 mg/day given daily 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- 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	Fluoxetine 20 mg	N	Fluoxetine 60 mg
Moderate	94	11%	95	37%	85	38%
Marked	94	4%	95	6%	85	18%

In a second continuous dosing double-blind, cross-over study, patients (N=19) were treated with fluoxetine 20 to 60 mg/day (mean dose = 27 mg/day) and placebo daily throughout the menstrual cycle for a period of 3 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 another continuous dosing double-blind, parallel group study, patients with LLPDD (N=42) were treated daily with fluoxetine 20 mg/day, bupropion 300 mg/day, or placebo for 2 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 3 placebo-controlled trials (*see* CLINICAL TRIALS).

The essential features of PMDD, according to the 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 reevaluate 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.

Pimozide — Concomitant use in patients taking pimozide is contraindicated (*see* PRECAUTIONS).

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

WARNINGS

Clinical Worsening and Suicide Risk — Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug versus placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (*see* PRECAUTIONS *and* DOSAGE AND ADMINISTRATION, Discontinuation of Treatment with SARAFEM, for a description of the risks of discontinuation of SARAFEM).

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for SARAFEM should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

It should be noted that SARAFEM is not approved for use in treating any indications in the pediatric population.

Screening Patients for Bipolar Disorder — A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that SARAFEM is not approved for use in treating bipolar depression.

Rash and Possibly Allergic Events — In 4 clinical trials for PMDD, 4% of 415 patients treated with SARAFEM reported rash and/or urticaria. None of these cases were classified as serious and 2 of 415 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 one was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Other patients have had systemic syndromes suggestive of serum sickness.

Since the introduction of fluoxetine for other indications, 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, SARAFEM should be discontinued.

Serotonin Syndrome — The development of a potentially life-threatening serotonin syndrome may occur with SNRIs and SSRIs, including SARAFEM treatment, particularly with

concomitant use of serotonergic drugs (including triptans) and with drugs which impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

The concomitant use of SARAFEM with MAOIs intended to treat depression is contraindicated *(see* CONTRAINDICATIONS *and* Drug Interactions *under* PRECAUTIONS).

If concomitant treatment of SARAFEM with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (*see* Drug Interactions *under* PRECAUTIONS).

The concomitant use of SARAFEM with serotonin precursors (such as tryptophan) is not recommended (*see* Drug Interactions *under* PRECAUTIONS).

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 with the rapid hydroxylators. The rate of debrisoquin hydroxylation is felt to depend on the level of CYP2D6 isozyme activity. Thus, this study suggests that drugs which inhibit CYP2D6, such as certain SSRIs, including fluoxetine, will produce elevated plasma levels of thioridazine (*see* PRECAUTIONS).

Thioridazine administration produces a dose-related prolongation of the QT_c 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

Abnormal Bleeding — Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding (*see* Drug Interactions). Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of SARAFEM with NSAIDs, aspirin, or other drugs that affect coagulation.

Anxiety and Insomnia — In 2 placebo-controlled trials of fluoxetine in PMDD, treatment-emergent adverse events were assessed. Rates were as follows for SARAFEM 20 mg (the recommended dose) continuous and intermittent pooled, SARAFEM 60 mg continuous, and pooled placebo, respectively: anxiety (3%, 9%, and 4%); nervousness (5%, 9%, and 3%); and insomnia (9%, 26%, and 7%). For individual rates for SARAFEM 20 mg given as continuous and intermittent dosing, see Table 2 and accompanying footnote under ADVERSE REACTIONS. Events associated with discontinuation for SARAFEM 20 mg continuous and intermittent pooled, SARAFEM 60 mg continuous, and pooled placebo, respectively, were: anxiety (0%, 6%, and 1%); nervousness (1%, 0%, and 0.5%); and insomnia (1%, 4%, and 0.5%). 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 3 *under* ADVERSE REACTIONS).

Altered Appetite and Weight — In 2 placebo-controlled trials of fluoxetine in PMDD, rates for anorexia were as follows for SARAFEM 20 mg (the recommended dose) continuous and intermittent pooled, SARAFEM 60 mg continuous, and pooled placebo, respectively: 4%, 13%, and 2%. For individual rates for SARAFEM 20 mg continuous and intermittent, see footnote accompanying Table 2 under ADVERSE REACTIONS. In 2 placebo-controlled trials (only one of which included a dose of 60 mg/day), 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 3 *and* Other events observed in US clinical trials *under* ADVERSE REACTIONS).

