

PROZAC[®]
FLUOXETINE CAPSULES, USP
FLUOXETINE ORAL SOLUTION, USP

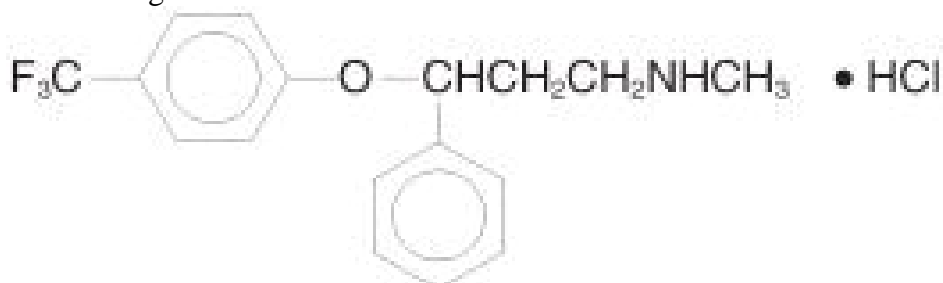
WARNING

Suicidality in Children and Adolescents — Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Prozac or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Prozac is approved for use in pediatric patients with MDD and obsessive compulsive disorder (OCD). (See WARNINGS and PRECAUTIONS, Pediatric Use.)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

Prozac[®] (fluoxetine capsules, USP and fluoxetine oral solution, USP) is a psychotropic drug for oral administration. It is also marketed for the treatment of premenstrual dysphoric disorder (Sarafem[®], fluoxetine hydrochloride). It is designated (\pm)-N-methyl-3-phenyl-3-[(α,α,α -trifluoro-*p*-tolyl)oxy]propylamine hydrochloride and has the empirical formula of C₁₇H₁₈F₃NO • HCl. Its molecular weight is 345.79. The structural formula is:



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

Each Pulvule[®] contains fluoxetine hydrochloride equivalent to 10 mg (32.3 μ mol), 20 mg (64.7 μ mol), or 40 mg (129.3 μ mol) of fluoxetine. The Pulvules also contain starch, gelatin, silicone, titanium dioxide, iron oxide, and other inactive ingredients. The 10- and 20-mg Pulvules also contain FD&C Blue No. 1, and the 40-mg Pulvule also contains FD&C Blue No. 1 and FD&C Yellow No. 6.

The oral solution contains fluoxetine hydrochloride equivalent to 20 mg/5 mL (64.7 μmol) of fluoxetine. It also contains alcohol 0.23%, benzoic acid, flavoring agent, glycerin, purified water, and sucrose.

Prozac Weekly™ capsules, a delayed-release formulation, contain enteric-coated pellets of fluoxetine hydrochloride equivalent to 90 mg (291 μmol) of fluoxetine. The capsules also contain D&C Yellow No. 10, FD&C Blue No. 2, gelatin, hypromellose, hydroxypropyl methylcellulose acetate succinate, sodium lauryl sulfate, sucrose, sugar spheres, talc, titanium dioxide, triethyl citrate, and other inactive ingredients.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The antidepressant, antiobsessive compulsive, and antibulimic actions of fluoxetine are presumed to be linked to its inhibition of CNS neuronal uptake of serotonin. Studies at clinically relevant doses in man have demonstrated that fluoxetine blocks the uptake of serotonin into human platelets. Studies in animals also suggest that fluoxetine is a much more potent uptake inhibitor of serotonin than of norepinephrine.

Antagonism of muscarinic, histaminergic, and α_1 -adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects of classical tricyclic antidepressant (TCA) drugs. Fluoxetine binds to these and other membrane receptors from brain tissue much less potently in vitro than do the tricyclic drugs.

Absorption, Distribution, Metabolism, and Excretion

Systemic bioavailability — 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 Pulvule, oral solution, and Prozac Weekly capsule dosage forms of fluoxetine are bioequivalent. Food does not appear to affect the systemic bioavailability of fluoxetine, although it may delay its absorption by 1 to 2 hours, which is probably not clinically significant. Thus, fluoxetine may be administered with or without food. Prozac Weekly capsules, a delayed-release formulation, contain enteric-coated pellets that resist dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. The enteric coating delays the onset of absorption of fluoxetine 1 to 2 hours relative to the immediate-release formulations.

Protein binding — Over the concentration range from 200 to 1000 ng/mL, approximately 94.5% of fluoxetine is bound in vitro to human serum proteins, including albumin and α_1 -glycoprotein. The interaction between fluoxetine and other highly protein-bound drugs has not been fully evaluated, but may be important (*see* PRECAUTIONS).

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

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

Clinical issues related to metabolism/elimination — The complexity of the metabolism of fluoxetine has several consequences that may potentially affect fluoxetine's clinical use.

Variability in metabolism — A subset (about 7%) of the population has reduced activity of the drug metabolizing enzyme cytochrome P450 2D6 (CYP2D6). Such individuals are referred to as “poor metabolizers” of drugs such as debrisoquin, dextromethorphan, and the TCAs. In a study involving labeled and unlabeled enantiomers administered as a racemate, these individuals metabolized *S*-fluoxetine at a slower rate and thus achieved higher concentrations of *S*-fluoxetine. Consequently, concentrations of *S*-norfluoxetine at steady state were lower. The metabolism of *R*-fluoxetine in these poor metabolizers appears normal. When compared with normal metabolizers, the total sum at steady state of the plasma concentrations of the 4 active enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. Alternative, nonsaturable pathways (non-2D6) also contribute to the metabolism of fluoxetine. This explains how fluoxetine achieves a steady-state concentration rather than increasing without limit.

Because fluoxetine’s metabolism, like that of a number of other compounds including TCAs and other selective serotonin reuptake inhibitors (SSRIs), involves the CYP2D6 system, concomitant therapy with drugs also metabolized by this enzyme system (such as the TCAs) may lead to drug interactions (*see* Drug Interactions *under* PRECAUTIONS).

Accumulation and slow elimination — The relatively slow elimination of fluoxetine (elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration) and its active metabolite, norfluoxetine (elimination half-life of 4 to 16 days after acute and chronic administration), leads to significant accumulation of these active species in chronic use and delayed attainment of steady state, even when a fixed dose is used. After 30 days of dosing at 40 mg/day, plasma concentrations of fluoxetine in the range of 91 to 302 ng/mL and norfluoxetine in the range of 72 to 258 ng/mL have been observed. Plasma concentrations of fluoxetine were higher than those predicted by single-dose studies, because fluoxetine’s metabolism is not proportional to dose. Norfluoxetine, however, appears to have linear pharmacokinetics. Its mean terminal half-life after a single dose was 8.6 days and after multiple dosing was 9.3 days. Steady-state levels after prolonged dosing are similar to levels seen at 4 to 5 weeks.

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

Weekly dosing — Administration of Prozac Weekly once weekly results in increased fluctuation between peak and trough concentrations of fluoxetine and norfluoxetine compared with once-daily dosing [for fluoxetine: 24% (daily) to 164% (weekly) and for norfluoxetine: 17% (daily) to 43% (weekly)]. Plasma concentrations may not necessarily be predictive of clinical response. Peak concentrations from once-weekly doses of Prozac Weekly capsules of fluoxetine are in the range of the average concentration for 20-mg once-daily dosing. Average trough concentrations are 76% lower for fluoxetine and 47% lower for norfluoxetine than the concentrations maintained by 20-mg once-daily dosing. Average steady-state concentrations of either once-daily or once-weekly dosing are in relative proportion to the total dose administered. Average steady-state fluoxetine concentrations are approximately 50% lower following the once-weekly regimen compared with the once-daily regimen.

C_{\max} for fluoxetine following the 90-mg dose was approximately 1.7-fold higher than the C_{\max} value for the established 20-mg once-daily regimen following transition the next day to the once-weekly regimen. In contrast, when the first 90-mg once-weekly dose and the last 20-mg once-daily dose were separated by 1 week, C_{\max} values were similar. Also, there was a transient increase in the average steady-state concentrations of fluoxetine observed following transition the next day to the once-weekly regimen. From a pharmacokinetic perspective, it may be better to separate the first 90-mg weekly dose and the last 20-mg once-daily dose by 1 week (*see* DOSAGE AND ADMINISTRATION).

Liver disease — As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of fluoxetine. The elimination half-life of fluoxetine was prolonged in a study of cirrhotic patients, with a mean of 7.6 days compared with the range of 2 to 3 days seen in subjects without liver disease; norfluoxetine elimination was also delayed, with a mean duration of 12 days for cirrhotic patients compared with the range of 7 to 9 days in normal subjects. This suggests that the use of fluoxetine in patients with liver disease must be approached with caution. If fluoxetine is administered to patients with liver disease, a lower or less frequent dose should be used (*see* PRECAUTIONS *and* DOSAGE AND ADMINISTRATION).

Renal disease — In depressed patients on dialysis (N=12), fluoxetine administered as 20 mg once daily for 2 months produced steady-state fluoxetine and norfluoxetine plasma concentrations comparable with those seen in patients with normal renal function. While the possibility exists that renally excreted metabolites of fluoxetine may accumulate to higher levels in patients with severe renal dysfunction, use of a lower or less frequent dose is not routinely necessary in renally impaired patients (*see* Use in Patients with Concomitant Illness *under* PRECAUTIONS *and* DOSAGE AND ADMINISTRATION).

Age

Geriatric pharmacokinetics — The disposition of single doses of fluoxetine in healthy elderly subjects (>65 years of age) did not differ significantly from that in younger normal subjects. However, given the long half-life and nonlinear disposition of 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 for concomitant diseases. The effects of age upon the metabolism of fluoxetine have been investigated in 260 elderly but otherwise healthy depressed patients (≥ 60 years of age) who received 20 mg fluoxetine for 6 weeks. Combined fluoxetine plus norfluoxetine plasma concentrations were 209.3 ± 85.7 ng/mL at the end of 6 weeks. No unusual age-associated pattern of adverse events was observed in those elderly patients.

Pediatric pharmacokinetics (children and adolescents) — Fluoxetine pharmacokinetics were evaluated in 21 pediatric patients (10 children ages 6 to <13, 11 adolescents ages 13 to <18) diagnosed with major depressive disorder or obsessive compulsive disorder (OCD). Fluoxetine 20 mg/day was administered for up to 62 days. The average steady-state concentrations of fluoxetine in these children were 2-fold higher than in adolescents (171 and 86 ng/mL, respectively). The average norfluoxetine steady-state concentrations in these children were 1.5-fold higher than in adolescents (195 and 113 ng/mL, respectively). These differences can be almost entirely explained by differences in weight. No gender-associated difference in fluoxetine pharmacokinetics was observed. Similar ranges of fluoxetine and norfluoxetine plasma concentrations were observed in another study in 94 pediatric patients (ages 8 to <18) diagnosed with major depressive disorder.

