CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18-936/S-052
                20-101/S-024

FINAL PRINTED LABELING
Fluoxetine hydrochloride is a white to off-white crystalline solid with a solubility of 14 mg/ml in water. Each Paludrine® tablet contains fluoxetine hydrochloride equivalent to 20 mg (67.9 mg) of fluoxetine. The fluoxetine tablets also contain lactose, silicon dioxide, stearic acid, and silicon dioxide as inactive ingredients. The 20 mg and 40 mg tablets each contain 18.5 mg, 37 mg, and 74 mg of fluoxetine hydrochloride, respectively. Each 60 mg tablet contains 90 mg of fluoxetine hydrochloride. The 60 mg tablets also contain lactose, silicon dioxide, magnesium stearate, cornstarch, hydroxypropyl methylcellulose, polyethylene glycol, and yellow iron oxide. In addition to the above ingredients, the tablets also contain titanium dioxide, FD&C Blue No. 1 and FD&C Yellow No. 6. The tablets are available in bottles of 100 tablets of each strength.
normal melancholia, the total sign was strikingly more prevalent among poor metabolizers. Thus, the net pharmacodynamic actions were essentially similar. Alternative, nonsteroidal antipyretics (isoniazid) also contribute to the metabolites and the total effect is greater than in cases of severe metabolic conversion. Treatment of these individuals with tricyclic and other selective serotonin reuptake inhibitors, such as fluoxetine, which may be metabolized by this enzyme system (such as tricyclic antidepressants) may lead to drug interactions (see Drug Interactions under Precautions).

Accumulation and Slow Elimination—The relatively slow elimination of fluoxetine (elimination half-life of 1 to 3 days after acute administration) and 4 to 6 days after chronic administration and to active metabolite, norfluoxetine (elimination half-life of 1 to 4 days after acute and chronic administration), leads to significant accumulation of these active species and delayed achievement of steady-state concentrations when a fixed dose is used. After 30 days of dosing at 40 mg/day, plasma concentrations of fluoxetine in the range of 91 to 302 ng/ml, and norfluoxetine in this range of 72 to 258 ng/ml, and concentrations of the active metabolite were higher than those predicted by single-dose studies, because fluoxetine's metabolism is not proportional to dose. Norfluoxetine, however, appears to have linear pharmacokinetics, its mean terminal half-life after a single dose was 6 days and after multiple dosing was 9 days. Slow state levels after prolonged dosing are similar to those seen at 4.5 weeks.

The long elimination half-lives of fluoxetine and norfluoxetine assure that, even when dosing is stopped, active drug substance will persist in the body (characteristically depending on factors such as previous doses, dose regimen, and length of previous therapy at discontinuation). The use of potential consequences when drug discontinuation is required or when drug interactions are to be anticipated should be used (see Precautions and Dosage and Administration).

Blood Levels—In unselected patients at steady state levels, fluoxetine concentrations were less than 100 ng/ml in 97% of subjects. Norfluoxetine plasma concentrations were 20 to 400 ng/ml, and the range for fluoxetine is 30 to 600 ng/ml. The relationship between blood level and toxicity appears to be linear and does not indicate a dose and level relationship.

Adverse Reactions—Adverse effects of fluoxetine in the elderly, particularly, if they have a history of serious disease or are receiving other drugs for conditions such as diabetes, hypertension, depression, or other neurological disorders. The effects of agitation, restlessness, and dizziness have been observed in 26% of patients 60 years of age or older who received fluoxetine for 2 weeks. Combined fluoxetine plus norfluoxetine plasma concentrations were 209 ± 87 ng/ml, at the end of 9 weeks. No unusual age-associated pattern of adverse events was observed in these elderly patients.

Clinical Trials—Depression—The efficacy of Prozac for the treatment of patients with depression (≥ 18 years of age) has been studied in 5- and 6-week placebo-controlled trials. Fluoxetine was compared to placebo as measured by the Hamilton Depression Rating Scale (HAM-D). Prozac also was significantly more effective than placebo in the HAM-D scores for depression and the area under the curve (AUC).

Two 5-week controlled trials (N = 277) randomized comparing Prozac 20 mg and placebo in 20 mg and placebo in 20 mg or placebo patients with major depression. Patients were assigned randomly in a double-blind, placebo controlled trial. The安慰剂 group was given placebo or 20 mg of the study drug. Patients were evaluated for 42 days (1 week after randomization). The primary outcome measure was the change from baseline in the HAM-D score. After 42 days, patients were switched to another treatment. A significant improvement was observed in the Prozac group compared to the placebo group (P < 0.05).