Activation of Mania/Hypomania — No patients treated with SARAFEM in 4 PMDD clinical trials (N=415) 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.

Hyponatremia

Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including fluoxetine. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported and appeared to be reversible when SARAFEM was discontinued. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk. Discontinuation of fluoxetine should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. More severe and/or acute cases have been associated with hallucination, syncope, seizure, coma, respiratory arrest, and death.

Seizures — No patients treated with SARAFEM in 4 PMDD clinical trials (N=415) 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.

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.

Discontinuation of Treatment with SARAFEM — During marketing of SARAFEM and other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment with SARAFEM. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate. Plasma fluoxetine and norfluoxetine concentration decrease gradually at the conclusion of therapy, which may minimize the risk of discontinuation symptoms with this drug (*see* DOSAGE AND ADMINISTRATION).

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

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with SARAFEM and should counsel them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions" is available for SARAFEM. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the

Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking SARAFEM.

Patients should be cautioned about the concomitant use of fluoxetine and NSAIDs, aspirin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents have been associated with an increased risk of bleeding.

Clinical Worsening and Suicide Risk — Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Serotonin Syndrome — Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of SARAFEM and triptans, tramadol or other serotonergic agents.

Laboratory Tests

There are no specific laboratory tests recommended.

Drug Interactions

As with all drugs, the potential for interaction by a variety of mechanisms (e.g., pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc.) is a possibility (*see* Accumulation and slow elimination *under* CLINICAL PHARMACOLOGY).

Drugs metabolized by CYP2D6 — Fluoxetine inhibits the activity of CYP2D6, and may make individuals with normal CYP2D6 metabolic activity resemble a poor metabolizer. Coadministration of fluoxetine with other drugs that are metabolized by CYP2D6, including certain antidepressants (e.g., TCAs), antipsychotics (e.g., phenothiazines and most atypicals), and antiarrhythmics (e.g., propafenone, flecainide, and others) should be approached with caution. Therapy with medications that are predominantly metabolized by the CYP2D6 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 CYP2D6, the need for decreased dose of the original medication should be considered. Drugs with a narrow therapeutic index represent the greatest concern (e.g., flecainide, propafenone, vinblastine, and TCAs). Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, thioridazine should not be administered with fluoxetine or within a minimum of 5 weeks after fluoxetine has been discontinued (*see* CONTRAINDICATIONS *and* WARNINGS).

Drugs metabolized by CYP3A4 — In an in vivo interaction study involving coadministration of fluoxetine with single doses of terfenadine (a CYP3A4 substrate), no increase in plasma terfenadine concentrations occurred with concomitant fluoxetine. In addition, in vitro studies have shown ketoconazole, a potent inhibitor of CYP3A4 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 CYP3A4 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. Clinical studies of pimozide with other antidepressants demonstrate an increase in drug interaction or QT_c prolongation. While a specific study with pimozide and fluoxetine has not been conducted, the potential for drug interactions or QT_c prolongation warrants restricting the concurrent use of pimozide and fluoxetine. Concomitant use of fluoxetine and pimozide is contraindicated (*see* CONTRAINDICATIONS). 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 2 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 3 weeks or longer after fluoxetine is discontinued. Thus, the dose of TCA may need to be reduced and plasma TCA concentrations may need to be monitored temporarily when fluoxetine is coadministered or has been recently discontinued (*see* Accumulation and slow elimination *under* CLINICAL PHARMACOLOGY, *and* Drugs metabolized by CYP2D6 *under* Drug Interactions).

Serotonergic drugs — Based on the mechanism of action of SNRIs and SSRIs, including SARAFEM, and the potential for serotonin syndrome, caution is advised when SARAFEM is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort (*see* Serotonin Syndrome *under* WARNINGS). The concomitant use of SARAFEM with other SSRIs, SNRIs or tryptophan is not recommended (*see* Tryptophan).

