PRODUCT MONOGRAPH

[Pr]PROZAC® (fluoxetine hydrochloride) Capsules
10 mg and 20 mg

[Pr]PROZAC® (fluoxetine hydrochloride) Oral Solution
20 mg/5 mL

Antidepressant / Antiobsessional / Antibulimic

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Product	Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients*
Prozac Capsules	oral	capsules / 10 mg and 20 mg	There is no gluten, lactose, sulfite, or tartrazine in PROZAC
Prozac Oral Solution	oral	oral solution / 20 mg/5 mL	Sucrose

**For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Adults

Depression

PROZAC (fluoxetine) is indicated for the symptomatic relief of Major Depressive Disorder (MDD).

Bulimia Nervosa

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

Obsessive-Compulsive Disorder

PROZAC is indicated for the symptomatic treatment of obsessive-compulsive disorder (OCD).

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

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

Long-term use of PROZAC: The effectiveness of PROZAC in long-term use in bulimia nervosa (i.e. for more than 16 weeks) and in obsessive-compulsive disorder (i.e. for more than 13

weeks) has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use PROZAC in these indications for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Geriatrics (≥60 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population may be associated with differences in safety or effectiveness, and a brief discussion can be found in the appropriate sections (WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics; DOSAGE AND ADMINISTRATION)

Pediatrics (<18 years of age): PROZAC is not indicated for use in patients below the age of 18 years. See WARNINGS AND PRECAUTIONS, General, Potential Association with Behavioural and Emotional Changes, including Self-Harm; see also DOSAGE AND ADMINISTRATION section.

CONTRAINDICATIONS

Hypersensitivity - PROZAC (fluoxetine) is contraindicated in patients with known hypersensitivity to the drug or the excipients of the product. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING section.

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 PROZAC, or other serotonin reuptake inhibitors (SSRIs), in combination with a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued PROZAC and then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome (e.g., serotonin syndrome). Therefore, **PROZAC should not be used in combination with an MAOI, including either within a minimum of 14 days of discontinuing therapy with an MAOI, or a minimum of 5 weeks of discontinuing therapy with PROZAC.** Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks should be allowed after stopping PROZAC before starting an MAOI. Limited reports suggest that intravenously administered dantrolene (Dantrium®) or orally administered cyproheptadine (Periactin®) may benefit patients experiencing such reactions. See DRUG INTERACTIONS section.

Thioridazine - Thioridazine should not be administered concomitantly with PROZAC or within a minimum of 5 weeks after PROZAC has been discontinued, nor should PROZAC be administered within 2 weeks after thioridazine has been discontinued.

Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsades de pointes-type arrhythmias, and sudden death. This effect appears to be dose-related.

An *in vivo* study suggests that drugs which inhibit P4502D_6, including certain SSRI's such as paroxetine, fluoxetine and fluvoxamine, will elevate plasma levels of thioridazine. Therefore, PROZAC should not be used in combination with thioridazine. See DRUG INTERACTIONS section.

WARNINGS AND PRECAUTIONS

General

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

Pediatrics - Placebo-Controlled Clinical Trial Data

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

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

Adults and Pediatrics - Additional data

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

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

Discontinuation Symptoms

Patients currently taking SSRIs or newer anti-depressants should NOT be discontinued abruptly, due to risk of discontinuation symptoms. PROZAC has only rarely been associated with such symptoms. At the time that a medical decision is made to discontinue an SSRI or other newer anti-depressant drug, a gradual reduction in the dose rather than an abrupt cessation, except for fluoxetine, is recommended. Plasma fluoxetine and norfluoxetine concentrations decrease gradually at the conclusion of therapy which makes dose tapering unnecessary in most patients taking this drug (see WARNINGS AND PRECAUTIONS, Dependence; and ADVERSE REACTIONS, Adverse Events Subsequent to Discontinuation section; and DOSAGE AND ADMINISTRATION, Discontinuation of Treatment section).

Implications of the Long Elimination Half-Life of Fluoxetine:

Because of the long elimination half-lives of fluoxetine and its major active metabolite norfluoxetine, changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment (see ACTION AND CLINICAL PHARMACOLOGY; and DOSAGE AND ADMINISTRATION sections). Even when dosing is stopped, active drug substance will persist in the body for weeks due to the long elimination half-lives of fluoxetine and norfluoxetine. This is of potential consequence when

drug discontinuation is required or when drugs are prescribed that might interact with fluoxetine and norfluoxetine following discontinuation of PROZAC.

Safety of Prozac in Pregnant Women: Effects on Newborns:
Post-marketing reports indicate that some neonates exposed to PROZAC, other SSRIs (selective serotonin reuptake inhibitors), or newer anti-depressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. When treating a pregnant woman with PROZAC during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women; and DOSAGE AND ADMINISTRATION sections).

Weight Change:
Significant weight loss, especially in underweight depressed patients and the elderly, may be an undesirable result of treatment with PROZAC. PROZAC should be given with caution to patients suffering from anorexia nervosa and only if the expected benefits (e.g. co-morbid depression) markedly outweigh the potential weight reducing effect of the drug.

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

Allergic Reactions (Rash and Accompanying Events):
During premarketing testing, 7% of 10,782 patients developed various types of rashes and/or urticaria. Among these cases, 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 these allergic reactions include rash, fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

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

Since the introduction of fluoxetine, systemic events, possibly related to vasculitis, and including lupus-like syndrome, have developed in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic events.

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

Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis,

have been reported rarely. These events have occurred with dyspnea as the only preceding symptom.

Whether these systemic events and rash have a common underlying cause or are due to different etiologies or pathogenic processes is not known. Furthermore, a specific underlying immunologic basis for these events has not been identified. Upon the appearance of rash or of other possibly allergic phenomena for which an alternative etiology cannot be identified, PROZAC should be discontinued. Particular caution should be exercised in patients with a history of allergic reactions.

The following additional PRECAUTIONS are listed alphabetically.

Carcinogenesis and Mutagenesis
For animal data, see Part II: TOXICOLOGY section.

Cardiovascular
PROZAC has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from premarketing clinical studies. Retrospective evaluation of EKGs in some of these studies showed no conduction abnormalities that resulted in heart block. The mean heart rate was reduced by approximately 3 beats/minute.