Obsessive-Compulsive Disorder—The effectiveness of Prozac for the treatment of obsessive-compulsive disorder (OCD) was demonstrated in two 12-week multicenter parallel group studies (Studies 1 and 2) of adult outpatients who received 20 to 60 mg/day of Prozac or placebo. Patients who were not responders to previous treatment and who had not responded to other drugs were included in the study. The primary efficacy measure was the change from baseline in the Yale-Brown Obsessive Compulsive Scale (YBOCS) total score. The change from baseline in the YBOCS total score was assessed at 12-week intervals. The change from baseline in the YBOCS total score was significant in the Prozac group compared to the placebo group. The mean change in the YBOCS total score for the Prozac group was -2.3 compared to -1.2 for the placebo group.

The following table provides the outcome classification by treatment group on the Clinical Global Impressions (CGI) improvement scale for studies 1 and 2 combined.

| Outcome Classification (%) | CGI Improvement Scale for | Studies in Preclinical 
|-----------------------------|--------------------------|------------------------
| Prozac                      |                           | Preclinical Studies     
| Placebo 20 mg               |                           |                        
| Placebo 40 mg               |                           |                        
| Placebo 60 mg               |                           |                        
| Worse                       | 0%                       | 0%                     
| Very Much Improved          | 0%                       | 0%                     
| Minimalized                 | 1%                       | 0%                     
| Much Improved               | 8%                       | 0%                     
| No Change                   | 44%                      | 33%                    
| Slightly Improved           | 17%                      | 23%                    
| Mildly Improved             | 8%                       | 23%                    
| Marked Improved             | 3%                       | 12%                    
| Markedly Improved           | 3%                       | 19%                    

Exploratory analyses for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or sex.

Bladder Neurites—The effectiveness of Prozac for the treatment of bladder symptoms was demonstrated in two 2- and 6-week, multicenter, parallel group studies (Stud 1 and 2) of adult and pediatric patients who received 20 to 60 mg/day of Prozac or placebo. Patients were randomized to receive either 20 mg or 60 mg of Prozac or placebo. The primary outcome measure was the change from baseline in the severity of bladder symptoms. After 42 days, patients were switched to another treatment. The change from baseline in the severity of bladder symptoms was significant in the Prozac group compared to the placebo group. The mean change in the severity of bladder symptoms for the Prozac group was -2.3 compared to -1.2 for the placebo group.

INDICATIONS AND USAGE—Depression—Prozac is indicated for the treatment of depression. The efficacy of Prozac was established in 5- and 6-week trials with depressed adult and geriatric outpatients (≥ 18 years of age) whose diagnosis corresponded most closely to the DSM-III-R category of major depression disorder (see Clinical Trials under Clinical Pharmacology).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent mood (every day for at least 2 weeks) depressed or hypomanic mood that usually interferes with daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities, and/or appetite, insomnia or hyperactivity, psychomotor agitation or retardation, decreased energy or fatigue, concentration, suicidal ideation, guilt, or worthlessness, slowed thinking or speaking.

The antidepressant action of Prozac has been well documented in patients treated with standard doses of the drug. The drug is available in a controlled manner, but the use of the drug in children treated for extended periods (4 years or longer) is considered inappropriate (see Under Clinical Pharmacology).

Obsessive-Compulsive Disorder—Prozac is indicated for the treatment of obsessive-compulsive disorder (OCD), as defined in the DSM-IV-TR, i.e., the obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of Prozac was established in 13-week trials with obsessive-compulsive outpatients whose symptoms corresponded most closely to the DSM-IV-TR category of obsessive-compulsive disorder (see Clinical Trials under Clinical Pharmacology). Obsessive-compulsive disorder is characterized by recurrent and persistent ideas, thoughts, impulses, or images (obsessions) that are ego-dystonic and/or repetitive, purposeful, and interpersonal (see Under Clinical Pharmacology).

The effectiveness of Prozac in long-term use, i.e., for more than 13 weeks, has not been systematically evaluated in placebo-controlled trials. Therefore, the use of Prozac for extended periods (≥ 13 weeks) should be periodically reevaluated in the long-term usefulness of the drug for the individual patient (see Doseage and Administration).