Higher average steady-state fluoxetine and norfluoxetine concentrations were observed in children relative to adults; however, these concentrations were within the range of concentrations observed in the adult population. As in adults, fluoxetine and norfluoxetine accumulated extensively following multiple oral dosing; steady-state concentrations were achieved within 3 to 4 weeks of daily dosing.

CLINICAL TRIALS

Major Depressive Disorder

Daily Dosing

Adult — The efficacy of Prozac for the treatment of patients with major depressive disorder (≥ 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 (HAM-D). Prozac was also significantly more effective than placebo on the HAM-D subscores for depressed mood, sleep disturbance, and the anxiety subfactor.

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 (≥ 60 years of age) with major depressive disorder. In these studies, Prozac produced a significantly higher rate of response and remission as defined, respectively, by a 50% decrease in the HAM-D score and a total endpoint HAM-D score of ≤ 8 . Prozac was well tolerated and the rate of treatment discontinuations due to adverse events did not differ between Prozac (12%) and placebo (9%).

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 depressive disorder 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 depressive disorder for 2 weeks or a modified HAMD-17 score of ≥ 14 for 3 weeks) was observed for patients taking Prozac compared with those on placebo.

Pediatric (children and adolescents) — The efficacy of Prozac 20 mg/day for the treatment of major depressive disorder in pediatric outpatients (N=315 randomized; 170 children ages 8 to < 13 , 145 adolescents ages 13 to ≤ 18) has been studied in two 8- to 9-week placebo-controlled clinical trials.

In both studies independently, Prozac produced a statistically significantly greater mean change on the Childhood Depression Rating Scale-Revised (CDRS-R) total score from baseline to endpoint than did placebo.

Subgroup analyses on the CDRS-R total score did not suggest any differential responsiveness on the basis of age or gender.

Weekly dosing for maintenance/continuation treatment

A longer-term study was conducted involving adult outpatients meeting DSM-IV criteria for major depressive disorder who had responded (defined as having a modified HAMD-17 score of ≤ 9 , a CGI-Severity rating of ≤ 2 , and no longer meeting criteria for major depressive disorder) for 3 consecutive weeks at the end of 13 weeks of open-label treatment with Prozac 20 mg once daily. These patients were randomized to double-blind, once-weekly continuation treatment with Prozac Weekly, Prozac 20 mg once daily, or placebo. Prozac Weekly once weekly and Prozac 20 mg once daily demonstrated superior efficacy (having a significantly longer time to relapse of depressive symptoms) compared with placebo for a period of 25 weeks. However, the equivalence of these 2 treatments during continuation therapy has not been established.

Obsessive Compulsive Disorder

Adult — The effectiveness of Prozac for the treatment of obsessive compulsive disorder (OCD) was demonstrated in two 13-week, multicenter, parallel group studies (Studies 1 and 2) of adult outpatients who received fixed Prozac doses of 20, 40, or 60 mg/day (on a once-a-day 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 4 to 6 units on the YBOCS total score, compared with a 1-unit reduction for placebo patients. In Study 2, patients receiving Prozac experienced mean reductions of approximately 4 to 9 units on the YBOCS total score, compared with a 1-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 numerically better responses 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:

Outcome Classification (%) on CGI Improvement Scale for Completers in Pool of Two OCD Studies

Outcome Classification	Placebo	Prozac		
		20 mg	40 mg	60 mg
Worse	8%	0%	0%	0%
No change	64%	41%	33%	29%
Minimally improved	17%	23%	28%	24%
Much improved	8%	28%	27%	28%
Very much improved	3%	8%	12%	19%

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

Pediatric (children and adolescents) — In one 13-week clinical trial in pediatric patients (N=103 randomized; 75 children ages 7 to <13, 28 adolescents ages 13 to <18) with OCD, patients received Prozac 10 mg/day for 2 weeks, followed by 20 mg/day for 2 weeks. The dose was then adjusted in the range of 20 to 60 mg/day on the basis of clinical response and tolerability. Prozac produced a statistically significantly greater mean change from baseline to endpoint than did placebo as measured by the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS).

Subgroup analyses on outcome did not suggest any differential responsiveness on the basis of age or gender.

Bulimia Nervosa

The effectiveness of Prozac for the treatment of bulimia was demonstrated in two 8-week and one 16-week, multicenter, parallel group studies of adult outpatients meeting DSM-III-R criteria for bulimia. Patients in the 8-week studies received either 20 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 median binge-eating and vomiting frequencies 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 number of binge-eating and vomiting episodes per week. The statistically significantly superior effect of 60 mg versus placebo was present as early as Week 1

and persisted throughout each study. The Prozac-related reduction in bulimic episodes appeared to be independent of 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 on median reduction from baseline in frequency of bulimic behaviors at endpoint, ranged from 1 to 2 episodes per week for binge-eating and 2 to 4 episodes per week for vomiting. The size of the effect was related to baseline frequency, with greater reductions seen 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.

In a longer-term trial, 150 patients meeting DSM-IV criteria for bulimia nervosa, purging subtype, who had responded during a single-blind, 8-week acute treatment phase with Prozac 60 mg/day, were randomized to continuation of Prozac 60 mg/day or placebo, for up to 52 weeks of observation for relapse. Response during the single-blind phase was defined by having achieved at least a 50% decrease in vomiting frequency compared with baseline. Relapse during the double-blind phase was defined as a persistent return to baseline vomiting frequency or physician judgment that the patient had relapsed. Patients receiving continued Prozac 60 mg/day experienced a significantly longer time to relapse over the subsequent 52 weeks compared with those receiving placebo.

Panic Disorder

The effectiveness of Prozac in the treatment of panic disorder was demonstrated in 2 double-blind, randomized, placebo-controlled, multicenter studies of adult outpatients who had a primary diagnosis of panic disorder (DSM-IV), with or without agoraphobia.

Study 1 (N=180 randomized) was a 12-week flexible-dose study. Prozac was initiated at 10 mg/day for the first week, after which patients were dosed in the range of 20 to 60 mg/day on the basis of clinical response and tolerability. A statistically significantly greater percentage of Prozac-treated patients were free from panic attacks at endpoint than placebo-treated patients, 42% versus 28%, respectively.

Study 2 (N=214 randomized) was a 12-week flexible-dose study. Prozac was initiated at 10 mg/day for the first week, after which patients were dosed in a range of 20 to 60 mg/day on the basis of clinical response and tolerability. A statistically significantly greater percentage of Prozac-treated patients were free from panic attacks at endpoint than placebo-treated patients, 62% versus 44%, respectively.

INDICATIONS AND USAGE

Major Depressive Disorder

Prozac is indicated for the treatment of major depressive disorder.

Adult — The efficacy of Prozac was established in 5- and 6-week trials with depressed adult and geriatric outpatients (≥ 18 years of age) whose diagnoses corresponded most closely to the DSM-III (currently DSM-IV) category of major depressive disorder (*see* CLINICAL TRIALS).

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 in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

The effects of Prozac in hospitalized depressed patients have not been adequately studied.

The efficacy of Prozac 20 mg once daily in maintaining a response in major depressive disorder for up to 38 weeks following 12 weeks of open-label acute treatment (50 weeks total) was demonstrated in a placebo-controlled trial.

The efficacy of Prozac Weekly once weekly in maintaining a response in major depressive disorder has been demonstrated in a placebo-controlled trial for up to 25 weeks following open-label acute treatment of 13 weeks with Prozac 20 mg daily for a total treatment of 38 weeks. However, it is unknown whether or not Prozac Weekly given on a once-weekly basis provides the same level of protection from relapse as that provided by Prozac 20 mg daily (*see CLINICAL TRIALS*).

Pediatric (children and adolescents) — The efficacy of Prozac in children and adolescents was established in two 8- to 9-week placebo-controlled clinical trials in depressed outpatients whose diagnoses corresponded most closely to the DSM-III-R or DSM-IV category of major depressive disorder (*see CLINICAL TRIALS*).

The usefulness of the drug in adult and pediatric patients receiving fluoxetine for extended periods should be reevaluated periodically.

Obsessive Compulsive Disorder

Adult — Prozac is indicated for the treatment of obsessions and compulsions in patients with obsessive compulsive disorder (OCD), as defined in 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 category of OCD (*see CLINICAL TRIALS*).

OCD 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 for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (*see DOSAGE AND ADMINISTRATION*).

Pediatric (children and adolescents) — The efficacy of Prozac in children and adolescents was established in a 13-week, dose titration, clinical trial in patients with OCD, as defined in DSM-IV (*see CLINICAL TRIALS*).

Bulimia Nervosa

Prozac is indicated for the treatment of binge-eating and vomiting 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, i.e., at least 3 bulimic episodes per week for 6 months (*see CLINICAL TRIALS*).

The efficacy of Prozac 60 mg/day in maintaining a response, in patients with bulimia who responded during an 8-week acute treatment phase while taking Prozac 60 mg/day and were then observed for relapse during a period of up to 52 weeks, was demonstrated in a placebo-controlled trial (*see CLINICAL TRIALS*). Nevertheless, 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*).

Panic Disorder

Prozac is indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks, and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.

The efficacy of Prozac was established in two 12-week clinical trials in patients whose diagnoses corresponded to the DSM-IV category of panic disorder (*see* CLINICAL TRIALS).

Panic disorder (DSM-IV) is characterized by recurrent, unexpected panic attacks, i.e., a discrete period of intense fear or discomfort in which 4 or more of the following symptoms develop abruptly and reach a peak within 10 minutes: 1) palpitations, pounding heart, or accelerated heart rate; 2) sweating; 3) trembling or shaking; 4) sensations of shortness of breath or smothering; 5) feeling of choking; 6) chest pain or discomfort; 7) nausea or abdominal distress; 8) feeling dizzy, unsteady, lightheaded, or faint; 9) fear of losing control; 10) fear of dying; 11) paresthesias (numbness or tingling sensations); 12) chills or hot flashes.

The effectiveness of Prozac in long-term use, i.e., for more than 12 weeks, has not been established 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 hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) in patients receiving fluoxetine in combination with a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued fluoxetine and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, Prozac should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI. Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks [perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses (*see* Accumulation and slow elimination *under* CLINICAL PHARMACOLOGY)] should be allowed after stopping Prozac before starting an MAOI.

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

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

WARNINGS

Clinical Worsening and Suicide Risk — Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of

24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

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

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

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

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

consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

It should be noted that Prozac is approved in the pediatric population only for major depressive disorder and obsessive compulsive disorder.

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

Rash and Possibly Allergic Events — In US fluoxetine clinical trials as of May 8, 1995, 7% of 10,782 patients developed various types of rashes and/or urticaria. Among the cases of rash and/or urticaria reported in premarketing clinical trials, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

In premarketing clinical trials, 2 patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but one was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Other patients have had systemic syndromes suggestive of serum sickness.