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

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

Dependence
Discontinuation of Treatment with PROZAC (Post-Marketing and Clinical Trials):
When discontinuing treatment, patients should be monitored for symptoms which may be associated with discontinuation (e.g. headache, insomnia, paresthesias, nervousness, anxiety, nausea, sweating, numbness, dizziness, jitteriness, asthenia or other symptoms which may be of clinical significance).

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

Dependence Liability:
PROZAC has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. Physicians should carefully evaluate patients for history of

drug abuse and follow such patients closely, observing them for signs of misuse or abuse of PROZAC.

Endocrine and Metabolism

Diabetes:

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.

Hematologic

Abnormal Bleeding:

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.

Hepatic/Biliary/Pancreatic

Hepatic Impairment:

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

Neurologic

Seizures:

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

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

Serotonin Syndrome /Neuroleptic Malignant Syndrome:

On rare occasions serotonin syndrome or neuroleptic malignant syndrome-like events have occurred in association with treatment with SSRIs, including PROZAC, particularly when given in combination with other serotonergic and/or neuroleptic drugs. As these syndromes may result in potentially life-threatening conditions, treatment with PROZAC should be discontinued if such events (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated. PROZAC should not be used in combination with MAO inhibitors or serotonin-precursors (such as L-tryptophan, oxitriptan) and should be used with caution in combination with other serotonergic drugs (triptans, certain tricyclic antidepressants, lithium, tramadol, St. John's Wort) due to the risk of serotonergic syndrome (see CONTRAINDICATIONS and DRUG INTERACTIONS).

Psychiatric

Suicide:

The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. As with other drugs with similar pharmacological action (antidepressants), isolated cases of suicidal ideation and suicidal behaviors have been reported during fluoxetine therapy or early after treatment discontinuation. Close supervision of high-risk patients should accompany drug therapy and consideration should be given to the possible need for hospitalization. Physicians should encourage patients of all ages to report any new or worsened distressing thoughts or feelings occurring at any time. In order to minimize the opportunity for overdosage, prescriptions for fluoxetine should be written for the smallest quantity of drug consistent with good patient management.

Because of the well established comorbidity between depression and other psychiatric disorders, the same precautions observed when treating patients with depression should be observed when treating patients with other psychiatric disorders (see WARNINGS AND PRECAUTIONS: General: Potential Association with Behavioral and Emotional Changes, Including Self-Harm section).

Activation of Mania/Hypomania:

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

A major depressive episode may be the initial presentation of bipolar disorder. Patients with bipolar disorder may be at an increased risk of experiencing manic episodes when treated with antidepressants alone. Therefore, the decision to initiate symptomatic treatment of depression should only be made after patients have been adequately assessed to determine if they are at risk for bipolar disorder.

Electroconvulsive Therapy (ECT):

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

Renal

Severe Renal Impairment:

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

Hyponatremia:

Several cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been

reported. The hyponatremia appeared to be reversible when PROZAC was discontinued. Although these cases were complex with varying possible etiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted.

In two 6-week controlled studies in patients ≥60 years of age, 10 of 323 fluoxetine patients and 6 of 327 placebo recipients had a lowering of serum sodium below the reference range; this difference was not statistically significant. The lowest observed concentration of sodium in a fluoxetine treated patient was 129 mmol/L. The observed decreases were not clinically significant.

Special Populations

Pregnant Women:

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

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

Nursing Women:

Lactation:

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

In one breast milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng/mL. The concentration in the mother's plasma was 295.0 ng/mL. No adverse effects on the infant were reported. In another case, a 6-week infant, nursed by a mother on PROZAC, developed crying, decreased sleep, vomiting and watery stools. The breast milk showed concentrations of 69 ng/mL for fluoxetine and 90 ng/mL for norfluoxetine. In the infant's plasma, the concentrations of fluoxetine and norfluoxetine on the second day of feeding were 340 and 208 ng/mL, respectively.

Pediatrics (<18 years of age):
PROZAC is not indicated for use in patients below the age of 18 years. See WARNINGS AND PRECAUTION, General, Potential Asociation with Behavioural and Emotional Changes, including Self-Harm. See also DOSAGE AND ADMINISTRATION, Pediatrics; and INDICATIONS AND CLINICAL USE, Pediatrics sections.

Geriatrics (≥60 years of age):
Evaluation of patients over the age of 60 who received PROZAC 20 mg daily revealed no unusual pattern of adverse events relative to the clinical experience in younger patients. These data are however insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients who have concomitant systemic illnesses or who are receiving concomitant drugs. See INDICATIONS AND CLINICAL USE, and DOSAGE AND ADMINISTRATION sections.

ADVERSE REACTIONS

Overview

Commonly Observed

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

Adverse Events Leading to Discontinuation of Treatment

Fifteen percent of approximately 4,000 patients who received PROZAC in North American clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation from depression trials in adults and elderly, included: psychiatric, primarily nervousness, anxiety, and insomnia; digestive, primarily nausea; nervous system, primarily dizziness, asthenia, and headaches; skin, primarily rash and pruritus.

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

Adverse Events Subsequent to Discontinuation

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

Serious Adverse Reactions

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

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

Post-marketing experience also confirms the profile of adverse reactions commonly reported during clinical trials with PROZAC including allergic skin reactions.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Multiple doses of Prozac had been administered to 10,782 patients with various diagnoses in US clinical trials as of May 8, 1995. Adverse events were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a limited (i.e., reduced) number of standardized event categories.

Adults

In the tables and tabulations that follow, COSTART Dictionary terminology has been used to classify reported adverse events. The stated frequencies represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. It is important to emphasize that events reported during therapy were not necessarily caused by it.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and

nondrug factors to the side effect incidence rate in the population studied.

Table 1: Treatment-Emergent Adverse Events Incidence in Fluoxetine versus Placebo Trials Listed by Indication

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

Percentage of Patients Reporting Event								
	DEPRESSION * (Adults)		**DEPRESSION (Elderly)**		**OCD***		**BULIMIA***	
Body System/ Adverse Event	Fluoxetine (N=1728)	Placebo (N=975)	Fluoxetine (N=335)	Placebo (N=336)	Fluoxetine (N=266)	Placebo (N=89)	Fluoxetine (N=450)	Placebo (N=267)
Vasodilatation	3	2	--	--	5	0	2	1
Urogenital System								
Abnormal Ejaculation†	--	--	--	--	7	--	7	--
Impotence†	2	--	--	--	--	--	7	--

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

-- Incidence less than 1%

* The most common treatment-emergent adverse events associated with the use of PROZAC (incidence of at least 5% for PROZAC and at least twice that for placebo within at least one of the indications) for the treatment of depression, OCD, and bulimia in US controlled clinical trials.