Triptans — There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of SARAFEM with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (*see* Serotonin Syndrome *under* WARNINGS).

Potential effects of coadministration of drugs tightly bound to plasma proteins — Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (e.g., warfarin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound fluoxetine by other tightly bound drugs (*see* Accumulation and slow elimination *under* CLINICAL PHARMACOLOGY).

Drugs that interfere with hemostasis (NSAIDs, aspirin, warfarin, etc.) — Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin potentiated the risk of bleeding. Thus, patients should be cautioned about the use of such drugs concurrently with fluoxetine.

Warfarin — Altered anticoagulant effects, including increased bleeding, have been reported when fluoxetine is coadministered with warfarin. Patients receiving warfarin therapy should receive careful coagulation monitoring when fluoxetine is initiated or stopped.

Electroconvulsive therapy (ECT) — 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 or mutagenicity from in vitro or animal studies. Impairment of fertility in adult animals at doses up to 12.5 mg/kg/day (approximately 1.5 times the MRHD on a mg/m^2 basis) was not observed.

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 adult 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 (*see* Pediatric Use).

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 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.

Nonteratogenic Effects — Neonates exposed to fluoxetine and other SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), 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 SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (*see* Monoamine oxidase inhibitors *under* CONTRAINDICATIONS).

Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1-2 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. There is currently no corroborative evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first study that has investigated the potential risk. The study did not include enough cases with exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk.

When treating a pregnant woman with fluoxetine during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment (*see* DOSAGE AND ADMINISTRATION). Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

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 one breast-milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng/mL. The concentration in the mother’s plasma was 295.0 ng/mL. No adverse effects on the infant were reported. In another case, an infant nursed by a mother on 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 the pediatric population have not been established (*see* BOX WARNING *and* WARNINGS, Clinical Worsening and Suicide Risk). Anyone considering the use of SARAFEM in a child or adolescent must balance the potential risks with the clinical need.

Significant toxicity, including myotoxicity, long-term neurobehavioral and reproductive toxicity, and impaired bone development, has been observed following exposure of juvenile animals to fluoxetine. Some of these effects occurred at clinically relevant exposures.

In a study in which fluoxetine (3, 10, or 30 mg/kg) was orally administered to young rats from weaning (Postnatal Day 21) through adulthood (Day 90), male and female sexual development was delayed at all doses, and growth (body weight gain, femur length) was decreased during the dosing period in animals receiving the highest dose. At the end of the treatment period, serum levels of creatine kinase (marker of muscle damage) were increased at the intermediate and high doses, and abnormal muscle and reproductive organ histopathology (skeletal muscle degeneration and necrosis, testicular degeneration and necrosis, epididymal vacuolation and hypospermia) was observed at the high dose. When animals were evaluated after a recovery period (up to 11 weeks after cessation of dosing), neurobehavioral abnormalities (decreased reactivity at all doses and learning deficit at the high dose) and reproductive functional impairment (decreased mating at all doses and impaired fertility at the high dose) were seen; in addition, testicular and epididymal microscopic lesions and decreased sperm concentrations were found in the high dose group, indicating that the reproductive organ effects seen at the end of treatment were irreversible. The reversibility of fluoxetine-induced muscle damage was not assessed. Adverse effects similar to those observed in rats treated with fluoxetine during the juvenile period have not been reported after administration of fluoxetine to adult animals. Plasma exposures (AUC) to fluoxetine in juvenile rats receiving the low, intermediate, and high dose in this study were approximately 0.1-0.2, 1-2, and 5-10 times, respectively, the average exposure in pediatric patients receiving the maximum recommended dose (MRD) of 20 mg/day. Rat exposures to the major metabolite, norfluoxetine, were approximately 0.3-0.8, 1-8, and 3-20 times, respectively, pediatric exposure at the MRD.

A specific effect of fluoxetine on bone development has been reported in mice treated with fluoxetine during the juvenile period. When mice were treated with fluoxetine (5 or 20 mg/kg, intraperitoneal) for 4 weeks starting at 4 weeks of age, bone formation was reduced resulting in decreased bone mineral content and density. These doses did not affect overall growth (body weight gain or femoral length). The doses administered to juvenile mice in this study are approximately 0.5 and 2 times the MRD for pediatric patients on a body surface area (mg/m^2) basis.