Since the introduction of Prozac, 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.

Serotonin Syndrome — The development of a potentially life-threatening serotonin syndrome may occur with Prozac treatment, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs which impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia),

neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

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

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

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

Potential Interaction with Thioridazine — In a study of 19 healthy male subjects, which included 6 slow and 13 rapid hydroxylators of debrisoquin, a single 25-mg oral dose of thioridazine produced a 2.4-fold higher C_{max} and a 4.5-fold higher AUC for thioridazine in the slow hydroxylators compared with the rapid hydroxylators. The rate of debrisoquin hydroxylation is felt to depend on the level of CYP2D6 isozyme activity. Thus, this study suggests that drugs which inhibit CYP2D6, such as certain SSRIs, including fluoxetine, will produce elevated plasma levels of thioridazine (*see* PRECAUTIONS).

Thioridazine administration produces a dose-related prolongation of the QT_c interval, which is associated with serious ventricular arrhythmias, such as torsades de pointes-type arrhythmias, and sudden death. This risk is expected to increase with fluoxetine-induced inhibition of thioridazine metabolism (*see* CONTRAINDICATIONS).

PRECAUTIONS

General

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

Anxiety and Insomnia — In US placebo-controlled clinical trials for major depressive disorder, 12% to 16% of patients treated with Prozac and 7% to 9% of patients treated with placebo reported anxiety, nervousness, or insomnia.

In US placebo-controlled clinical trials for OCD, insomnia was reported in 28% of patients treated with Prozac and in 22% of patients treated with placebo. Anxiety was reported in 14% of patients treated with Prozac and in 7% of patients treated with placebo.

In US placebo-controlled clinical trials for bulimia nervosa, insomnia was reported in 33% of patients treated with Prozac 60 mg, and 13% of patients treated with placebo. Anxiety and nervousness were reported, respectively, in 15% and 11% of patients treated with Prozac 60 mg and in 9% and 5% of patients treated with placebo.

Among the most common adverse events associated with discontinuation (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 US placebo-controlled fluoxetine clinical trials were anxiety

(2% in OCD), insomnia (1% in combined indications and 2% in bulimia), and nervousness (1% in major depressive disorder) (*see* Table 3).

Altered Appetite and Weight — Significant weight loss, especially in underweight depressed or bulimic patients may be an undesirable result of treatment with Prozac.

In US placebo-controlled clinical trials for major depressive disorder, 11% of patients treated with Prozac and 2% of patients treated with placebo reported anorexia (decreased appetite). Weight loss was reported in 1.4% of patients treated with Prozac and in 0.5% of patients treated with placebo. However, only rarely have patients discontinued treatment with Prozac because of anorexia or weight loss (*see also* Pediatric Use *under* PRECAUTIONS).

In US placebo-controlled clinical trials for OCD, 17% of patients treated with Prozac and 10% of patients treated with placebo reported anorexia (decreased appetite). One patient discontinued treatment with Prozac because of anorexia (*see also* Pediatric Use *under* PRECAUTIONS).

In US placebo-controlled clinical trials for bulimia nervosa, 8% of patients treated with Prozac 60 mg and 4% of patients treated with placebo reported anorexia (decreased appetite). Patients treated with Prozac 60 mg on average lost 0.45 kg compared with a gain of 0.16 kg by patients treated with placebo in the 16-week double-blind trial. Weight change should be monitored during therapy.

Activation of Mania/Hypomania — In US placebo-controlled clinical trials for major depressive disorder, mania/hypomania was reported in 0.1% of patients treated with Prozac and 0.1% of patients treated with placebo. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed drugs effective in the treatment of major depressive disorder (*see also* Pediatric Use *under* PRECAUTIONS).

In US placebo-controlled clinical trials for OCD, mania/hypomania was reported in 0.8% of patients treated with Prozac and no patients treated with placebo. No patients reported mania/hypomania in US placebo-controlled clinical trials for bulimia. In all US Prozac clinical trials as of May 8, 1995, 0.7% of 10,782 patients reported mania/hypomania (*see also* Pediatric Use *under* PRECAUTIONS).

Hyponatremia — 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 was 129 mmol/L. The observed decreases were not clinically significant.

Seizures — In US placebo-controlled clinical trials for major depressive disorder, convulsions (or events described as possibly having been seizures) were reported in 0.1% of patients treated with Prozac and 0.2% of patients treated with placebo. No patients reported convulsions in US placebo-controlled clinical trials for either OCD or bulimia. In all US Prozac clinical trials as of May 8, 1995, 0.2% of 10,782 patients reported convulsions. The percentage appears to be similar to that associated with other marketed drugs effective in the treatment of major depressive disorder. Prozac should be introduced with care in patients with a history of seizures.

The Long Elimination Half-Lives of Fluoxetine and its Metabolites — Because of the long elimination half-lives of the parent drug and its major active metabolite, changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment (*see* CLINICAL PHARMACOLOGY *and* DOSAGE AND ADMINISTRATION).

Use in Patients with Concomitant Illness — Clinical experience with Prozac in patients with concomitant systemic illness is limited. Caution is advisable in using Prozac in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Fluoxetine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 312 patients who received Prozac in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately 3 beats/min.

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower or less frequent dose should be used in patients with cirrhosis.

Studies in depressed patients on dialysis did not reveal excessive accumulation of fluoxetine or norfluoxetine in plasma (*see* Renal disease *under* CLINICAL PHARMACOLOGY). Use of a lower or less frequent dose for renally impaired patients is not routinely necessary (*see* DOSAGE AND ADMINISTRATION).

In patients with diabetes, Prozac may alter glycemic control. Hypoglycemia has occurred during therapy with Prozac, 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 Prozac is instituted or discontinued.

Interference with Cognitive and Motor Performance — Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

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

Information for Patients

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Prozac and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for Prozac. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

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

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

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

Because Prozac may impair judgment, thinking, or motor skills, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.

Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs, or alcohol.

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

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast-feeding an infant.

Patients should be advised to notify their physician if they develop a rash or hives.

Laboratory Tests

There are no specific laboratory tests recommended.

Drug Interactions

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

Drugs metabolized by CYP2D6 — Approximately 7% of the normal population has a genetic defect that leads to reduced levels of activity of the cytochrome P450 isoenzyme 2D6. Such individuals have been referred to as “poor metabolizers” of drugs such as debrisoquin, dextromethorphan, and TCAs. Many drugs, such as most drugs effective in the treatment of major depressive disorder, including fluoxetine and other selective uptake inhibitors of serotonin,

are metabolized by this isoenzyme; thus, both the pharmacokinetic properties and relative proportion of metabolites are altered in poor metabolizers. However, for fluoxetine and its metabolite, the sum of the plasma concentrations of the 4 active enantiomers is comparable between poor and extensive metabolizers (*see Variability in metabolism under CLINICAL PHARMACOLOGY*).

Fluoxetine, like other agents that are metabolized by CYP2D6, inhibits the activity of this isoenzyme, and thus may make normal metabolizers resemble poor metabolizers. Therapy with medications that are predominantly metabolized by the CYP2D6 system and that have a relatively narrow therapeutic index (see list below) should be initiated at the low end of the dose range if a patient is receiving fluoxetine concurrently or has taken it in the previous 5 weeks. Thus, his/her dosing requirements resemble those of poor metabolizers. If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need for decreased dose of the original medication should be considered. Drugs with a narrow therapeutic index represent the greatest concern (e.g., flecainide, vinblastine, and TCAs). Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, thioridazine should not be administered with fluoxetine or within a minimum of 5 weeks after fluoxetine has been discontinued (*see CONTRAINDICATIONS and WARNINGS*).

Drugs metabolized by CYP3A4 — In an in vivo interaction study involving coadministration of fluoxetine with single doses of terfenadine (a CYP3A4 substrate), no increase in plasma terfenadine concentrations occurred with concomitant fluoxetine. In addition, in vitro studies have shown ketoconazole, a potent inhibitor of CYP3A4 activity, to be at least 100 times more potent than fluoxetine or norfluoxetine as an inhibitor of the metabolism of several substrates for this enzyme, including astemizole, cisapride, and midazolam. These data indicate that fluoxetine's extent of inhibition of CYP3A4 activity is not likely to be of clinical significance.

CNS active drugs — The risk of using 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*).

Anticonvulsants — Patients on stable doses of phenytoin and carbamazepine have developed elevated plasma anticonvulsant concentrations and clinical anticonvulsant toxicity following initiation of concomitant fluoxetine treatment.

Antipsychotics — Some clinical data suggests a possible pharmacodynamic and/or pharmacokinetic interaction between SSRIs and antipsychotics. Elevation of blood levels of haloperidol and clozapine has been observed in patients receiving concomitant fluoxetine. Clinical studies of pimozide with other antidepressants demonstrate an increase in drug interaction or QT_c prolongation. While a specific study with pimozide and fluoxetine has not been conducted, the potential for drug interactions or QT_c prolongation warrants restricting the concurrent use of pimozide and Prozac. Concomitant use of Prozac and pimozide is contraindicated (*see CONTRAINDICATIONS*). For thioridazine, see *CONTRAINDICATIONS and WARNINGS*.

Benzodiazepines — The half-life of concurrently administered diazepam may be prolonged in some patients (*see Accumulation and slow elimination under CLINICAL PHARMACOLOGY*). Coadministration of alprazolam and fluoxetine has resulted in increased alprazolam plasma

concentrations and in further psychomotor performance decrement due to increased alprazolam levels.

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

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

Monoamine oxidase inhibitors — See CONTRAINDICATIONS.

Other drugs effective in the treatment of major depressive disorder — In 2 studies, previously stable plasma levels of imipramine and desipramine have increased greater than 2- to 10-fold when fluoxetine has been administered in combination. This influence may persist for 3 weeks or longer after fluoxetine is discontinued. Thus, the dose of TCA may need to be reduced and plasma TCA concentrations may need to be monitored temporarily when fluoxetine is coadministered or has been recently discontinued (*see* Accumulation and slow elimination *under* CLINICAL PHARMACOLOGY, *and* Drugs metabolized by CYP2D6 *under* Drug Interactions).

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

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

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

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

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

There is no evidence of carcinogenicity or mutagenicity from in vitro or animal studies. Impairment of fertility in adult animals at doses up to 12.5 mg/kg/day (approximately 1.5 times the MRHD on a mg/m² basis) was not observed.

Carcinogenicity — The dietary administration of fluoxetine to rats and mice for 2 years at doses of up to 10 and 12 mg/kg/day, respectively [approximately 1.2 and 0.7 times, respectively, the maximum recommended human dose (MRHD) of 80 mg on a mg/m² basis], produced no evidence of carcinogenicity.

Mutagenicity — Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Impairment of fertility — Two fertility studies conducted in adult rats at doses of up to 7.5 and 12.5 mg/kg/day (approximately 0.9 and 1.5 times the MRHD on a mg/m² basis) indicated that fluoxetine had no adverse effects on fertility (*see* Pediatric Use).