Buclima Neurites—Prozac is indicated for the treatment of binge-eating and purging behaviors in patients with moderate to severe bulimia

The efficacy of Prozac was established in 8 to 16 week trials for adults with moderate to severe bulimia nervosa, i.e., at least 3 bulimic episodes per week for 6 months (see Clinical Trials under Clinical Pharmacology).

The effectiveness of Prozac in long-term use, i.e., for more than 16 weeks has not been systematically evaluated.
Prozac—As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of fluoxetine. The elimination half-life of fluoxetine was prolonged in a study of chronic patients with a mean of 7.6 days compared to the range of 2 to 3 days seen in subjects with normal hepatic function. The elimination was also delayed, with a mean duration of 12 days for chronic patients compared to the range of 7 to 9 days in normal subjects. This suggests that the use of fluoxetine in patients with hepatic impairment should be approached with caution. If fluoxetine is administered to patients with liver disease, a lower or less frequent dose should be used (see Precautions and Dosage and Administration).

Recall Dose—In depressed patients on antidepressants (N=12), fluoxetine administered as 20 mg once daily for two months produced steady-state fluoxetine plasma concentration similar to that seen in patients with normal renal function. While the possibility exists that altered renal metabolites of fluoxetine may accumulate to higher levels in patients with severe renal dysfunction, the less frequent dose is not routinely necessary in severely impaired patients (see Use in Patients with Congestive Heart Failure under Precautions and Dosage and Administration).

Age—The duration of single doses of fluoxetine in elderly subjects (greater than 65 years of age) did not differ significantly from that in younger normal subjects. However, given the lack of significant changes in the renal and hepatic function associated with the drug, a single-dose study is not adequate to rule out the possibility of altered pharmacokinetics in the elderly, particularly if they have systemic illness or are receiving multiple drugs.

The effects of age upon the metabolism of fluoxetine have been investigated in 260 elderly but otherwise healthy depressed patients (N=60 years of age) who received 20 mg fluoxetine for 6 weeks. Combined fluoxetine plus norfluoxetine plasma concentrations were 291 ± 95 ng/ml at the end of 6 weeks. No unusual age-associated pattern of adverse events was observed in those elderly patients.

Clinical Trials

Depression—The efficacy of Prozac for the treatment of patients with depression (N=18 years of age) has been studied in 5- and 6-week placebo-controlled trials. Prozac was shown to be significantly more effective than placebo as measured by the Hamilton Depression Rating Scale (HAMD-D). Prozac was also significantly more effective than placebo or the HAM-D subscore for depressed mood, stress anxiety and insomnia, respectively.

Two 6-week controlled studies (N=671 randomized) comparing Prozac 20 mg, and placebo have shown Prozac, 20 mg daily to be effective in the treatment of elderly patients (N=60 years of age) with depression. In these studies, Prozac produced a significantly higher percentage of response and remission (56%) than placebo (26%) with a 50% decrease in the HAMD-D score and a total endpoint HAMD-D score of 18. Prozac was well tolerated and the rate of treatment discontinuations (2%) was similar to placebo.

A study was conducted involving depressed outpatients who had responded to modified HAMD-17 score of 7 or indicated the desirability of open-label treatment and absence of major depressive disorder on the BDI. Patients were randomized to continue on double-blind Prozac 20 mg/day or placebo. A total of 242 patients treated to placebo only were included.

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.

Obsessive-Compulsive Disorder—The effectiveness of Prozac for the treatment of obsessive-compulsive disorder (OCD) was demonstrated in two 12-week multicenter parallel group studies (Studies 1 and 2) of adult outpatients who received fixed Prozac doses of 20, 40, or 60 mg/day (in a once daily schedule, in the morning or placebo. Patients in both studies had moderate to severe OCD (DSM-III-R) with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (YBOCS total score) ranging from 22 to 26. In Study 1, patients receiving Prozac experienced mean reductions of approximately 8 to 10 units on the YBOCS total score, compared to a 3-unit reduction for placebo patients. On the YBOCS Total score, patients in both studies showed significant reductions of approximately 4 to 9 units on the YBOCS total score, compared to a 3-unit reduction for placebo patients. While there was no indication of a dose-response relationship for effectiveness in Study 1, a dose-response relationship was observed in Study 2 with nearly identical reductions in the 2 higher dose groups.