In another mouse study, administration of fluoxetine (10 mg/kg intraperitoneal) during early postnatal development (Postnatal Days 4 to 21) produced abnormal emotional behaviors (decreased exploratory behavior in elevated plus-maze, increased shock avoidance latency) in adulthood (12 weeks of age). The dose used in this study is approximately equal to the pediatric MRD on a mg/m^2 basis. Because of the early dosing period in this study, the significance of these findings to the approved pediatric use in humans is uncertain.

Geriatric Use

The diagnosis of PMDD is not applicable to postmenopausal women.

ADVERSE REACTIONS

In 1 of 3 placebo-controlled, continuous-dosing trials and 1 placebo-controlled, intermittent-dosing trial of fluoxetine in PMDD, treatment-emergent adverse events reporting

rates were assessed. The information from Table 2 included under ADVERSE REACTIONS is based on data from the continuous-dosing trial at the recommended dose of SARAFEM (SARAFEM 20 mg, N=104; placebo, N=108) and data from the intermittent-dosing trial of fluoxetine in PMDD (SARAFEM 20 mg, N=86; placebo, N=88). In addition, a broader set of information on treatment-emergent adverse events in the population of female patients, 18 to 45 years of age from the US placebo-controlled depression, OCD, and bulimia clinical trials, is presented for comparison (*see* Table 3).

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 placebo-controlled PMDD clinical trials — Table 2 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 2: Most Common Treatment-Emergent Adverse Events: Incidence in PMDD Placebo-Controlled Clinical Trials

	Percentage of Patients Reporting Event		
Body System/Adverse Event[1]	SARAFEM 20 mg/day Continuously (N=104)	SARAFEM 20 mg/day Intermittently (N=86)	Placebo (Pooled) (N=196)
Body as a Whole			
Headache	13	15	11
Asthenia	12	8	4
Pain	9	3	7
Accidental injury	8	1	5
Infection	7	0	3
Flu syndrome	12	3	7
Digestive System			
Nausea	13	9	6
Diarrhea	6	2	6
Nervous System			

Insomnia	9	10	7
Dizziness	7	2	3
Nervousness	7	3	3
Thinking abnormal[2]	6	5	0
Libido decreased	3	9	1
Respiratory System			
Rhinitis	23	16	15
Pharyngitis	10	6	5

[1] Included in the table are events reported by at least 5% of patients taking SARAFEM 20 mg either continuously or intermittently. For additional adverse event terms referenced in PRECAUTIONS, reporting rates for SARAFEM 20 mg continuous and intermittent were, respectively: anxiety 4.8%, 1.2% and anorexia 3.8%, 3.5%.
[2] Thinking abnormal is the COSTART term that captures concentration difficulties.

Incidence in US depression, OCD, and bulimia placebo-controlled clinical trials (excluding data from extensions of trials) — Table 3 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 to 45 years from US placebo-controlled clinical trials in the treatment of depression, OCD, and bulimia.

Table 3: Treatment-Emergent Adverse Events: Incidence in Female Patients Ages 18 to 45 Years in US Depression, OCD, and Bulimia Placebo-Controlled Clinical Trials

	Percentage of Patients Reporting Event	
Body System/Adverse Event[1]	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[2]	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

[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.
[2] Thinking abnormal is the COSTART term that captures concentration difficulties.
-- Incidence less than 0.5%.

Associated with discontinuation in two placebo-controlled PMDD clinical trials — In a continuous-dosing PMDD placebo-controlled trial, the most common adverse event (incidence at least 2% for SARAFEM 20 mg and greater than placebo) associated with discontinuation was nausea (3% for SARAFEM 20 mg, N=104 and 1% for placebo, N=108). In an intermittent-dosing placebo-controlled trial, no events associated with discontinuation reached an incidence of 2% for SARAFEM 20 mg. In these clinical trials, 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 to 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 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 to 45) receiving fluoxetine for indications other than PMDD, decreased libido was seen at an incidence of 4% for fluoxetine compared with 1% for placebo.

There have been spontaneous reports in women (age 18 to 45) taking fluoxetine for indications other than PMDD of orgasmic dysfunction, including anorgasmia.