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

Table 2: Combined Treatment-Emergent Adverse Events Incidence for Patients Treated with PROZAC versus Placebo

Percentage of patients reporting event		
	Depression, OCD, and bulimia combined	
Body System/Adverse Event *	**PROZAC (N=2444)**	**Placebo (N=1331)**
Body as a Whole		
Headache	21	20
Asthenia	12	6
Flu syndrome	5	4
Fever	2	1
Cardiovascular System		
Vasodilatation	3	1
Palpitation	2	1
Digestive System		
Nausea	23	10
Diarrhea	12	8
Anorexia	11	3
Dry mouth	10	7
Dyspepsia	8	5
Flatulence	3	2
Vomiting	3	2

Percentage of patients reporting event		
	Depression, OCD, and bulimia combined	
Body System/Adverse Event *	**PROZAC (N=2444)**	**Placebo (N=1331)**
Metabolic and Nutritional Disorders		
Weight loss	2	1
Nervous System		
Insomnia	20	11
Anxiety	13	8
Nervousness	13	9
Somnolence	13	6
Dizziness	10	7
Tremor	10	3
Libido decreased	4	--
Respiratory System		
Pharyngitis	5	4
Yawn	3	--
Skin and Appendages		
Sweating	8	3
Rash	4	3
Pruritus	3	2
Special Senses		
Abnormal vision	3	1

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

-- Incidence less than 1%.

Table 3 lists the adverse events associated with discontinuation of PROZAC treatment (incidence at least twice that for placebo and at least 1% for PROZAC in clinical trials collecting only a primary event associated with discontinuation) in depression, OCD, and bulimia. For symptoms associated with discontinuation of PROZAC in clinical trials and post-marketing, see ADVERSE REACTION: Post-Market Adverse Drug Reactions section.

Table 3: Adverse Events Associated with Discontinuation of PROZAC Treatment

Depression, OCD, and Bulimia Combined (N=1108)	**Depression (N=392)**	**OCD (N=266)**	**Bulimia (N=450)**
--	--	Anxiety (2%)	--
Insomnia (1%)	--	--	Insomnia (2%)

--	Nervousness (1%)	--	--
--	--	Rash (1%)	--

Male and Female Sexual Dysfunction with SSRIs

Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance, cited in product labeling, are likely to underestimate their actual incidence. In patients enrolled in depression, OCD, and bulimia placebo-controlled clinical trials, decreased libido was the only sexual side effect reported by at least 2% of patients taking fluoxetine (4% fluoxetine, < 1% placebo). There have been spontaneous reports in women taking fluoxetine of orgasmic dysfunction, including anorgasmia.

There are no adequate and well-controlled studies examining sexual dysfunction with fluoxetine treatment. Priapism has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Treatment-Emergent Adverse Events

Following is a list of all treatment-emergent adverse events reported at anytime by individuals taking fluoxetine in US clinical trials (10,782 patients) except: (1) those listed in the body or footnotes of Tables 1 or 2 above or elsewhere in labelling; (2) those for which the COSTART terms were uninformative or misleading; (3) those events for which a causal relationship to PROZAC use was considered remote; and (4) events occurring in only 1 patient treated with PROZAC and which did not have a substantial probability of being acutely life-threatening.

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

Body as a Whole

Frequent: chills

Infrequent: chills and fever, face edema, intentional overdose, malaise, pelvic pain, suicide attempt

Rare: abdominal syndrome acute, hypothermia, intentional injury, neuroleptic malignant syndrome‡, photosensitivity reaction.

*characterized by the clustering of clinical features of changes in mental state and neuromuscular activity, in combination with autonomic nervous system dysfunction.

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

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

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

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

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

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

Nervous System
Frequent: agitation, amnesia, confusion, emotional lability, sleep disorder
Infrequent: abnormal gait, acute brain syndrome, akathisia, apathy, ataxia, buccoglossal syndrome, CNS depression, CNS stimulation, depersonalization, euphoria, hallucinations,

hostility, hyperkinesia, hypertonia, hypesthesia, incoordination, libido increased, myoclonus, neuralgia, neuropathy, neurosis, paranoid reaction, personality disorder†, psychosis, vertigo.
Rare: abnormal electroencephalogram, antisocial reaction, circumoral paresthesia, coma, delusions, dysarthria, dystonia, extrapyramidal syndrome, foot drop, hyperesthesia, neuritis, paralysis, reflexes decreased, reflexes increased, stupor.

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

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

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

Urogenital System
Frequent: urinary frequency
Infrequent: abortion*, albuminuria, amenorrhea*, anorgasmia, breast enlargement, breast pain, cystitis, dysuria, female lactation*, fibrocystic breast*, hematuria, leukorrhea*, menorrhagia*, metrorrhagia*, nocturia, polyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage*
Rare: breast engorgement, glycosuria, hypomenorrhea*, kidney pain, oliguria, priapism*, uterine hemorrhage*, uterine fibroids enlarged*.

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

Post-Market Adverse Drug Reactions

Voluntary reports of adverse events temporally associated with PROZAC that have been received since market introduction and that may have no causal relationship with the drug include the following: aplastic anemia, atrial fibrillation, cataract, cerebral vascular accident, cholestatic jaundice, confusion, dyskinesia (including, for example, a case of buccal-lingual-masticatory syndrome with involuntary tongue protrusion reported to develop in a 77-year-old female after 5 weeks of fluoxetine therapy and which completely resolved over the next few months following drug discontinuation), eosinophilic pneumonia, epidermal necrolysis, erythema 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, serotonin syndrome (a range of signs and symptoms that can rarely, in most severe cases, resemble neuroleptic malignant syndrome), Stevens-Johnson syndrome, sudden unexpected death, suicidal ideation, thrombocytopenia, thrombocytopenic purpura, vaginal bleeding after drug withdrawal, ventricular tachycardia (including torsades de pointes-type arrhythmias) and violent behaviours.