Pregnancy

Pregnancy Category C — In embryo-fetal development studies in rats and rabbits, there was no evidence of teratogenicity following administration of up to 12.5 and 15 mg/kg/day, respectively (1.5 and 3.6 times, respectively, the MRHD of 80 mg on a mg/m² basis) throughout organogenesis. However, in rat reproduction studies, an increase in stillborn pups, a decrease in pup weight, and an increase in pup deaths during the first 7 days postpartum occurred following maternal exposure to 12 mg/kg/day (1.5 times the MRHD on a mg/m² basis) during gestation or 7.5 mg/kg/day (0.9 times the MRHD on a mg/m² basis) during gestation and lactation. There was no evidence of developmental neurotoxicity in the surviving offspring of rats treated with 12 mg/kg/day during gestation. The no-effect dose for rat pup mortality was 5 mg/kg/day (0.6 times the MRHD on a mg/m² basis). Prozac should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects — Neonates exposed to Prozac and other SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (*see* Monoamine oxidase inhibitors *under* CONTRAINDICATIONS). 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).

Labor and Delivery

The effect of Prozac on labor and delivery in humans is unknown. However, because fluoxetine crosses the placenta and because of the possibility that fluoxetine may have adverse effects on the newborn, fluoxetine should be used during labor and delivery only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Because Prozac is excreted in human milk, nursing while on Prozac is not recommended. In one breast-milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng/mL. The

concentration in the mother's plasma was 295.0 ng/mL. No adverse effects on the infant were reported. In another case, an infant nursed by a mother on Prozac developed crying, sleep disturbance, vomiting, and watery stools. The infant's plasma drug levels were 340 ng/mL of fluoxetine and 208 ng/mL of norfluoxetine on the second day of feeding.

Pediatric Use

The efficacy of Prozac for the treatment of major depressive disorder was demonstrated in two 8- to 9-week placebo-controlled clinical trials with 315 pediatric outpatients ages 8 to ≤ 18 (*see CLINICAL TRIALS*).

The efficacy of Prozac for the treatment of OCD was demonstrated in one 13-week placebo-controlled clinical trial with 103 pediatric outpatients ages 7 to <18 (*see CLINICAL TRIALS*).

The safety and effectiveness in pediatric patients <8 years of age in major depressive disorder and <7 years of age in OCD have not been established.

Fluoxetine pharmacokinetics were evaluated in 21 pediatric patients (ages 6 to ≤ 18) with major depressive disorder or OCD (*see Pharmacokinetics under CLINICAL PHARMACOLOGY*).

The acute adverse event profiles observed in the 3 studies (N=418 randomized; 228 fluoxetine-treated, 190 placebo-treated) were generally similar to that observed in adult studies with fluoxetine. The longer-term adverse event profile observed in the 19-week major depressive disorder study (N=219 randomized; 109 fluoxetine-treated, 110 placebo-treated) was also similar to that observed in adult trials with fluoxetine (*see ADVERSE REACTIONS*).

Manic reaction, including mania and hypomania, was reported in 6 (1 mania, 5 hypomania) out of 228 (2.6%) fluoxetine-treated patients and in 0 out of 190 (0%) placebo-treated patients. Mania/hypomania led to the discontinuation of 4 (1.8%) fluoxetine-treated patients from the acute phases of the 3 studies combined. Consequently, regular monitoring for the occurrence of mania/hypomania is recommended.

As with other SSRIs, decreased weight gain has been observed in association with the use of fluoxetine in children and adolescent patients. After 19 weeks of treatment in a clinical trial, pediatric subjects treated with fluoxetine gained an average of 1.1 cm less in height ($p=0.004$) and 1.1 kg less in weight ($p=0.008$) than subjects treated with placebo. In addition, fluoxetine treatment was associated with a decrease in alkaline phosphatase levels. The safety of fluoxetine treatment for pediatric patients has not been systematically assessed for chronic treatment longer than several months in duration. In particular, there are no studies that directly evaluate the longer-term effects of fluoxetine on the growth, development, and maturation of children and adolescent patients. Therefore, height and weight should be monitored periodically in pediatric patients receiving fluoxetine.

(*See WARNINGS, Clinical Worsening and Suicide Risk.*)

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

In a study in which fluoxetine (3, 10, or 30 mg/kg) was orally administered to young rats from weaning (Postnatal Day 21) through adulthood (Day 90), male and female sexual development was delayed at all doses, and growth (body weight gain, femur length) was decreased during the dosing period in animals receiving the highest dose. At the end of the treatment period, serum levels of creatine kinase (marker of muscle damage) were increased at the intermediate and high doses, and abnormal muscle and reproductive organ histopathology (skeletal muscle degeneration and necrosis, testicular degeneration and necrosis, epididymal vacuolation and

hypospermia) was observed at the high dose. When animals were evaluated after a recovery period (up to 11 weeks after cessation of dosing), neurobehavioral abnormalities (decreased reactivity at all doses and learning deficit at the high dose) and reproductive functional impairment (decreased mating at all doses and impaired fertility at the high dose) were seen; in addition, testicular and epididymal microscopic lesions and decreased sperm concentrations were found in the high dose group, indicating that the reproductive organ effects seen at the end of treatment were irreversible. The reversibility of fluoxetine-induced muscle damage was not assessed. Adverse effects similar to those observed in rats treated with fluoxetine during the juvenile period have not been reported after administration of fluoxetine to adult animals. Plasma exposures (AUC) to fluoxetine in juvenile rats receiving the low, intermediate, and high dose in this study were approximately 0.1-0.2, 1-2, and 5-10 times, respectively, the average exposure in pediatric patients receiving the maximum recommended dose (MRD) of 20 mg/day. Rat exposures to the major metabolite, norfluoxetine, were approximately 0.3-0.8, 1-8, and 3-20 times, respectively, pediatric exposure at the MRD.

A specific effect of fluoxetine on bone development has been reported in mice treated with fluoxetine during the juvenile period. When mice were treated with fluoxetine (5 or 20 mg/kg, intraperitoneal) for 4 weeks starting at 4 weeks of age, bone formation was reduced resulting in decreased bone mineral content and density. These doses did not affect overall growth (body weight gain or femoral length). The doses administered to juvenile mice in this study are approximately 0.5 and 2 times the MRD for pediatric patients on a body surface area (mg/m²) basis.

In another mouse study, administration of fluoxetine (10 mg/kg intraperitoneal) during early postnatal development (Postnatal Days 4 to 21) produced abnormal emotional behaviors (decreased exploratory behavior in elevated plus-maze, increased shock avoidance latency) in adulthood (12 weeks of age). The dose used in this study is approximately equal to the pediatric MRD on a mg/m² basis. Because of the early dosing period in this study, the significance of these findings to the approved pediatric use in humans is uncertain.

Prozac is approved for use in pediatric patients with MDD and OCD (*see* BOX WARNING and WARNINGS, Clinical Worsening and Suicide Risk). Anyone considering the use of Prozac in a child or adolescent must balance the potential risks with the clinical need.

Geriatric Use

US fluoxetine clinical trials as of May 8, 1995 (10,782 patients) included 687 patients \geq 65 years of age and 93 patients \geq 75 years of age. The efficacy in geriatric patients has been established (*see* CLINICAL TRIALS). For pharmacokinetic information in geriatric patients, see Age under CLINICAL PHARMACOLOGY. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with other SSRIs, fluoxetine has been associated with cases of clinically significant hyponatremia in elderly patients (*see* Hyponatremia under PRECAUTIONS).

ADVERSE REACTIONS

Multiple doses of Prozac had been administered to 10,782 patients with various diagnoses in US clinical trials as of May 8, 1995. In addition, there have been 425 patients administered Prozac in panic clinical trials. Adverse events were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without

first grouping similar types of events into a limited (i.e., reduced) number of standardized event categories.

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

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

Incidence in major depressive disorder, OCD, bulimia, and panic disorder placebo-controlled clinical trials (excluding data from extensions of trials) — Table 1 enumerates 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 1 of the indications) for the treatment of major depressive disorder, OCD, and bulimia in US controlled clinical trials and panic disorder in US plus non-US controlled 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 major depressive disorder, OCD, and bulimia controlled clinical trials and US plus non-US panic disorder controlled clinical trials. Table 2 provides combined data for the pool of studies that are provided separately by indication in Table 1.

Table 1: Most Common Treatment-Emergent Adverse Events: Incidence in Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Placebo-Controlled Clinical Trials¹

Body System/ Adverse Event	Percentage of Patients Reporting Event							
	Major Depressive Disorder		OCD		Bulimia		Panic Disorder	
	Prozac (N=1728)	Placebo (N=975)	Prozac (N=266)	Placebo (N=89)	Prozac (N=450)	Placebo (N=267)	Prozac (N=425)	Placebo (N=342)
Body as a Whole								
Asthenia	9	5	15	11	21	9	7	7
Flu syndrome	3	4	10	7	8	3	5	5
Cardiovascular System								
Vasodilatation	3	2	5	--	2	1	1	--
Digestive System								
Nausea	21	9	26	13	29	11	12	7
Diarrhea	12	8	18	13	8	6	9	4
Anorexia	11	2	17	10	8	4	4	1
Dry mouth	10	7	12	3	9	6	4	4
Dyspepsia	7	5	10	4	10	6	6	2
Nervous System								
Insomnia	16	9	28	22	33	13	10	7
Anxiety	12	7	14	7	15	9	6	2

Nervousness	14	9	14	15	11	5	8	6
Somnolence	13	6	17	7	13	5	5	2
Tremor	10	3	9	1	13	1	3	1
Libido decreased	3	--	11	2	5	1	1	2
Abnormal dreams	1	1	5	2	5	3	1	1
Respiratory System								
Pharyngitis	3	3	11	9	10	5	3	3
Sinusitis	1	4	5	2	6	4	2	3
Yawn	--	--	7	--	11	--	1	--
Skin and Appendages								
Sweating	8	3	7	--	8	3	2	2
Rash	4	3	6	3	4	4	2	2
Urogenital System								
Impotence ²	2	--	--	--	7	--	1	--
Abnormal ejaculation ²	--	--	7	--	7	--	2	1

¹ Includes US data for major depressive disorder, OCD, bulimia, and panic disorder clinical trials, plus non-US data for panic disorder clinical trials.

² Denominator used was for males only (N=690 Prozac major depressive disorder; N=410 placebo major depressive disorder; N=116 Prozac OCD; N=43 placebo OCD; N=14 Prozac bulimia; N=1 placebo bulimia; N=162 Prozac panic; N=121 placebo panic).

-- Incidence less than 1%.