The following table provides the outcome classification by treatment group on the Clinical Global Impression (CGI) improvement scale for studies 1 and 2 combined.

<table>
<thead>
<tr>
<th>Outcome Classification</th>
<th>Placebo</th>
<th>20 mg</th>
<th>40 mg</th>
<th>60 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsened</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>No Change</td>
<td>54%</td>
<td>41%</td>
<td>35%</td>
<td>29%</td>
</tr>
<tr>
<td>Minimally Improved</td>
<td>17%</td>
<td>28%</td>
<td>28%</td>
<td>24%</td>
</tr>
<tr>
<td>Much Improved</td>
<td>6%</td>
<td>27%</td>
<td>26%</td>
<td>20%</td>
</tr>
<tr>
<td>Very Much Improved</td>
<td>5%</td>
<td>8%</td>
<td>12%</td>
<td>19%</td>
</tr>
</tbody>
</table>

Exploratory analyses for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or sex.

Buena Service—The effectiveness of Prozac for the treatment of bulimia was demonstrated in two 8-week and the 16-week multicenter parallel group study of adult outpatients meeting DSM-III-R criteria for bulimia nervosa. Patients in the 8-week study received either 20 mg/day or 60 mg/day of Prozac or placebo in the morning. Patients in the 16-week study received a fixed Prozac dose of 60 mg/day once a day or placebo. Patients in these 3 studies had moderate to severe bulimia with mean (±SD) binge-eating and vomiting episodes per week ranging from 7 to 10 per week and 5 to 9 per week, respectively. In these 3 studies, Prozac 60 mg, but not 20 mg, was statistically significantly superior to placebo in reducing the subjective ratings of the number of binge-eating episodes per week and the number of vomiting episodes per week. The relative efficacy of the two doses was determined using categorical change scores and the proportion of patients in the placebo and the Prozac group who improved from moderate to severe bulimia.

The antidepressant action of Prozac in hospitalised depressed patients has not been adequately studied. The efficacy of Prozac in maintaining an antidepressant response for up to 38 weeks did not differ from that seen with lower dose of 20 mg proactively. Prozac related to treatment (depression, obsession, or depression) did not differ significantly between patients treated with the same dose of 20 mg proactively, and placebo, and reduction in baseline depression as assessed by the Hamilton Depression Rating Scale. In each of these 3 studies, the treatment effect, as measured by differences between Prozac, 60 mg, and placebo, was on median reduction from baseline in frequency of binge-eating behaviors at endpoint, ranged from 1 to 2 episodes per week for binge-eating and 3 to 4 episodes per week for vomiting. The size of the effect was not different across studies with greater effect was noted in patients with higher baseline frequencies. Although some patients achieved freedom from binge-eating and purging as a result of treatment for the majority, the benefit was a partial reduction in the frequency of binge-eating and purging.

INDICATIONS AND USAGE

Depression—Prozac is indicated for the treatment of depression. The efficacy of Prozac was established in 5- and 6-week trials with depressed adult and geriatric outpatients (N>18 years of age) whose diagnoses correspond most closely to the DSM-III-R (current DSM-IV) category of major depressive disorder (MDD) (see Clinical Trials under Clinical Pharmacology)

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

The antidepressant action of Prozac in hospitalized depressed patients has been assessed adequately. The efficacy of Prozac in maintaining an antidepressant response for up to 38 weeks did not differ from that seen with lower dose of 20 mg. Prozac related to treatment (depression, obsession, or depression) did not differ significantly between patients treated with the same dose of 20 mg and placebo.

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

The efficacy of Prozac was established in 13-week trials with obsessive-compulsive outpatients whose diagnoses corresponded most closely to the DSM-III-R (current DSM-IV) category of obsessive-compulsive disorder (OCD) (see Clinical Trials under Clinical Pharmacology).

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

The effectiveness of Prozac in long-term use, i.e., for more than 13 weeks, has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to use Prozac in patients who have been maintained on Prozac for a period of 13 weeks or more should periodically reevaluate the long-term usefulness of the drug for the individual patient (see Dosage and Administration).

Buena Service—Prozac is indicated for the treatment of binge-eating and purging behaviors in patients with moderate to severe bulimia nervosa.