DRUG INTERACTIONS

Serious Drug Interactions
Monoamine Oxidase Inhibitors: See CONTRAINDICATIONS
Thioridazine: See CONTRAINDICATIONS

Overview
PROZAC, like other agents that are metabolized by the P4502D6 system, inhibits the activity of this isoenzyme. Therefore, co-therapy with medications that are predominantly metabolized by the P4502D6 system and that have a relatively narrow therapeutic index (e.g. flecainide, encainide, vinblastine, carbamazepine and tricyclic antidepressants) should be initiated at the low end of the dose range if a patient is receiving fluoxetine concurrently, or has taken it in the previous 5 weeks. If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by P4502D6, the need for decreased dose of the original medication should be considered. The aforementioned drugs with a narrow therapeutic index represent the greatest concern.

Other drugs that have demonstrated increased plasma values or magnified effects when co-administered with fluoxetine include: phenytoin, antipsychotics, benzodiazapines, thioridazine (see CONTRAINDICATIONS), St. John's Wort and warfarin.

As fluoxetine is highly bound to plasma proteins, co-administration with another drug which is also highly bound (e.g. warfarin, digitoxin) may result in adverse effects due to an increase in plasma levels of either unbound drug.

There are little data available on the concomitant use of fluoxetine and alcohol.

Drug-Drug Interactions
Monoamine Oxidase Inhibitors: Combined use of PROZAC and MAO inhibitors is contraindicated due to the potential for serious reactions with features resembling serotonin syndrome or neuroleptic malignant syndrome (See CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS, Serotonin Syndrome/Neuroleptic Malignant Syndrome).

Thioridazine: Potential Interactions with Thioridazine (see also CONTRAINDICATIONS):
In a study of 19 healthy male subjects, which included 6 slow and 13 rapid hydroxylators of

debrisoquin, a single 25 mg oral dose of thioridazine produced a 2.4-fold higher C_{max} and a 4.5-fold higher AUC for thioridazine in the slow hydroxylators compared to the rapid hydroxylators. The rate of debrisoquin hydroxylation is felt to depend on the level of cytochrome P4502D6 isozyme activity. Thus, this study suggests that drugs which inhibit P4502D6, such as certain SSRIs, including fluoxetine, will produce elevated plasma levels of thioridazine.

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. Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, thioridazine should not be concomitantly administered, nor within a minimum of 5 weeks after fluoxetine has been discontinued, nor should PROZAC be administered within 2 weeks after thioridazine has been discontinued (see CONTRAINDICATIONS).

Drugs Tightly Bound to Plasma Protein: Because fluoxetine is highly bound to plasma protein, the administration of fluoxetine to a patient taking another drug which is tightly bound to protein (e.g. warfarin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein bound fluoxetine by other tightly bound drugs.

Drugs Metabolized by P4502D6 Isoenzyme: Approximately 3 to 10% of the normal population has a genetic defect that leads to reduced levels of activity of the cytochrome P450 isoenzyme P4502D6. Such individuals have been referred to as "poor metabolizers" of drugs such as debrisoquine, dextrometorphan, sparteine, tricyclic antidepressants (e.g. nortryptiline, amitriptyline, imipramine, and desipramine), phenothiazine neuroleptics (e.g. perphenazine and thioridazine) and Type 1C antiarrhythmics (e.g. propafenone and flecainide).

Conversely, approximately 90 to 97% of the normal population do not have this genetic defect, and are known as "extensive metabolizers". PROZAC, like other agents that are metabolized by the P4502D6 system, inhibits the activity of this isoenzyme, and thus may make normal "extensive" metabolizers resemble "poor metabolizers". Therapy with medications that are predominantly metabolized by the P4502D6 system and that have a relatively narrow therapeutic index (e.g. flecainide, encainida, vinblastine, carbamazepine and tricyclic antidepressants) should be initiated at the low end of the dose range if a patient is receiving fluoxetine concurrently, or has taken it in the previous 5 weeks.

If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by P4502D6 the need for decreased dose of the original medication should be considered. The aforementioned drugs with a narrow therapeutic index represent the greatest concern.

Drugs Metabolized by Cytochrome P4503A4: In an *in vivo* interaction study involving co-administration of fluoxetine with single doses of terfenadine (a cytochrome P4503A4 substrate), no increase in plasma terfenadine concentrations occurred with concomitant fluoxetine. In addition, *in vitro* studies have shown ketoconazole, a potent inhibitor of P4503A4 activity, to be at least 100 times more potent than fluoxetine or norfluoxetine as an inhibitor of the metabolism of several substrates for this enzyme, including astemizole, cisapride, and midazolam. These data

indicate that fluoxetine's extent of inhibition of cytochrome P4503A4 activity is not likely to be of clinical significance.

Tricyclic Antidepressants: In two studies, previously stable plasma levels of imipramine and desipramine have increased greater than 2 to 10-fold when fluoxetine has been administered in combination. This influence may persist for three weeks or longer after fluoxetine is discontinued. Thus, the dose of tricyclic antidepressant (TCA) may need to be reduced and plasma TCA concentrations may need to be monitored temporarily when fluoxetine is coadministered or has been recently discontinued. See WARNINGS AND PRECAUTIONS; and ACTION AND CLINICAL PHARMACOLOGY, Accumulation and Slow Elimination sections.

Lithium: There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with fluoxetine. Cases of lithium toxicity have been reported. Lithium levels should be monitored when these drugs are administered concomitantly.

Tryptophan: Five patients receiving PROZAC in combination with tryptophan experienced adverse reactions, including agitation, restlessness and gastrointestinal distress.

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

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

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

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

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

Serotonergic Drugs: Based on the mechanism of action of fluoxetine and the potential for serotonin syndrome, caution is advised when PROZAC® is coadministered with other drugs or agents that may affect the serotonergic neurotransmitter systems, such as tryptophan, triptans, serotonin reuptake inhibitors, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort (see WARNINGS AND PRECAUTIONS, Serotonin Syndrome/Neuroleptic Malignant Syndrome).