Table 2: Treatment-Emergent Adverse Events: Incidence in Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Placebo-Controlled Clinical Trials¹

Body System/ Adverse Event ²	Percentage of Patients Reporting Event Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Combined	
	Prozac (N=2869)	Placebo (N=1673)
Body as a Whole		
Headache	21	19
Asthenia	11	6
Flu syndrome	5	4
Fever	2	1
Cardiovascular System		
Vasodilatation	2	1
Digestive System		
Nausea	22	9
Diarrhea	11	7
Anorexia	10	3
Dry mouth	9	6
Dyspepsia	8	4
Constipation	5	4
Flatulence	3	2
Vomiting	3	2

Metabolic and Nutritional Disorders		
Weight loss	2	1
Nervous System		
Insomnia	19	10
Nervousness	13	8
Anxiety	12	6
Somnolence	12	5
Dizziness	9	6
Tremor	9	2
Libido decreased	4	1
Thinking abnormal	2	1
Respiratory System		
Yawn	3	--
Skin and Appendages		
Sweating	7	3
Rash	4	3
Pruritus	3	2
Special Senses		
Abnormal vision	2	1

¹ Includes US data for major depressive disorder, OCD, bulimia, and panic disorder clinical trials, plus non-US data for panic disorder clinical trials.

² Included are events reported by at least 2% of patients taking Prozac, except the following events, which had an incidence on placebo \geq Prozac (major depressive disorder, OCD, bulimia, and panic disorder combined): abdominal pain, abnormal dreams, accidental injury, back pain, cough increased, major depressive disorder (includes suicidal thoughts), dysmenorrhea, infection, myalgia, pain, paresthesia, pharyngitis, rhinitis, sinusitis.

-- Incidence less than 1%.

Associated with discontinuation in major depressive disorder, OCD, bulimia, and panic disorder placebo-controlled clinical trials (excluding data from extensions of trials) — 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 major depressive disorder, OCD, bulimia, and panic disorder clinical trials, plus non-US panic disorder clinical trials.

Table 3: Most Common Adverse Events Associated with Discontinuation in Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Placebo-Controlled Clinical Trials¹

Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Combined (N=1533)	Major Depressive Disorder (N=392)	OCD (N=266)	Bulimia (N=450)	Panic Disorder (N=425)
Anxiety (1%)	--	Anxiety (2%)	--	Anxiety (2%)
--	--	--	Insomnia (2%)	--
--	Nervousness (1%)	--	--	Nervousness (1%)

--	--	Rash (1%)	--	--
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¹ Includes US major depressive disorder, OCD, bulimia, and panic disorder clinical trials, plus non-US panic disorder clinical trials.

Other adverse events in pediatric patients (children and adolescents) — Treatment-emergent adverse events were collected in 322 pediatric patients (180 fluoxetine-treated, 142 placebo-treated). The overall profile of adverse events was generally similar to that seen in adult studies, as shown in Tables 1 and 2. However, the following adverse events (excluding those which appear in the body or footnotes of Tables 1 and 2 and those for which the COSTART terms were uninformative or misleading) were reported at an incidence of at least 2% for fluoxetine and greater than placebo: thirst, hyperkinesia, agitation, personality disorder, epistaxis, urinary frequency, and menorrhagia.

The most common adverse event (incidence at least 1% for fluoxetine and greater than placebo) associated with discontinuation in 3 pediatric placebo-controlled trials (N=418 randomized; 228 fluoxetine-treated; 190 placebo-treated) was mania/hypomania (1.8% for fluoxetine-treated, 0% for placebo-treated). In these clinical trials, only a primary event associated with discontinuation was collected.

Events observed in Prozac Weekly clinical trials — Treatment-emergent adverse events in clinical trials with Prozac Weekly were similar to the adverse events reported by patients in clinical trials with Prozac daily. In a placebo-controlled clinical trial, more patients taking Prozac Weekly reported diarrhea than patients taking placebo (10% versus 3%, respectively) or taking Prozac 20 mg daily (10% versus 5%, respectively).

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 US major depressive disorder, 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.

Other Events Observed in Clinical Trials

Following is a list of all treatment-emergent adverse events reported at anytime by individuals taking fluoxetine in US clinical trials as of May 8, 1995 (10,782 patients) except (1) those listed in the body or footnotes of Tables 1 or 2 above or elsewhere in labeling; (2) those for which the COSTART terms were uninformative or misleading; (3) those events for which a causal relationship to 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 classified within body system categories using the following definitions: frequent adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in less than 1/1000 patients.

Body as a Whole — *Frequent*: chest pain, chills; *Infrequent*: chills and fever, face edema, intentional overdose, malaise, pelvic pain, suicide attempt; *Rare*: acute abdominal syndrome, hypothermia, intentional injury, neuroleptic malignant syndrome¹, photosensitivity reaction.

Cardiovascular System — *Frequent*: hemorrhage, hypertension, palpitation; *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 disorder², 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*: abortion³, albuminuria, amenorrhea³, anorgasmia, breast enlargement, breast pain, cystitis, dysuria, female lactation³, fibrocystic breast³, hematuria, leukorrhea³, menorrhagia³, metrorrhagia³, nocturia, polyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage³; *Rare*: breast engorgement, glycosuria, hypomenorrhea³, kidney pain, oliguria, priapism³, uterine hemorrhage³, uterine fibroids enlarged³.

¹ Neuroleptic malignant syndrome is the COSTART term which best captures serotonin syndrome.

² Personality disorder is the COSTART term for designating nonaggressive objectionable behavior.

³ Adjusted for gender.

Postintroduction Reports

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 its most severe form, 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 behaviors.

DRUG ABUSE AND DEPENDENCE

Controlled substance class — Prozac is not a controlled substance.

Physical and psychological dependence — Prozac has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. While the premarketing clinical experience with Prozac did not reveal any tendency for a withdrawal syndrome or any drug seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of Prozac (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

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

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

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

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

Animal Experience

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

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

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

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

Management of Overdose

Treatment should consist of those general measures employed in the management of overdosage with any drug effective in the treatment of major depressive disorder.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for fluoxetine are known.

A specific caution involves patients who are taking or have recently taken fluoxetine and might ingest excessive quantities of a TCA. In such a case, accumulation of the parent tricyclic and/or an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (*see* Other drugs effective in the treatment of major depressive disorder *under* PRECAUTIONS).

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

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

DOSAGE AND ADMINISTRATION

Major Depressive Disorder

Initial Treatment

Adult — In controlled trials used to support the efficacy of fluoxetine, patients were administered morning doses ranging from 20 to 80 mg/day. Studies comparing fluoxetine 20, 40, and 60 mg/day to placebo indicate that 20 mg/day is sufficient to obtain a satisfactory response in major depressive disorder in most cases. Consequently, a dose of 20 mg/day, administered in the morning, is recommended as the initial dose.

A dose increase may be considered after several weeks if insufficient clinical improvement is observed. Doses above 20 mg/day may be administered on a once-a-day (morning) or BID schedule (i.e., morning and noon) and should not exceed a maximum dose of 80 mg/day.

Pediatric (children and adolescents) — In the short-term (8 to 9 week) controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of major depressive disorder, patients were administered fluoxetine doses of 10 to 20 mg/day (*see* CLINICAL TRIALS). Treatment should be initiated with a dose of 10 or 20 mg/day. After 1 week at 10 mg/day, the dose should be increased to 20 mg/day.

However, due to higher plasma levels in lower weight children, the starting and target dose in this group may be 10 mg/day. A dose increase to 20 mg/day may be considered after several weeks if insufficient clinical improvement is observed.

All patients — As with other drugs effective in the treatment of major depressive disorder, the full effect may be delayed until 4 weeks of treatment or longer.

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

Maintenance/Continuation/Extended Treatment

It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Whether the dose needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Daily Dosing

Systematic evaluation of Prozac in adult patients has shown that its efficacy in major depressive disorder is maintained for periods of up to 38 weeks following 12 weeks of open-label acute treatment (50 weeks total) at a dose of 20 mg/day (*see* CLINICAL TRIALS).

Weekly Dosing

Systematic evaluation of Prozac Weekly in adult patients has shown that its efficacy in major depressive disorder is maintained for periods of up to 25 weeks with once-weekly dosing following 13 weeks of open-label treatment with Prozac 20 mg once daily. However, therapeutic equivalence of Prozac Weekly given on a once-weekly basis with Prozac 20 mg given daily for delaying time to relapse has not been established (*see* CLINICAL TRIALS).

Weekly dosing with Prozac Weekly capsules is recommended to be initiated 7 days after the last daily dose of Prozac 20 mg (*see* Weekly dosing *under* CLINICAL PHARMACOLOGY).

If satisfactory response is not maintained with Prozac Weekly, consider reestablishing a daily dosing regimen (*see* CLINICAL TRIALS).

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* Other drugs effective in the treatment of major depressive disorder *under* PRECAUTIONS, Drug Interactions).

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

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

Obsessive Compulsive Disorder

Initial Treatment

Adult — In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of OCD, patients were administered fixed daily doses of 20, 40, or 60 mg of fluoxetine or placebo (*see* CLINICAL TRIALS). In 1 of these studies, no dose-response relationship for effectiveness was demonstrated. Consequently, a dose of 20 mg/day, administered in the morning, is recommended as the initial dose. Since there was a suggestion of a possible dose-response relationship for effectiveness in the second study, a dose increase may be considered after several weeks if insufficient clinical improvement is observed. The full therapeutic effect may be delayed until 5 weeks of treatment or longer.

Doses above 20 mg/day may be administered on a once-a-day (i.e., morning) or BID schedule (i.e., morning and noon). A dose range of 20 to 60 mg/day is recommended; however, doses of up to 80 mg/day have been well tolerated in open studies of OCD. The maximum fluoxetine dose should not exceed 80 mg/day.

Pediatric (children and adolescents) — In the controlled clinical trial of fluoxetine supporting its effectiveness in the treatment of OCD, patients were administered fluoxetine doses in the range of 10 to 60 mg/day (*see* CLINICAL TRIALS).

In adolescents and higher weight children, treatment should be initiated with a dose of 10 mg/day. After 2 weeks, the dose should be increased to 20 mg/day. Additional dose increases

may be considered after several more weeks if insufficient clinical improvement is observed. A dose range of 20 to 60 mg/day is recommended.

In lower weight children, treatment should be initiated with a dose of 10 mg/day. Additional dose increases may be considered after several more weeks if insufficient clinical improvement is observed. A dose range of 20 to 30 mg/day is recommended. Experience with daily doses greater than 20 mg is very minimal, and there is no experience with doses greater than 60 mg.

All patients — As with the use of Prozac in the treatment of major depressive disorder, a lower or less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent dosage should also be considered for the elderly (*see Geriatric Use under PRECAUTIONS*), and for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely necessary (*see Liver disease and Renal disease under CLINICAL PHARMACOLOGY, and Use in Patients with Concomitant Illness under PRECAUTIONS*).