There are no adequate and well-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 2 or 3 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 one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in less than 1/1000 patients.

Body as a Whole — *Frequent:* chest pain and chills; *Infrequent:* chills and fever, face edema, intentional overdose, malaise, pelvic pain, suicide attempt; *Rare:* acute abdominal syndrome, 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[1], 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[2], albuminuria, amenorrhea[2], anorgasmia, breast enlargement, breast pain, cystitis, dysuria, female lactation[2], fibrocystic breast[2], hematuria, leukorrhea[2], menorrhagia[2], metrorrhagia[2], nocturia, polyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage[2]; *Rare:* breast engorgement, glycosuria, hypomenorrhea[2], kidney pain, oliguria, uterine hemorrhage[2], uterine fibroids enlarged[2].

[1] Personality disorder is the COSTART term for designating non-aggressive objectionable behavior.
[2] 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, 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 multiforme, 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, 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 (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

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

Among 633 adult patients who overdosed on fluoxetine hydrochloride alone, 34 resulted in a fatal outcome, 378 completely recovered, and 15 patients experienced sequelae after overdosage, including abnormal accommodation, abnormal gait, confusion, unresponsiveness, nervousness, pulmonary dysfunction, vertigo, tremor, elevated blood pressure, impotence, movement disorder, and hypomania. The remaining 206 patients had an unknown outcome. The most common signs and symptoms associated with 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 6 overdoses in children that resulted in fatalities. The largest ingestion in pediatric patients was 3 grams which was non-lethal.

Other important adverse events reported with fluoxetine overdose (single or multiple drugs) include coma, delirium, ECG abnormalities (such as QT interval prolongation and ventricular tachycardia, including torsades de pointes-type arrhythmias), hypotension, mania, neuroleptic malignant syndrome-like events, pyrexia, stupor, and syncope.

Animal Experience

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

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

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

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

Management of Overdose

Treatment should consist of those general measures employed in the management of overdosage with any 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 TCA. In such a case, accumulation of the parent tricyclic and/or an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (*see* 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 given continuously (every day of the menstrual cycle) or intermittently (defined as starting a daily dose 14 days prior to the anticipated onset of menstruation through the first full day of menses and repeating with each new cycle). The dosing regimen should be determined by the physician based on individual patient characteristics. In a study comparing continuous dosing of 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 with 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 given continuously and up to 3 months at a dose of 20 mg/day given intermittently (*see* CLINICAL TRIALS). Patients should be periodically reassessed to determine the need for continued treatment.

Special Populations

Treatment of Pregnant Women During the Third Trimester

Neonates exposed to fluoxetine and other SSRIs or SNRIs, 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.

Discontinuation of Treatment with SARAFEM

Symptoms associated with discontinuation of SARAFEM and other SSRIs and SNRIs, have been reported (*see* PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate. Plasma fluoxetine and norfluoxetine concentration decrease gradually at the conclusion of therapy which may minimize the risk of discontinuation symptoms with this drug.

HOW SUPPLIED

SARAFEM® (fluoxetine hydrochloride) Pulvules®[1] are available in 10-mg[2] and 20-mg[2] capsule strengths.

The 10-mg Pulvule has an opaque lavender body and cap and is imprinted with 10 mg on the body and Sarafem on the cap:

N 0430-0435-14 - 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 Sarafem on the cap:

N 0430-0436-14 - Blisters of 28

[1] Pulvule and the paraboloidal shape of the capsule are registered trademarks of Eli Lilly and Company.
[2] Equivalent to fluoxetine base.

Store at Controlled Room Temperature, 15° to 30°C (59° to 86°F).
Protect from light.
Prozac® is a registered trademark of Eli Lilly and Company.

ANIMAL TOXICOLOGY

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

Literature revised December 17, 2007

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Rockaway, NJ 07866, USA

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Medication Guide

Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with your or your family member's antidepressant medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. **Talk to your, or your family member's, healthcare provider about:**

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**
2. **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.
3. **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**
   - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
   - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
   - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying

- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

This Medication Guide has been approved by the US Food and Drug Administration for all antidepressants.

Patient Information revised June 21, 2007

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