*Triptans ($5HT_1$ agonists)***:** There have been rare postmarketing reports describing patients with

weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and the $5HT_1$ agonist, sumatriptan. If concomitant treatment with triptan and an SSRI (e.g. fluoxetine, fluvoxamine, paroxetine, sertraline, or citalopram) is clinically warranted, appropriate observation of the patient is advised. The possibility of such interactions should also be considered if other $5HT_1$ agonists are to be used in combination with SSRIs (see WARNINGS AND PRECAUTIONS, Serotonin Syndrome/Neuroleptic Malignant Syndrome).

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

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

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

Drug-Food Interactions
Absorption of fluoxetine is not affected by food.

Drug-Herb Interactions
Interactions with PROZAC and herbal remedy St. John's Wort may occur (see Drug-Drug Interactions section).

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions
Interaction with lifestyle interactions have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

PROZAC (fluoxetine) is not indicated for use in children under 18 year of age (see WARNINGS AND PRECAUTIONS: General: Potential Association with Behavioural and Emotional Changes, Including Self-Harm).

General

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

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

Dose Adjustment

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

Switching Patients to a Tricyclic Antidepressant (TCA)

Dosage of a TCA may need to be reduced and plasma TCA concentrations may need to be monitored temporarily when fluoxetine is coadministered or has been recently discontinued (see DRUG INTERACTIONS: Tricyclic Antidepresants section).

Switching Patients to or from A Monoamine Oxidase Inhibitor (MAOI)

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with PROZAC. In addition, at least 5 weeks, perhaps longer, should be allowed after stopping PROZAC before starting MAOI (see CONTRAINDICATIONS section).

Discontinuation of Treatment

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

Despite its long-half life, symptoms associated with the discontinuation of PROZAC have been reported in clinical trials and post–marketing. Patients should be monitored for these and other symptoms when discontinuing treatment, regardless of the indication for which PROZAC is being prescribed. PROZAC (fluoxetine) has been only rarely associated with such symptoms. Plasma fluoxetine and norfluoxetine concentrations decrease gradually at the conclusion of therapy, which makes dose tapering unnecessary in most patients (See WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).

Adults:

Depression

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

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

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

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

Special Patient Populations
For any indication:
Treatment of Pregnant Women During the Third Trimester:
Post-marketing reports indicate that some neonates exposed to PROZAC, SSRIs or other newer anti-depressants, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see WARNINGS AND PRECAUTIONS). When treating pregnant women with PROZAC during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering PROZAC in the third trimester.

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

Use in Children: PROZAC (fluoxetine) is not indicated for use in children under 18 year of age (see WARNINGS AND PRECAUTIONS: General: Potential Association with Behavioural and Emotional Changes, Including Self-Harm).

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

OVERDOSAGE

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

Management of Overdosage:

There are no specific antidotes for PROZAC.

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

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

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

Induction of emesis is not recommended.

Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

Activated charcoal should be considered in treating overdose.

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

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

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

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

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

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

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

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

Animal Experience:
Studies in animals do not provide precise or necessarily valid information about the treatment of human overdose.

However, animal experiments can provide useful insights into possible treatment strategies.

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

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

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

ACTION AND CLINICAL PHARMACOLOGY

Pharmacodynamics

The antidepressant, antiobsessional, and antibulimic actions of PROZAC (fluoxetine) are presumed to be linked to its ability to selectively inhibit the neuronal reuptake of serotonin. At clinically relevant doses fluoxetine blocks the uptake of serotonin into human platelets. Antagonism of muscarinic, histaminergic and α_1- adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative and cardiovascular effects of classical tricyclic antidepressant drugs. *In vitro* receptor binding studies have demonstrated that fluoxetine binds to these and other membrane receptors [opiate, serotonergic (5-HT_1, 5-HT_2), adrenergic (α_1,α_2,β) and dopaminergic] much less potently than do the tricyclic drugs.

Pharmacokinetics

Absorption, Distribution, Metabolism, and Excretion

Fluoxetine is well absorbed after oral administration. In man, following a single oral 40 mg dose, peak plasma concentrations of fluoxetine from 15 to 55 ng/mL are observed after 6 to 8 hours. The capsule and oral solution dosage forms of PROZAC are bioequivalent. Food does not appear to affect the systemic bioavailability of fluoxetine, although it may delay its absorption inconsequentially. Thus, PROZAC may be administered with or without food.

Fluoxetine is extensively metabolized in the liver to norfluoxetine, and other unidentified metabolites. The pharmacological activity of norfluoxetine, which is formed by demethylation of fluoxetine appears to be similar to that of the parent drug. Norfluoxetine contributes to the long duration of action of PROZAC. The primary route of elimination appears to be hepatic metabolism to inactive metabolites excreted by the kidney. The elimination half-life of fluoxetine is 4 to 6 days and that of its active metabolite is 4 to 16 days.

Clinical Issues Related to Metabolism/Elimination:

Variability in Metabolism:

The metabolism of fluoxetine, like that of a number of other compounds, including tricyclic antidepressants and some selective serotonin reuptake inhibitors (SSRIs), involves the P4502D6 system. Concomitant therapy with fluoxetine and the aforementioned drugs may lead to clinically significant drug interactions (see DRUG INTERACTIONS section).

Accumulation and Slow Elimination:

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

Kinetic Data:

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

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

Protein Binding:

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

DRUG INTERACTIONS section).

Special Populations and Conditions

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

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

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

STORAGE AND STABILITY

PROZAC Capsules:
Store capsules at 15°- 30° C.

PROZAC Oral Solution:
Store oral solution at 15°- 30° C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

PROZAC® (fluoxetine hydrochloride) Capsules
PROZAC 10 mg capsules contain: fluoxetine hydrochloride equivalent to 10 mg (32.3 µmoles) of fluoxetine, starch, and silicone. The capsule shell contains F D & C Blue No. 1, iron oxide yellow, titanium dioxide, gelatin, sodium lauryl sulfate, sodium propionate, benzyl alcohol, methyl paraben, propyl paraben, butyl paraben, carboxymethylcellulose sodium, and edetate calcium disodium.

PROZAC 20 mg capsules contain: fluoxetine hydrochloride equivalent to 20 mg (64.7 µmoles) of fluoxetine, starch, and silicone. The capsule shell contains F D & C Blue No. 1, iron oxide yellow, titanium dioxide, gelatin, sodium lauryl sulfate, sodium propionate, benzyl alcohol, methyl paraben, propyl paraben, butyl paraben, carboxymethylcellulose sodium, and edetate calcium disodium.