Maintenance/Continuation Treatment

While there are no systematic studies that answer the question of how long to continue Prozac, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of Prozac after 13 weeks has not been documented in controlled trials, adult patients have been continued in therapy under double-blind conditions for up to an additional 6 months without loss of benefit. However, dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for treatment.

Bulimia Nervosa

Initial Treatment

In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of bulimia nervosa, patients were administered fixed daily fluoxetine doses of 20 or 60 mg, or placebo (*see CLINICAL TRIALS*). Only the 60-mg dose was statistically significantly superior to placebo in reducing the frequency of binge-eating and vomiting. Consequently, the recommended dose is 60 mg/day, administered in the morning. For some patients it may be advisable to titrate up to this target dose over several days. Fluoxetine doses above 60 mg/day have not been systematically studied in patients with bulimia.

As with the use of Prozac in the treatment of major depressive disorder and OCD, a lower or less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent dosage should also be considered for the elderly (*see Geriatric Use under PRECAUTIONS*), and for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely necessary (*see Liver disease and Renal disease under CLINICAL PHARMACOLOGY, and Use in Patients with Concomitant Illness under PRECAUTIONS*).

Maintenance/Continuation Treatment

Systematic evaluation of continuing Prozac 60 mg/day for periods of up to 52 weeks in patients with bulimia who have responded while taking Prozac 60 mg/day during an 8-week acute treatment phase has demonstrated a benefit of such maintenance treatment (*see CLINICAL TRIALS*). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment.

Panic Disorder

Initial Treatment

In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of panic disorder, patients were administered fluoxetine doses in the range of 10 to 60 mg/day (*see* CLINICAL TRIALS). Treatment should be initiated with a dose of 10 mg/day. After 1 week, the dose should be increased to 20 mg/day. The most frequently administered dose in the 2 flexible-dose clinical trials was 20 mg/day.

A dose increase may be considered after several weeks if no clinical improvement is observed. Fluoxetine doses above 60 mg/day have not been systematically evaluated in patients with panic disorder.

As with the use of Prozac in other indications, a lower or less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent dosage should also be considered for the elderly (*see* Geriatric Use *under* PRECAUTIONS), and for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely necessary (*see* Liver disease *and* Renal disease *under* CLINICAL PHARMACOLOGY, *and* Use in Patients with Concomitant Illness *under* PRECAUTIONS).

Maintenance/Continuation Treatment

While there are no systematic studies that answer the question of how long to continue Prozac, panic disorder is a chronic condition and it is reasonable to consider continuation for a responding patient. Nevertheless, patients should be periodically reassessed to determine the need for continued treatment.

Special Populations

Treatment of Pregnant Women During the Third Trimester

Neonates exposed to Prozac and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (*see* PRECAUTIONS). When treating pregnant women with 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.

Discontinuation of Treatment with Prozac

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

HOW SUPPLIED

The following products are manufactured by Eli Lilly and Company for Dista Products Company.

Prozac[®] Pulvules[®], USP, are available in:

The 10-mg¹, Pulvule is opaque green and green, imprinted with DISTA 3104 on the cap and Prozac 10 mg on the body:

NDC 0777-3104-02 (PU3104²) - Bottles of 100

The 20-mg¹ Pulvule is an opaque green cap and off-white body, imprinted with DISTA 3105 on the cap and Prozac 20 mg on the body:

NDC 0777-3105-30 (PU3105²) - Bottles of 30
 NDC 0777-3105-02 (PU3105²) - Bottles of 100
 NDC 0777-3105-07 (PU3105²) - Bottles of 2000

The 40-mg¹ Pulvule is an opaque green cap and opaque orange body, imprinted with DISTA 3107 on the cap and Prozac 40 mg on the body:

NDC 0777-3107-30 (PU3107²) - Bottles of 30

The following is manufactured by OSG Norwich Pharmaceuticals, Inc., North Norwich, NY, 13814, for Dista Products Company:

Liquid, Oral Solution is available in:

20 mg¹ per 5 mL with mint flavor:

NDC 0777-5120-58 (MS-5120³) - Bottles of 120 mL

Prozac[®] Weekly[™] Capsules are available in:

The 90-mg¹ capsule is an opaque green cap and clear body containing discretely visible white pellets through the clear body of the capsule, imprinted with Lilly on the cap and 3004 and 90 mg on the body.

NDC 0002-3004-75 (PU3004) - Blister package of 4

¹ Fluoxetine base equivalent.

² Protect from light.

³ Dispense in a tight, light-resistant container.

Store at Controlled Room Temperature, 15° to 30°C (59° to 86°F).

ANIMAL TOXICOLOGY

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

Medication Guide

About Using Antidepressants in Children and Teenagers

What is the most important information I should know if my child is being prescribed an antidepressant?

Parents or guardians need to think about 4 important things when their child is prescribed an antidepressant:

1. There is a risk of suicidal thoughts or actions
2. How to try to prevent suicidal thoughts or actions in your child
3. You should watch for certain signs if your child is taking an antidepressant
4. There are benefits and risks when using antidepressants

1. There is a Risk of Suicidal Thoughts or Actions

Children and teenagers sometimes think about suicide, and many report trying to kill themselves.

Antidepressants increase suicidal thoughts and actions in some children and teenagers. But suicidal thoughts and actions can also be caused by depression, a serious medical condition that is commonly treated with antidepressants. Thinking about killing yourself or trying to kill yourself is called *suicidality* or *being suicidal*.

A large study combined the results of 24 different studies of children and teenagers with depression or other illnesses. In these studies, patients took either a placebo (sugar pill) or an antidepressant for 1 to 4 months. ***No one committed suicide in these studies***, but some patients became suicidal. On sugar pills, 2 out of every 100 became suicidal. On the antidepressants, 4 out of every 100 patients became suicidal.

For some children and teenagers, the risks of suicidal actions may be especially high. These include patients with

- Bipolar illness (sometimes called manic-depressive illness)
- A family history of bipolar illness
- A personal or family history of attempting suicide

If any of these are present, make sure you tell your health care provider before your child takes an antidepressant.

2. How to Try to Prevent Suicidal Thoughts and Actions

To try to prevent suicidal thoughts and actions in your child, pay close attention to changes in her or his moods or actions, especially if the changes occur suddenly. Other important people in your child's life can help by paying attention as well (e.g., your child, brothers and sisters, teachers, and other important people). The changes to look out for are listed in Section 3, on what to watch for.

Whenever an antidepressant is started or its dose is changed, pay close attention to your child.

After starting an antidepressant, your child should generally see his or her health care provider

- Once a week for the first 4 weeks
- Every 2 weeks for the next 4 weeks
- After taking the antidepressant for 12 weeks
- After 12 weeks, follow your health care provider's advice about how often to come back
- More often if problems or questions arise (see Section 3)

You should call your child's health care provider between visits if needed.

3. You Should Watch for Certain Signs If Your Child is Taking an Antidepressant

Contact your child's health care provider ***right away*** if your child exhibits any of the following signs for the first time, or if they seem worse, or worry you, your child, or your child's teacher:

- Thoughts about suicide or dying
- Attempts to commit suicide
- New or worse depression
- New or worse anxiety
- Feeling very agitated or restless
- Panic attacks
- Difficulty sleeping (insomnia)
- New or worse irritability
- Acting aggressive, being angry, or violent
- Acting on dangerous impulses
- An extreme increase in activity and talking
- Other unusual changes in behavior or mood

Never let your child stop taking an antidepressant without first talking to his or her health care provider. Stopping an antidepressant suddenly can cause other symptoms.

4. There are Benefits and Risks When Using Antidepressants

Antidepressants are used to treat depression and other illnesses. Depression and other illnesses can lead to suicide. In some children and teenagers, treatment with an antidepressant increases suicidal thinking or actions. It is important to discuss all the risks of treating depression and also the risks of not treating it. You and your child should discuss all treatment choices with your health care provider, not just the use of antidepressants.

Other side effects can occur with antidepressants (see section below).

Of all the antidepressants, only fluoxetine (Prozac[®]) has been FDA approved to treat pediatric depression.

For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine (Prozac[®]), sertraline (Zoloft[®]), fluvoxamine, and clomipramine (Anafranil[®]).

Your health care provider may suggest other antidepressants based on the past experience of your child or other family members.

Is this all I need to know if my child is being prescribed an antidepressant?

No. This is a warning about the risk for suicidality. Other side effects can occur with antidepressants. Be sure to ask your health care provider to explain all the side effects of the particular drug he or she is prescribing. Also ask about drugs to avoid when taking an antidepressant. Ask your health care provider or pharmacist where to find more information.

Prozac[®] is a registered trademark of Eli Lilly and Company.

Zoloft[®] is a registered trademark of Pfizer Pharmaceuticals.

Anafranil[®] is a registered trademark of Mallinckrodt Inc.

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

Literature revised August 9, 2006

**Eli Lilly and Company
Indianapolis, IN 46285, USA**

www.lilly.com

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PRINTED IN USA

SYMBYAX[®]

(olanzapine and fluoxetine HCl capsules)

WARNING

Suicidality in Children and Adolescents — Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of SYMBYAX or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SYMBYAX is not approved for use in pediatric patients. (*See WARNINGS and PRECAUTIONS, Pediatric Use.*)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis — Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infections (e.g., pneumonia) in nature. SYMBYAX (olanzapine and fluoxetine HCl) is not approved for the treatment of patients with dementia-related psychosis (*see WARNINGS*).

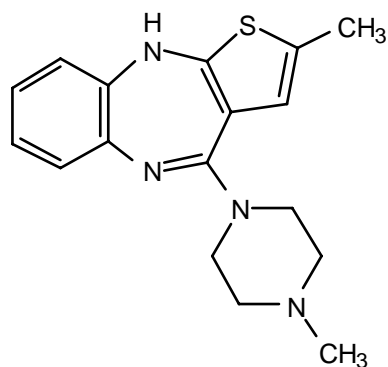
DESCRIPTION

SYMBYAX[®] (olanzapine and fluoxetine HCl capsules) combines 2 psychotropic agents, olanzapine (the active ingredient in Zyprexa[®], and Zyprexa Zydis[®]) and fluoxetine hydrochloride (the active ingredient in Prozac[®], Prozac Weekly[™], and Sarafem[®]).

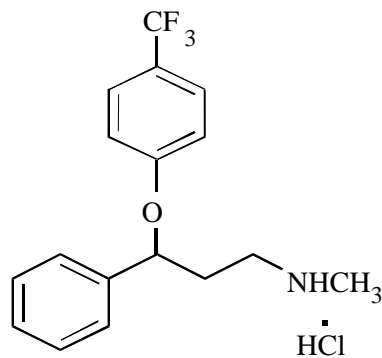
Olanzapine belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-*b*] [1,5]benzodiazepine. The molecular formula is C₁₇H₂₀N₄S, which corresponds to a molecular weight of 312.44.