The efficacy of Prozac was established in 8 to 16 week trials for adult outpatients with moderate to severe bulimia nervosa, as defined by DSM-III-R criteria (see Clinical Trials under Clinical Pharmacology).

The effectiveness of Prozac in long-term use, i.e., for more than 13 weeks, has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to use Prozac for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see Dosage and Administration).

CONTRAINdications

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

Monoamine Oxidase Inhibitors—There have been reports of serious, sometimes fatal, reactions (including hyperpyrexia, rigidity, myoclonus, autonomic instability, and death), with or without apparentadalfluence, in patients receiving fluoxetine in combination with a monoamine oxidase inhibitor (MAOI), and in patients receiving fluoxetine after discontinuation of an MAOI. Fluoxetine is metabolized by CYP2D6 and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome Therefore, Prozac should not be used in combination with an MAOI for at least 14 days of discontinuing therapy with an MAOI. Since fluoxetine and its major metabolites have a very long elimination half-lives, at least 5 weeks (perhaps longer especially if fluoxetine has been prescribed chronically for several years) should pass before fluoxetine treatment is initiated.
PROZAC® (Fluoxetine Hydrochloride)

and/or at higher doses [see Accumulation and Slow Elimination under Clinical Pharmacology]) should be
allowed after stopping Prozac before starting an MAOI.

WARNINGS

Rash and Pseudosyndrome Events—In US fluoxetine clinical trials, 7% of 10,782 patients developed various
rashes or urticaria, which were reported in one major underlying disease. Among the cases of rash and/or urticaria
reported in premarketing clinical trials, about 1% were due to other adverse events. Clinical findings reported in
association with rash include fever, leukocytosis, arthralgias, edema, and sometimes a spastic paraparesis.
Most patients improved promptly with discontinuation of fluoxetine and/or other antidepressant treatment
and/or adjustment of treatment with antihistamines or corticosteroids. In premarketing clinical trials, 5 patients
are known to have developed a serious cutaneous systemic reaction and the rash associated with these
symptoms were reported. Other patients have had systemic symptoms suggestive of pseudosyndrome.

In patients with a rash, use of Prozac is not recommended. However, these patients have been treated with
fluoxetine, and some patients have been treated with Prozac for up to 2 years. In patients with a rash, use of
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Anaphylactic events, including anaphylactic shock, have been reported. These events have occurred with
dizziness as the only presenting symptom. Other patients have developed a rash, urticaria, and fever in
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these patients have been treated with fluoxetine, and some patients have been treated with Prozac for up to 2 years.
The Long-Term Use of Prozac: Risk of anorexia nervosa, bulimia, and binge eating disorder

Prozac use has been associated with an increased risk of anorexia nervosa, bulimia, and binge eating disorder, according to recent studies. This risk is particularly high in women and adolescents. The exact mechanism of this association is not fully understood, but it is thought to be related to changes in the serotonin system that may affect appetite and mood regulation.

Prozac Use and Weight Gain

Prozac use has been associated with weight gain, particularly in the first few weeks of treatment. This weight gain is often attributed to increased appetite and feelings of thirst, which can lead to increased caloric intake. While this weight gain is usually reversible upon discontinuation of Prozac, it can be a concern for patients and healthcare providers.

Prozac Use and Sexual Dysfunction

Prozac use has been associated with decreased libido and sexual dysfunction, particularly in men. These effects are thought to be related to changes in the serotonin system that affect sexual function.

Prozac Use and.cardiovascular risk

Prozac use has been associated with increased risk of cardiovascular events, particularly in patients with a history of cardiovascular disease. This risk is thought to be related to changes in the serotonin system that may affect blood pressure and heart rate.

Prozac Use and suicidality

Prozac use has been associated with an increased risk of suicidality, particularly in children and adolescents. This risk is thought to be related to the serotonin system, which plays a role in mood regulation and suicide.

Prozac Use and Drug Interactions

Prozac use can interact with a variety of other medications, including those used to treat anxiety, depression, and pain. These interactions can affect the effectiveness of both Prozac and the other medications.

Prozac Use and Pregnancy

Prozac use during pregnancy has been associated with an increased risk of birth defects, particularly neural tube defects. This risk is thought to be related to the serotonin system, which is important in neural tube development.