PROZAC® (fluoxetine hydrochloride) Oral Solution
PROZAC oral solution contains: fluoxetine hydrochloride equivalent to 20 mg/5mL (64.7 μmoles) of fluoxetine, benzoic acid, mint flavor, glycerin, purified water, and sucrose.

AVAILABILITY OF DOSAGE FORMS:
PROZAC® (fluoxetine hydrochloride) Capsules:
PROZAC (fluoxetine hydrochloride) 10 mg capsules are green and green, printed with Dista 3104 and PROZAC 10 mg, packaged in amber HDPE bottles of 100.

PROZAC (fluoxetine hydrochloride) 20 mg capsules are green and yellow, printed with Dista 3105 and PROZAC 20 mg, packaged in amber HDPE bottles of 100.

PROZAC® (fluoxetine hydrochloride) Oral Solution:
PROZAC (fluoxetine hydrochloride) oral solution is a clear colourless syrup solution 20 mg/5 mL with an odour of mint, packaged in amber glass bottles of 120 mL (MS-5120).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Fluoxetine hydrochloride

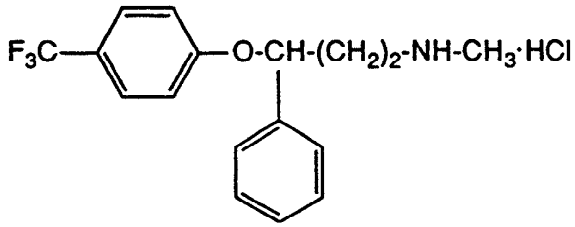
Chemical name: (+)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-p-tolyl)-oxy]-propylamine hydrochloride

Molecular formula and molecular weight: $C_{17}H_{18}F_3NO \bullet HCl$

345.79

Structural formula:

Physiochemical properties:



Description:	Fluoxetine is white to off-white crystalline solid.	
pKa:	9.5 (66% Dimethylformamide)	
Solubility Profile:	Solvent Water Benzene Ethyl Acetate	mg/mL 14 insoluble insoluble

CLINICAL TRIALS

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

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

A study was conducted involving depressed outpatients who had responded (modified HAMD-17 score of ≤7 during each of the last 3 weeks of open-label treatment and absence of major depression by DSM-III-R criteria) by the end of an initial 12-week open treatment phase on Prozac 20 mg/day. These patients (N=298) were randomized to continuation on double-blind Prozac 20 mg/day or placebo. At 38 weeks (50 weeks total), a statistically significantly lower relapse rate (defined as symptoms sufficient to meet a diagnosis of major depression for 2 weeks or a modified HAMD-17 score of ≥14 for 3 weeks) was observed for patients taking Prozac compared to those on placebo.

DETAILED PHARMACOLOGY

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

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

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

<u>Pharmacokinetics:</u>

Animal and In vitro

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

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

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

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

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

TOXICOLOGY

Acute Toxicity Studies:

Table 4: Toxicity Data of Fluoxetine and Norfluoxetine in Animals

Species	Route	Sex	Fluoxetine LD50 (mg/kg)	Norfluoxetine LD50 (mg/kg)
Mouse	Oral	F	248 ± 14	361 ± 14
	I.V.	F	45 ± 1.5	42 ± 3
Rat	Oral	M	467 ± 33	--
		F	437 ± 40	--
	I.V.	M	35 ± 1	--
		F	35 ± 1	35 ± 2
Guinea Pig	Oral	M	> 250	--
Cat	Oral	M/F	> 50	--
Dog	Oral	M/F	> 100	--
Monkey	Oral	M/F	> 50	--

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

Subchronic/Chronic/Carcinogenicity and Related Toxicity Studies:

Subchronic Toxicity Studies:

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

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

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

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

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

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

white blood cell counts were observed.

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

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

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

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

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

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

Juvenile Toxicology Study: In a juvenile toxicology study in CD rats, administration of 30 mg/kg of fluoxetine hydrochloride on postnatal days 21 through 90 resulted in increased serum activities of creatine kinase (CK) and aspartate aminotransferase (AST), which were accompanied microscopically by skeletal muscle degeneration, necrosis and regeneration. Femur lengths at 30mg/kg increased to a lesser extent compared with control rats. Other findings are discussed below in the Reproductive and Impairment of Fertility Studies.

Carcinogenicity Studies:
Rats were maintained for two years at dietary levels equivalent to a time-weighted average dose of ca. 0.45, 2 and 9 mg/kg/day. Age-related observations such as chromodacryorrhea, alopecia, and poor grooming increased at the high dose, especially in females. Weight gain and food consumption were depressed at the high dose and a handling-induced behaviour involving arching of the back and walking on toes was observed primarily in females in this group. Increased tissue levels of fluoxetine and norfluoxetine were observed at all doses, and phospholipidosis was observed primarily at the high dose. There were no significant increases in tumor incidence or animal mortality.

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

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

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

Impairment of fertility in adult animals at doses up to 12.5mg/kg/day (approximately 1.5 times the MRHD on a mg/m^2 basis) was not observed

In a juvenile toxicology study, fluoxetine hydrochloride was administered orally to CD rats (30/sex/group) at doses of 0, 3, 10, and 30 mg/kg/day from postnatal days 21 through 91 and evaluated for general clinical observations. Ten rats/sex/group were necropsied on postnatal day 91 and evaluated for changes in clinical chemistry, hematology, femur length, organ weights,

and histopathology. Following an approximately 11-week recovery period, sperm assessments were performed in all groups, and microscopic examination of testis and epididymides occurred in the 30mg/kg/day males only.

Plasma levels achieved at 30mg/kg/day were approximately 5 to 8 fold (fluoxetine) and 18 to 20 fold (norfluoxetine), and at 10 mg/kg approximately 2 fold (fluoxetine) and 8 fold (norfluoxetine) higher compared to plasma concentrations usually achieved in pediatric patients.

Administration of 30 mg/kg/day of fluoxetine hydrochloride on postnatal days 21 through 90 resulted in a substantial decrease in body weight gain with concomitant degeneration and necrosis of seminiferous tubules of the testis, epididymal epithelial vacuolation, epididymal sperm granuloma, and immaturity and inactivity of the female reproductive tract.