Fluoxetine hydrochloride is a selective serotonin reuptake inhibitor (SSRI). The chemical designation is (±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-*p*-tolyl)oxy]propylamine hydrochloride. The molecular formula is C₁₇H₁₈F₃NO•HCl, which corresponds to a molecular weight of 345.79.

The chemical structures are:



olanzapine



fluoxetine hydrochloride

Olanzapine is a yellow crystalline solid, which is practically insoluble in water.

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

SYMBYAX capsules are available for oral administration in the following strength combinations:

	6 mg/25 mg	6 mg/50 mg	12 mg/25 mg	12 mg/50 mg
olanzapine equivalent	6	6	12	12
fluoxetine base equivalent	25	50	25	50

Each capsule also contains pregelatinized starch, gelatin, dimethicone, titanium dioxide, sodium lauryl sulfate, edible black ink, red iron oxide, yellow iron oxide, and/or black iron oxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Although the exact mechanism of SYMBYAX is unknown, it has been proposed that the activation of 3 monoaminergic neural systems (serotonin, norepinephrine, and dopamine) is responsible for its enhanced antidepressant effect. This is supported by animal studies in which the olanzapine/fluoxetine combination has been shown to produce synergistic increases in norepinephrine and dopamine release in the prefrontal cortex compared with either component alone, as well as increases in serotonin.

Olanzapine is a psychotropic agent with high affinity binding to the following receptors: serotonin 5HT_{2A/2C} (K_i=4 and 11 nM, respectively), dopamine D₁₋₄ (K_i=11 to 31 nM), muscarinic M₁₋₅ (K_i=1.9 to 25 nM), histamine H₁ (K_i=7 nM), and adrenergic α₁ receptors (K_i=19 nM). Olanzapine binds weakly to GABA_A, BZD, and β-adrenergic receptors (K_i>10 μM). Fluoxetine is an inhibitor of the serotonin transporter and is a weak inhibitor of the norepinephrine and dopamine transporters.

Antagonism at receptors other than dopamine and 5HT₂ with similar receptor affinities may explain some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of muscarinic M₁₋₅ receptors may explain its anticholinergic effects. The antagonism of histamine H₁ receptors by olanzapine may explain the somnolence observed with this drug. The antagonism of α₁-adrenergic receptors by olanzapine may explain the orthostatic hypotension

observed with this drug. Fluoxetine has relatively low affinity for muscarinic, α_1 -adrenergic, and histamine H_1 receptors.

Pharmacokinetics

Fluoxetine (administered as a 60-mg single dose or 60 mg daily for 8 days) caused a small increase in the mean maximum concentration of olanzapine (16%) following a 5-mg dose, an increase in the mean area under the curve (17%) and a small decrease in mean apparent clearance of olanzapine (16%). In another study, a similar decrease in apparent clearance of olanzapine of 14% was observed following olanzapine doses of 6 or 12 mg with concomitant fluoxetine doses of 25 mg or more. The decrease in clearance reflects an increase in bioavailability. The terminal half-life is not affected, and therefore the time to reach steady state should not be altered. The overall steady-state plasma concentrations of olanzapine and fluoxetine when given as the combination in the therapeutic dose ranges were comparable with those typically attained with each of the monotherapies. The small change in olanzapine clearance, observed in both studies, likely reflects the inhibition of a minor metabolic pathway for olanzapine via CYP2D6 by fluoxetine, a potent CYP2D6 inhibitor, and was not deemed clinically significant. Therefore, the pharmacokinetics of the individual components is expected to reasonably characterize the overall pharmacokinetics of the combination.

Absorption and Bioavailability

SYMBYAX — Following a single oral 12-mg/50-mg dose of SYMBYAX, peak plasma concentrations of olanzapine and fluoxetine occur at approximately 4 and 6 hours, respectively. The effect of food on the absorption and bioavailability of SYMBYAX has not been evaluated. The bioavailability of olanzapine given as Zyprexa, and the bioavailability of fluoxetine given as Prozac were not affected by food. It is unlikely that there would be a significant food effect on the bioavailability of SYMBYAX.

Olanzapine — Olanzapine is well absorbed and reaches peak concentration approximately 6 hours following an oral dose. Food does not affect the rate or extent of olanzapine absorption when olanzapine is given as Zyprexa. It is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation.

Fluoxetine — Following a single oral 40-mg dose, peak plasma concentrations of fluoxetine from 15 to 55 ng/mL are observed after 6 to 8 hours. Food does not appear to affect the systemic bioavailability of fluoxetine given as Prozac, although it may delay its absorption by 1 to 2 hours, which is probably not clinically significant.

Distribution

SYMBYAX — The in vitro binding to human plasma proteins of the olanzapine/fluoxetine combination is similar to the binding of the individual components.

Olanzapine — Olanzapine is extensively distributed throughout the body, with a volume of distribution of approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7 to 1100 ng/mL, binding primarily to albumin and α_1 -acid glycoprotein.

Fluoxetine — Over the concentration range from 200 to 1000 ng/mL, approximately 94.5% of fluoxetine is bound in vitro to human serum proteins, including albumin and α_1 -glycoprotein. The interaction between fluoxetine and other highly protein-bound drugs has not been fully evaluated (*see* PRECAUTIONS, Drugs tightly bound to plasma proteins).

Metabolism and Elimination

SYMBYAX — SYMBYAX therapy yielded steady-state concentrations of norfluoxetine similar to those seen with fluoxetine in the therapeutic dose range.

Olanzapine — Olanzapine displays linear pharmacokinetics over the clinical dosing range. Its half-life ranges from 21 to 54 hours (5th to 95th percentile; mean of 30 hr), and apparent plasma clearance ranges from 12 to 47 L/hr (5th to 95th percentile; mean of 25 L/hr). Administration of

olanzapine once daily leads to steady-state concentrations in about 1 week that are approximately twice the concentrations after single doses. Plasma concentrations, half-life, and clearance of olanzapine may vary between individuals on the basis of smoking status, gender, and age (*see* Special Populations).

Following a single oral dose of ¹⁴C-labeled olanzapine, 7% of the dose of olanzapine was recovered in the urine as unchanged drug, indicating that olanzapine is highly metabolized. Approximately 57% and 30% of the dose was recovered in the urine and feces, respectively. In the plasma, olanzapine accounted for only 12% of the AUC for total radioactivity, indicating significant exposure to metabolites. After multiple dosing, the major circulating metabolites were the 10-N-glucuronide, present at steady state at 44% of the concentration of olanzapine, and 4'-N-desmethyl olanzapine, present at steady state at 31% of the concentration of olanzapine. Both metabolites lack pharmacological activity at the concentrations observed.

Direct glucuronidation and CYP450-mediated oxidation are the primary metabolic pathways for olanzapine. In vitro studies suggest that CYP1A2, CYP2D6, and the flavin-containing monooxygenase system are involved in olanzapine oxidation. CYP2D6-mediated oxidation appears to be a minor metabolic pathway in vivo, because the clearance of olanzapine is not reduced in subjects who are deficient in this enzyme.

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

Fluoxetine is extensively metabolized in the liver to its only identified active metabolite, norfluoxetine, via the CYP2D6 pathway. A number of unidentified metabolites exist.

In animal models, *S*-norfluoxetine is a potent and selective inhibitor of serotonin uptake and has activity essentially equivalent to *R*- or *S*-fluoxetine. *R*-norfluoxetine is significantly less potent than the parent drug in the inhibition of serotonin uptake. The primary route of elimination appears to be hepatic metabolism to inactive metabolites excreted by the kidney.

Clinical Issues Related to Metabolism and Elimination — The complexity of the metabolism of fluoxetine has several consequences that may potentially affect the clinical use of SYMBYAX.

Variability in metabolism — A subset (about 7%) of the population has reduced activity of the drug metabolizing enzyme CYP2D6. Such individuals are referred to as “poor metabolizers” of drugs such as debrisoquin, dextromethorphan, and the tricyclic antidepressants (TCAs). In a study involving labeled and unlabeled enantiomers administered as a racemate, these individuals metabolized *S*-fluoxetine at a slower rate and thus achieved higher concentrations of *S*-fluoxetine. Consequently, concentrations of *S*-norfluoxetine at steady state were lower. The metabolism of *R*-fluoxetine in these poor metabolizers appears normal. When compared with normal metabolizers, the total sum at steady state of the plasma concentrations of the 4 enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. Alternative nonsaturable pathways (non-CYP2D6) also contribute to the metabolism of fluoxetine. This explains how fluoxetine achieves a steady-state concentration rather than increasing without limit.

Because the metabolism of fluoxetine, like that of a number of other compounds including TCAs and other selective serotonin antidepressants, involves the CYP2D6 system, concomitant therapy with drugs also metabolized by this enzyme system (such as the TCAs) may lead to drug interactions (*see* PRECAUTIONS, Drug Interactions).

Accumulation and slow elimination — The relatively slow elimination of fluoxetine (elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration) and its active metabolite, norfluoxetine (elimination half-life of 4 to 16 days after acute and chronic administration), leads to significant accumulation of these active species in

chronic use and delayed attainment of steady state, even when a fixed dose is used. After 30 days of dosing at 40 mg/day, plasma concentrations of fluoxetine in the range of 91 to 302 ng/mL and norfluoxetine in the range of 72 to 258 ng/mL have been observed. Plasma concentrations of fluoxetine were higher than those predicted by single-dose studies, because the metabolism of fluoxetine is not proportional to dose. However, norfluoxetine appears to have linear pharmacokinetics. Its mean terminal half-life after a single dose was 8.6 days and after multiple dosing was 9.3 days. Steady-state levels after prolonged dosing are similar to levels seen at 4 to 5 weeks.

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

Special Populations

Geriatric — Based on the individual pharmacokinetic profiles of olanzapine and fluoxetine, the pharmacokinetics of SYMBYAX may be altered in geriatric patients. Caution should be used in dosing the elderly, especially if there are other factors that might additively influence drug metabolism and/or pharmacodynamic sensitivity.

In a study involving 24 healthy subjects, the mean elimination half-life of olanzapine was about 1.5 times greater in elderly subjects (>65 years of age) than in non-elderly subjects (≤65 years of age).

The disposition of single doses of fluoxetine in healthy elderly subjects (>65 years of age) did not differ significantly from that in younger normal subjects. However, given the long half-life and nonlinear disposition of 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 for concomitant diseases. The effects of age upon the metabolism of fluoxetine have been investigated in 260 elderly but otherwise healthy depressed patients (≥60 years of age) who received 20 mg fluoxetine for 6 weeks. Combined fluoxetine plus norfluoxetine plasma concentrations were 209.3 ± 85.7 ng/mL at the end of 6 weeks. No unusual age-associated pattern of adverse events was observed in those elderly patients.