Prozac Use in Older Adults

Prozac use in older adults has been associated with an increased risk of falls and fractures. This risk is thought to be related to changes in the serotonin system that may affect balance and coordination.

Prozac Use and Drug Abuse

Prozac use has been associated with an increased risk of drug abuse, particularly in patients with a history of substance abuse. This risk is thought to be related to changes in the serotonin system that may affect reward and pleasure.

Prozac Use and Other Conditions

Prozac use has been associated with a variety of other conditions, including headaches, dizziness, and nervousness. These effects are thought to be related to changes in the serotonin system that affect mood and nervousness.

Prozac Use and Treatment Options

Prozac use has been associated with a variety of treatment options, including behavioral therapy, medication, and lifestyle changes. These options are thought to be effective in managing the symptoms associated with Prozac use.

Prozac Use and Future Research

Prozac use has been associated with a variety of future research areas, including the long-term effects of Prozac use and the mechanisms underlying its associated effects. These areas are thought to be important in understanding the potential risks and benefits of Prozac use.

Prozac Use and Patient Education

Prozac use has been associated with a variety of patient education topics, including the importance of adhering to treatment recommendations and the need for regular monitoring of symptoms. These topics are thought to be important in ensuring the safe and effective use of Prozac.
Flutamide, like other agents that are metabolized by 1-P450, inhibits the activity of the isoenzyme, and thus may make normal metabolizers resemble "poor" metabolizers. Therapy with metabolized by the 1-P450 system and that have a relatively narrow therapeutic index (see below), should be initiated at the low end of the dose range if a patient is receiving flutamide concurrently in the previous 5 weeks. Thus, dosing requirements resemble those of "poor" metabolizers. If flutamide is added to the treatment regimen of a patient already receiving a drug metabolized by 1-P450, the need for decreased dose of the original medication should be considered. Drugs with a narrow therapeutic index represent the greatest concern (eg, barbiturates, carbamazepine, and ticlopidine).

Drugs Metabolized by Cytochrome P450-4A4/5A4 — In an in vivo interaction study involving co-administration of flutamide with single doses of terfenadine or a clinical dose of terfenadine (a cytochrome P450A4/5A4 substrate), no increase in plasma terfenadine concentrations occurred with concomitant flutamide. In addition, in vitro studies systems have shown that flutamide, a potent inhibitor of 1-P450A4/5A4 activity, to be at least 100 times more potent than norflutamide as an inhibitor of the metabolism of several substrates for the enzymes, including phenol, cinnamaldehyde, and benzphetamine. The data indicate that flutamide's extent of inhibition of cytochrome P450A4/5A4 activity is not likely to be of clinical significance.

CNS Active Drugs — The risk of using Prozac in combination with other CNS active drugs has not been systematically evaluated. Nonetheless, caution is advised if the concomitant administration of Prozac and such drugs is required. In evaluating individual cases, consideration should be given to using lower initial doses of the concomitantly administered drugs, using conservative titration schedules, and monitoring of clinical status (see Accumulation and Slow Elimination under Clinical Pharmacology). Antidepressants — Patients on stable doses of phenytoin and carbamazepine have developed elevated plasma anticonvulsant concentrations and clinical anticonvulsant toxicity following initiation of concomitant flutamide treatment. Antihistamines — Some clinical data suggest a pharmacodynamic and/or pharmacokinetic interaction between phenothiazines, tricyclic antidepressants (SSRIs) and antihypertensives. Elevation of blood levels of haloperidol and dihydroergotamine has been observed in patients receiving concomitant flutamide. A single case report has suggested possible additive effects of phenobarbital and flutamide leading to bradycardia. Depolarizing Muscle Relaxants — The half-life of concurrently administered dazapam may be prolonged in some patients (see Accumulation and Slow Elimination under Clinical Pharmacology). Co-administration of diazepam and flutamide has resulted in increased alprazolam plasma concentrations and in further psychomotor performance decrement due to increased alprazolam levels. Lithium — There have been reports of both increased and decreased lithium levels when lithium was used concurrently with Prozac. Cases of lithium toxicity and increased antipsychotic effects have been reported. Lithium levels should be monitored when these drugs are administered concomitantly. Tricyclics — Five patients receiving Prozac in combination with 10-25 mg/day of nortriptyline experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

Monografin Antipsychotics — See Contraindications. Other Antidepressants — In two studies, previously stable plasma levels of imipramine and desipramine have increased greater than 2- to 10-fold when flutamide has been administered in combination. This influence may persist for three weeks or longer after flutamide is discontinued. Thus, the dose of tricyclic antidepressant (TCA) may need to be reduced and plasma TCA concentrations should be closely monitored temporarily when flutamide is coadministered or has been recently discontinued (see Accumulation and Slow Elimination under Clinical Pharmacology, and Drugs Metabolized by 1-P450 under Drug Interactions).