Findings following an approximately 11-week recovery period in male rats administered 30mg/kg/day, consisted of testicular degeneration, seminiferous tubular sperm microgranulomas, epididymal epithelial cribriform change, epididymal epithelial vacuolation and epididymal sperm granulomas. All of the rats with cribriform change had testicular degeneration, and comparison to the treatment-phase rats indicted that the testicular degeneration was irreversible. In contrast, the reduction in degree and extent of epididymal vacuolation compared to the treatment-phase rats indicates that the vacuolation was reversible.

Sperm assessments in the 30-mg/kg males only indicated an approximately 30% decrease in sperm concentrations without affecting sperm morphology or motility. Decreased fertility was observed in this dose-group. Delays in sexual maturation occurred in the 10-mg/kg/day males and in the 30-mg/kg/day males and females. The significance of these findings in humans is unknown.

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

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

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

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PART III: CONSUMER INFORMATION

PROZAC®
(Fluoxetine Hydrochloride)
Capsules and Oral Solution

This leaflet is part III of a three-part "Product Monograph" published when PROZAC was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PROZAC. Contact your doctor or pharmacist if you have any questions about the drug.

Please read this information before you start to take your medicine, even if you have taken this drug before. Keep this information with your medicine in case you need to read it again.

ABOUT THIS MEDICATION

What the medication is used for:
PROZAC has been prescribed by your doctor to relieve your symptoms of:
- depression (feeling sad, a change in appetite or weight, difficulty concentrating or sleeping, feeling tired, headaches, unexplained aches and pain)
- bulimia (eating disorder, characterized by self-induced vomiting after eating)
- or obsessive-compulsive disorder (recurrent and intrusive thought, feeling, idea, or sensation; recurrent pattern of behaviour, or unwanted thoughts or actions)

What it does:
PROZAC (fluoxetine hydrochloride) belongs to a group of medicines called selective serotonin reuptake inhibitors (SSRIs). PROZAC is thought to work by increasing the levels of a chemical in the brain called serotonin (5-hydroxytryptamine).

When it should not be used:
Do not use PROZAC if you are:
- allergic to it or any of the components of its formulation (see list of components at the end of this section).
- currently or have recently taken the drug thioridazine.
- currently or have recently taken monamine oxidase anti-depressants (e.g. phenelzine sulphate, moclobemide).

The medicinal ingredient is:
PROZAC capsules and oral solution contain the active ingredient fluoxetine hydrochloride.

The nonmedicinal ingredients are:
Both PROZAC 10 mg and 20 mg capsules contain the following inactive ingredients: starch, silicone, F D & C Blue No. 1, iron oxide yellow, titanium dioxide; gelatin, sodium lauryl sulfate, sodium propioate, benzyl alcohol, methyl paraben, propyl paraben, butyl paraben, carboxymethylcellulose sodium, and edetate calcium disodium.

PROZAC Oral Solution contains the following inactive ingredients: benzoic acid, mint flavor, glycerin, purified water, and sucrose.

There is no gluten, lactose, sulfite, or tartrazine in PROZAC.

What dosage forms it comes in:
PROZAC Capsules:
PROZAC Capsules are available in 10 mg (green) and 20 mg (green and yellow) strengths.

PROZAC Oral Solution:
PROZAC oral solution (colourless, with a mint odour) is only available in 20 mg/ 5 mL.

WARNINGS AND PRECAUTIONS

During treatment with these types of medications, it is important that you and your doctor have good ongoing communication about how you are feeling.

Prozac is not for use in children under 18 years of age.

New or Worsened Emotional or Behaviour Problems
Particularly in the first few weeks or when doses are adjusted, a small number of patients taking drugs of this type may feel worse instead of better; for example, they may experience unusual feelings of agitation, hostility or anxiety, or have impulsive or disturbing thoughts such as thoughts of self-harm or harm to others. Should this happen to you, or those in your care if you are a caregiver or guardian, consult your doctor immediately, **do not discontinue your medication on your own.**

Before starting PROZAC, tell your doctor or pharmacists:
- if you have ever had an allergic reaction to any medication
- all your medical conditions, including a history of liver or kidney problems, seizures or blackouts, diabetes, and heart problems or abnormal bleeding
- any medications (prescription or nonprescription) you are taking or have recently taken, especially monoamine oxidase (MAO) inhibitors (e.g., phenelzine sulfate, tranylcypromine sulfate, moclobemide or selegeline) or thioridazine
- any natural or herbal products you are taking (e.g. St. John's Wort)
- if you are pregnant or thinking about becoming pregnant, or if you are breast feeding
- your habits of alcohol and /or street drug consumption
- if you drive a vehicle or perform hazardous tasks during your work

Effects on Pregnancy and Newborns

Post-marketing reports indicate that some newborns whose mothers took an SSRI (selective serotonin reuptake inhibitor) or other newer anti-depressant, such as PROZAC, during pregnancy have developed complications at birth requiring prolonged hospitalization, breathing support and tube feeding. Reported symptoms included feeding and/or breathing difficulties, seizures, tense or overly relaxed muscles, jitterriness and constant crying.

In most cases, the newer anti-depressant was taken during the third trimester of pregnancy. These symptoms are consistent with either a direct adverse effect of the anti-depressant on the baby, or possibly a discontinuation syndrome caused by sudden withdrawal from the drug. These symptoms normally resolve over time. However, if your baby experiences any of these symptoms, contact your doctor as soon as you can.

If you are pregnant and taking an SSRI, or other newer anti-depressant, you should discuss the risks and benefits of the various treatment options with your doctor. It is very important that you do NOT stop taking these medications without first consulting your doctor. See SIDE EFFECTS AND WHAT TO DO ABOUT THEM section for more information.

INTERACTIONS WITH THIS MEDICATION

Do not use PROZAC if you are taking or have recently taken monoamine oxidase (MAO) inhibitors or thioridazine.