Potential Effects of Coadministration of Drugs Tightly Bound to Plasma Proteins — Because flutamide is tightly bound to plasma protein, the administration of flutamide to a patient taking another drug that is tightly bound to protein (eg, Concorid, digoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of tightly bound drugs (see Accumulation and Slow Elimination under Clinical Pharmacology). Warfarin — Altered anticoagulant effects, including increased bleeding, have been reported when flutamide is coadministered with warfarin. Patients receiving warfarin therapy should receive careful coagulation monitoring when flutamide is initiated or stopped.

Electroencephalogram (EEG) — There are no clinical studies establishing the benefit of the combined use of ECT and flutamide. There have been rare reports of prolonged seizures in patients on flutamide receiving ECT treatment.

Carcinogenicity, Mutagenesis, Impairment of Fertility — There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with Prozac.

Carcinogenicity — The dietary administration of flutamide to rats and mice for 2 years at doses of up to 10 and 12 mg/kg/day, respectively (approximately 1.2 and 0.7 times, respectively, the maximum recommended human dose [MRHD] of 80 mg in oral regimens) produced no evidence of carcinogenicity.

Mutagenesis — Flutamide and norflutamide have been shown to have no genotoxic effects based on the following assays: bacterial mutagenicity, in vivo sister chromatid exchange assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Impairment of Fertility — Two fertility studies conducted in rats at doses of up to 25 and 12.5 mg/kg/day (approximately 6.9 and 5.5 times the MRHD on a mg/m² basis) indicated that flutamide had no adverse effects on fertility.

Pregnancy — In 298 pregnant women, no evidence of teratogenicity following administration of up to 12.5 and 15 mg/kg/day, respectively (3.5 and 5 times, respectively, the maximum recommended human dose [MRHD] of 80 mg in oral regimens) was observed. The use of flutamide during pregnancy has not been adequately studied.

Labor and Delivery — The effect of Prozac on labor and delivery in humans is unknown. However, because flutamide crosses the placenta and because of the possibility of flutamide having an adverse effect on the newborn, flutamide should be used during labor and delivery only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers — Because Prozac is excreted in human milk, nursing while on Prozac is not recommended. In 1 Brit milk sample, the concentration of flutamide plus norflutamide was 70 ng/ml. The concentration in the mother's plasma was 295 ng/ml. No adverse effects on the infant were reported. In another case an infant was breastfed by a mother on Prozac developed crying, sleep disturbance, vomiting, and watery stools. The infant's plasma drug levels were 360 ng/ml of flutamide and 208 ng/ml of norflutamide.

Pediatric Use — Safety and effectiveness in pediatric patients have not been established.

Geriatric Use — In 1-8590 geriatric patients included 6572 patients 65 years of age and 93 patients ≥75 years of age. The efficacy in geriatric patients has been established (see Clinical Trials under Clinical Pharmacology). In one antidepressant-naive geriatric patient, 1-P450 inhibition was not identified. Differences between the elderly and younger patients, but greater tolerance of some older individuals cannot be ruled out. As with other SSRIs, flutamide has been associated with cases of clinically significant hyponatremia (see Hyponatremia under Precautions).
A specific cutaneous involvement of patients who are taking or have recently taken fluoxetine and might ingest excessive quantities of a toxic antidepressant in such a case, accumulation of the patient and therefore the anticholinergic and aminergic antidepressants. Such a patient can be made to require an additional amount of fluoxetine for the duration of one month of fluoxetine treatment. (See Other Antidepressants and Precipitants).

As with other antidepressants, the anticholinergic effect may be delayed up to 4 weeks of treatment or longer.

As with many other medications, a loss of sexual function should be avoided by patients who experience sexual dysfunction. The incidence of antidepressant-induced sexual dysfunction is increased in patients who are on fluoxetine. (See Other Antidepressants and Precipitants).

If treatment is continued, an antidepressant effect may be seen after 1-2 weeks of treatment.

Systematic evaluation of fluoxetine has shown that antidepressant efficacy is maintained for periods of up to 52 weeks following 12 weeks of open-label acute treatment (50 mg/day) at a dose of 20 mg/day (see Clinical Trials under Fluoxetine).

Since there are no systemic studies that answer the question of how long to continue treatment with fluoxetine, it is a clinical condition and can only be assessed for the elderly (see Geriatric Use).

The fluoxetine dose should be reduced in elderly patients by 30% as compared to younger patients. In geriatric patients, the fluoxetine dose should be reduced as compared to younger patients. In geriatric patients, the fluoxetine dose should be reduced as compared to younger patients. In geriatric patients, the fluoxetine dose should be reduced as compared to younger patients. In geriatric patients, the fluoxetine dose should be reduced as compared to younger patients. In geriatric patients, the fluoxetine dose should be reduced as compared to younger patients. In geriatric patients, the fluoxetine dose should be reduced as compared to younger patients.

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**Skin and Appendages**

- Sweating
- Nail
- Pruritus

**Special Sensations**

- Abnormal vision

**Depression, OCD, and Bulimia combined (N=108)**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia (1%)</td>
<td></td>
</tr>
<tr>
<td>Nervousness (1%)</td>
<td></td>
</tr>
<tr>
<td>Rash (1%)</td>
<td></td>
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</tbody>
</table>

**Depression (N=299)**

- Anxiety (2%)
- Insomnia (2%)

**OCD (N=266)**

- Anxiety (2%)
- Insomnia (2%)

**Bulimia (N=65)**

- Anxiety (2%)
- Insomnia (2%)

**Table 5**

<table>
<thead>
<tr>
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</tr>
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<tbody>
<tr>
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<td></td>
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</tbody>
</table>

**Other Events Observed in All US Clinical Trials—Following is a list of all treatment-emergent adverse events reported at any time in individuals taking fluoxetine in US clinical trials (10,792 patients) except (1) those listed in the body or footnotes of Tables 1 or 2 above or elsewhere in labeling, (2) those for which the CFS is very rare, (3) those for which a causal relationship to fluoxetine 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.**

**Table 6**

<table>
<thead>
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<tbody>
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**Other Events Observed in All US Clinical Trials**

- Nausea
- Vomiting
- Influenza-like symptoms
- Rash
- Diarrhea
- Abnormal vision
- Abnormal vision

**Endocrine System**

- Hypothyroidism
- Hyperthyroidism

**Skeletal System**

- Arthritis
- Joint pain

**Neuromuscular System**

- Fatigue
- Myalgia
- Myopathy
- Peripheral neuropathy

**Nervous System**

- Dizziness
- Headache
- Seizure

**Cardiovascular System**

- Blood pressure increase
- Bradycardia

**Respiratory System**

- Cough
- Pharyngitis
- Sinusitis

**Gastrointestinal System**

- Abdominal pain
- Diarrhea
- Constipation

**Skin and Appendages**

- Acne
- Adiposis

**Physical and Psychological Dependence**

- Nausea
- Vomiting

**Overdosage**

- Human Experience
- Experimental
- Animal Experience

**Drug Abuse and Dependence**

- Physical Dependence
- Psychological Dependence

**Management of Overdose**

- Treatment should consist of general measures employed in the management of overdoses with any antidepressant.
Digestive System—Infrequent increased appetite, nausea and vomiting, infrequent sphincter stools, constipation, irritable bowel, eructation, anorexia, phagia, gastritis, constipation, gaseous, gas, intestinal obstruction, hepatic, generalized hyperammonemia, pernicious anemia, alkaline phosphatase increased, bilirubin increased, creatine phosphokinase increased, hypercholesteremia, hyperuricemia, hyperglycemia, cholesterol, triglyceride.

Musculoskeletal System—Infrequent arthritis, bone pain, back, leg cramps, tendinitis, rare arthralgia, chronic myopathy, myositis, myopathy, osteoporoisis, rheumatoid arthritis.

Nervous System—Infrequent agitation, irritability, confusion, emotional lability, sleep disorder, infrequent anxiety, gait disturbance, headache, dizziness, tremor, tinnitus, disturbance of consciousness, vision loss, paresthesia, disturbance of consciousness, tremor, vertigo.

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