You should tell your doctor if you are taking or have recently taken any medications (prescription, nonprescription or natural/herbal), especially:

- other anti-depressants, such as SSRIs, certain tricylics, drugs used to treat schizophrenia, or bipolar depression (e.g. lithium)
- drugs which may affect blood clotting and increase bleeding, such as drugs used to thin the blood (anticoagulants, e.g. warfarin), as well as acetylsalicylic acid (e.g. Aspirin) and other non-steroidal anti-inflammatory drugs (e.g. ibuprofen)
- certain medicines used to treat patients with irregular heart beats
- certain drugs use to treat diabetes
- other drugs that affect serotonin, such as lithium, linezolid, tramadol, drugs containing tryptophan, St. Johns Wort, triptans used to treat migraines
- sedatives such as benzodiazapines

As with many drugs that work directly on the brain, use of alcohol while taking PROZAC should be limited/moderate.

PROPER USE OF THIS MEDICATION

Usual dose:

- It is very important that you take PROZAC exactly as your doctor has instructed. Generally people take between 20 mg to 80 mg per day for depression and obsessive-compulsive disorder and between 20 and 60 mg per day for bulimia.
- PROZAC is usually taken once a day. It may be taken with or without food. If you are taking capsules, you should swallow the capsules whole; do not chew them.
- You should continue to take your medicine even if you do not feel better, as it may take a number of weeks for your medicine to work.
- Keep taking your PROZAC until the doctor tells you to stop.
- Talk to your doctor before you stop taking your medication on your own.

Remember:
This medicine has been prescribed only for you. Do not give it to anybody else, as they may experience undesirable effects, which may be serious.

Missed Dose
If you forget to take a dose of PROZAC, take it as soon as you remember. Take your next dose at the next scheduled time; do not try to make up for a missed dose by taking a double dose the next time.

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all other medications, PROZAC can cause some side effects. You may not experience any of them. For most patients, side effects are likely to be minor and temporary. However, some may be serious. Some of these side effects may be dose related. Consult your doctor if you experience these or other side effects, as the dose may have to be adjusted.

If you experience an allergic reaction (including skin rash, hives, swelling, trouble breathing) or any severe or unusual side effects, stop taking the drug and contact your doctor immediately.

The most common side effects of PROZAC are:

- nausea
- dizziness
- headache
- anxiety
- nervousness
- drowsiness
- insomnia
- fatigue
- weakness
- diarrhea
- upset stomach
- dry mouth
- loss of appetite
- excessive sweating

Prozac does not usually affect people's normal activities. However, some people feel sleepy while taking it, in which case they should not drive or operate machinery.

Although psychiatric disorders may be associated with decreases in sexual desire, performance and satisfaction, treatment with this medication may also affect sexual functioning.

New or Worsened Emotional or Behaviour Problems
A small number of patients taking a drug of this type may feel worse instead of better, such as experiencing new or worsened feelings of agitation, hostility, anxiety, or thoughts about suicide. Your doctor should be informed of such changes immediately. Close observation by a doctor is necessary in this situation. Do not discontinue your medication on your own. See also the WARNINGS AND PRECAUTIONS section.

Discontinuation Symptoms
Contact your doctor before stopping or reducing your dosage of PROZAC. Symptoms such as headache, insomnia, paresthesias (numbness, tingling, burning, or prickling sensation) nervousness, anxiety, nausea, sweating, dizziness, jitteriness and weakness and other symptoms have been reported after stopping PROZAC. These symptoms usually disappear without needing treatment. Tell your doctor immediately if you have these or any other symptoms. Your doctor may adjust the dosage of PROZAC to alleviate the symptoms. See WARNINGS AND PRECAUTIONS section for more information.

Effects on Newborns
Some newborns whose mothers took an SSRI (Selective Serotonin Uptake Inhibitor) or other newer antidepressants during pregnancy have shown such symptoms as breathing and feeding difficulties, jitteriness and constant crying. If your baby experiences any of these symptoms, contact your doctor as soon as you can. See WARNING AND PRECAUTIONS section for more information.

The following table is based on data from placebo-controlled clinical trials involving 10,782 patients.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Allergic reactions (skin rash, hives, swelling, trouble breathing)			✓*
Uncommon	Bruising or unusual bleeding from the skin or other areas		✓	
Uncommon	Hallucinations [strange visions or sounds]		✓	
Uncommon	Inability to urinate		✓	
Uncommon	Akathisia [feeling restless and unable to sit or stand still]		✓	
Uncommon	Seizures [i.e. loss of consciousness with uncontrollable shaking ("fit")]			✓*
Uncommon	Mania [overactive behaviour and thoughts]		✓	
Rare	Gastrointestinal bleeding [vomiting blood or passing blood in stools]		✓*	
Rare	Increased pressure in the eyes [symptoms of eye pain and blurred vision]		✓	
Rare	Liver disorder [symptoms include nausea, vomiting, loss of appetite combined with itching, yellowing of the skin or eyes, dark urine]		✓*	
Rare	Uncontrollable movements of the body or face		✓	
Rare	Low sodium level in blood [symptoms of tiredness, weakness, confusion combined with achy, stiff or uncoordinated muscles]		✓	
Very Rare	Serotonin		✓*	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
	syndrome [a combination of most or all of the following; confusion, restlessness, sweating, shaking, shivering, hallucinations, sudden jerking of the muscles, fast heartbeat]			
See Warnings & Precautions	New or worsened emotional or behavioural problems		✓*	

* If you think you have these side effects, it is important that you seek medical advice from your doctor immediately

This is not a complete list of side effects. For any unexpected effects while taking PROZAC, contact your doctor or pharmacist.

HOW TO STORE IT

Keep all medicines out of the reach of children. PROZAC should be stored in its original package at room temperature, in a dry place and out of direct sunlight. The expiry date of this medicine is printed on the package label. Do not use the medicine after the expiry date. If your doctor tells you to stop taking PROZAC or you find that they have passed their expiry date, please return any left over medicine to your pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Health Canada
Address Locator: 0201C2
Ottawa, ON K1A 1B9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

PROZAC Capsules and Prozac Oral Solution are manufactured by: Eli Lilly Canada Inc.

This leaflet was prepared by Eli Lilly Canada Inc., Toronto, Ontario, M1N 2E8. This leaflet, plus the full product monograph prepared for healthcare professionals can be obtained by contacting Eli Lilly Canada at: 1-888-545-5972 or visit the website at www.lilly.ca

For more information, please contact your healthcare professionals or pharmacist first, or Eli Lilly Canada Inc.

You may need to read this package insert again. Please do not throw it away until you have finished your medicine.

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