Renal Impairment — The pharmacokinetics of SYMBYAX has not been studied in patients with renal impairment. However, olanzapine and fluoxetine individual pharmacokinetics do not differ significantly in patients with renal impairment. SYMBYAX dosing adjustment based upon renal impairment is not routinely required.

Because olanzapine is highly metabolized before excretion and only 7% of the drug is excreted unchanged, renal dysfunction alone is unlikely to have a major impact on the pharmacokinetics of olanzapine. The pharmacokinetic characteristics of olanzapine were similar in patients with severe renal impairment and normal subjects, indicating that dosage adjustment based upon the degree of renal impairment is not required. In addition, olanzapine is not removed by dialysis. The effect of renal impairment on olanzapine metabolite elimination has not been studied.

In depressed patients on dialysis (N=12), fluoxetine administered as 20 mg once daily for 2 months produced steady-state fluoxetine and norfluoxetine plasma concentrations comparable with those seen in patients with normal renal function. While the possibility exists that renally excreted metabolites of fluoxetine may accumulate to higher levels in patients with severe renal dysfunction, use of a lower or less frequent dose is not routinely necessary in renally impaired patients.

Hepatic Impairment — Based on the individual pharmacokinetic profiles of olanzapine and fluoxetine, the pharmacokinetics of SYMBYAX may be altered in patients with hepatic impairment. The lowest starting dose should be considered for patients with hepatic impairment

(see PRECAUTIONS, Use in Patients with Concomitant Illness and DOSAGE AND ADMINISTRATION, Special Populations).

Although the presence of hepatic impairment may be expected to reduce the clearance of olanzapine, a study of the effect of impaired liver function in subjects (N=6) with clinically significant cirrhosis (Childs-Pugh Classification A and B) revealed little effect on the pharmacokinetics of olanzapine.

As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of fluoxetine. The elimination half-life of fluoxetine was prolonged in a study of cirrhotic patients, with a mean of 7.6 days compared with the range of 2 to 3 days seen in subjects without liver disease; norfluoxetine elimination was also delayed, with a mean duration of 12 days for cirrhotic patients compared with the range of 7 to 9 days in normal subjects.

Gender — Clearance of olanzapine is approximately 30% lower in women than in men. There were, however, no apparent differences between men and women in effectiveness or adverse effects. Dosage modifications based on gender should not be needed.

Smoking Status — Olanzapine clearance is about 40% higher in smokers than in nonsmokers, although dosage modifications are not routinely required.

Race — No SYMBYAX pharmacokinetic study was conducted to investigate the effects of race. Results from an olanzapine cross-study comparison between data obtained in Japan and data obtained in the US suggest that exposure to olanzapine may be about 2-fold greater in the Japanese when equivalent doses are administered. Olanzapine clinical study safety and efficacy data, however, did not suggest clinically significant differences among Caucasian patients, patients of African descent, and a 3rd pooled category including Asian and Hispanic patients. Dosage modifications for race, therefore, are not routinely required.

Combined Effects — The combined effects of age, smoking, and gender could lead to substantial pharmacokinetic differences in populations. The clearance of olanzapine in young smoking males, for example, may be 3 times higher than that in elderly nonsmoking females. SYMBYAX dosing modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of the olanzapine component (see DOSAGE AND ADMINISTRATION, Special Populations).

CLINICAL STUDIES

The efficacy of SYMBYAX for the treatment of depressive episodes associated with bipolar disorder was established in 2 identically designed, 8-week, randomized, double-blind, controlled studies of patients who met Diagnostic and Statistical Manual 4th edition (DSM-IV) criteria for Bipolar I Disorder, Depressed utilizing flexible dosing of SYMBYAX (6/25, 6/50, or 12/50 mg/day), olanzapine (5 to 20 mg/day), and placebo. These studies included patients (≥ 18 years of age) with or without psychotic symptoms and with or without a rapid cycling course.

The primary rating instrument used to assess depressive symptoms in these studies was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale with total scores ranging from 0 to 60. The primary outcome measure of these studies was the change from baseline to endpoint in the MADRS total score. In both studies, SYMBYAX was statistically significantly superior to both olanzapine monotherapy and placebo in reduction of the MADRS total score. The results of the studies are summarized below (Table 1).

**Table 1: MADRS Total Score
Mean Change from Baseline to Endpoint**

	Treatment Group	Baseline Mean	Change to Endpoint Mean¹
Study 1	SYMBYAX (N=40)	30	-16 ^a
	Olanzapine (N=182)	32	-12
	Placebo (N=181)	31	-10
Study 2	SYMBYAX (N=42)	32	-18 ^a
	Olanzapine (N=169)	33	-14
	Placebo (N=174)	31	-9

¹ Negative number denotes improvement from baseline.

^a Statistically significant compared to both olanzapine and placebo.

INDICATIONS AND USAGE

SYMBYAX is indicated for the treatment of depressive episodes associated with bipolar disorder. The efficacy of SYMBYAX was established in 2 identically designed, 8-week, randomized, double-blind clinical studies.

Unlike with unipolar depression, there are no established guidelines for the length of time patients with bipolar disorder experiencing a major depressive episode should be treated with agents containing antidepressant drugs.

The effectiveness of SYMBYAX for maintaining antidepressant response in this patient population beyond 8 weeks has not been established in controlled clinical studies. Physicians who elect to use SYMBYAX for extended periods should periodically reevaluate the benefits and long-term risks of the drug for the individual patient.

CONTRAINDICATIONS

Hypersensitivity — SYMBYAX is contraindicated in patients with a known hypersensitivity to the product or any component of the product.

Monoamine Oxidase Inhibitors (MAOI) — There have been reports of serious, sometimes fatal reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) in patients receiving fluoxetine in combination with an MAOI, and in patients who have recently discontinued fluoxetine and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, SYMBYAX should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI. Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks [perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses (*see* CLINICAL PHARMACOLOGY, Accumulation and slow elimination)] should be allowed after stopping SYMBYAX before starting an MAOI.

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

Thioridazine — Thioridazine should not be administered with SYMBYAX or administered within a minimum of 5 weeks after discontinuation of SYMBYAX (*see* WARNINGS, Thioridazine).

WARNINGS

Clinical Worsening and Suicide Risk — Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

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

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

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with

certain symptoms (*see* PRECAUTIONS *and* DOSAGE AND ADMINISTRATION, Discontinuation of Treatment with SYMBYAX, for a description of the risks of discontinuation of SYMBYAX).

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

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

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

Increased Mortality in Elderly Patients with Dementia-Related Psychosis — **Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. SYMBYAX (olanzapine and fluoxetine HCl) is not approved for the treatment of patients with dementia-related psychosis (*see* BOX WARNING).**

In olanzapine placebo-controlled clinical trials of elderly patients with dementia-related psychosis, the incidence of death in olanzapine-treated patients was significantly greater than placebo-treated patients (3.5% vs 1.5%, respectively).

Cerebrovascular Adverse Events (CVAE), Including Stroke, in Elderly Patients with Dementia-Related Psychosis — Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis.

Hyperglycemia and Diabetes Mellitus — Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including olanzapine alone, as well as olanzapine taken concomitantly with fluoxetine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise

risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Orthostatic Hypotension — SYMBYAX may induce orthostatic hypotension associated with dizziness, tachycardia, bradycardia, and in some patients, syncope, especially during the initial dose-titration period.

In the bipolar depression studies, statistically significantly more orthostatic changes occurred with the SYMBYAX group compared to placebo and olanzapine groups. Orthostatic systolic blood pressure decrease of at least 30 mm Hg occurred in 7.3% (6/82), 1.4% (5/346), and 1.4% (5/352) of the SYMBYAX, olanzapine and placebo groups, respectively. Among the group of controlled clinical studies with SYMBYAX, an orthostatic systolic blood pressure decrease of ≥ 30 mm Hg occurred in 4% (21/512) of SYMBYAX-treated patients, 5% (10/204) of fluoxetine-treated patients, 2% (16/644) of olanzapine-treated patients, and 2% (8/445) of placebo-treated patients. In this group of studies, the incidence of syncope in SYMBYAX-treated patients was 0.4% (2/571) compared to placebo 0.2% (1/477).

In a clinical pharmacology study of SYMBYAX, three healthy subjects were discontinued from the trial after experiencing severe, but self-limited, hypotension and bradycardia that occurred 2 to 9 hours following a single 12-mg/50-mg dose of SYMBYAX. Reactions consisting of this combination of hypotension and bradycardia (and also accompanied by sinus pause) have been observed in at least three other healthy subjects treated with various formulations of olanzapine (one oral, two intramuscular). In controlled clinical studies, the incidence of patients with a ≥ 20 bpm decrease in orthostatic pulse concomitantly with a ≥ 20 mm Hg decrease in orthostatic systolic blood pressure was 0.4% (2/549) in the SYMBYAX group, 0.2% (1/455) in the placebo group, 0.8% (5/659) in the olanzapine group, and 0% (0/241) in the fluoxetine group.

SYMBYAX should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, or conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

Allergic Events and Rash — In SYMBYAX premarketing controlled clinical studies, the overall incidence of rash or allergic events in SYMBYAX-treated patients [4.6% (26/571)] was similar to that of placebo [5.2% (25/477)]. The majority of the cases of rash and/or urticaria were mild; however, three patients discontinued (one due to rash, which was moderate in severity, and two due to allergic events, one of which included face edema).

In fluoxetine US clinical studies, 7% of 10,782 fluoxetine-treated patients developed various types of rashes and/or urticaria. Among the cases of rash and/or urticaria reported in premarketing clinical studies, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with

antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

In fluoxetine premarketing clinical studies, 2 patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but 1 was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Other patients have had systemic syndromes suggestive of serum sickness.

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

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

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

Whether these systemic events and rash have a common underlying cause or are due to different etiologies or pathogenic processes is not known. Furthermore, a specific underlying immunologic basis for these events has not been identified. Upon the appearance of rash or of other possible allergic phenomena for which an alternative etiology cannot be identified, SYMBYAX should be discontinued.

Serotonin Syndrome — The development of a potentially life-threatening serotonin syndrome may occur with SYMBYAX treatment, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs which impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

The concomitant use of SYMBYAX with MAOIs intended to treat depression is contraindicated (*see* CONTRAINDICATIONS, Monoamine Oxidase Inhibitors (MAOI) and PRECAUTIONS, Drug Interactions).

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

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

Neuroleptic Malignant Syndrome (NMS) — A potentially fatal symptom complex sometimes referred to as NMS has been reported in association with administration of antipsychotic drugs, including olanzapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and

medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If after recovering from NMS, a patient requires treatment with an antipsychotic, the patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia — A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses or may even arise after discontinuation of treatment.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

The incidence of dyskinetic movement in SYMBYAX-treated patients was infrequent. The mean score on the Abnormal Involuntary Movement Scale (AIMS) across clinical studies involving SYMBYAX-treated patients decreased from baseline. Nonetheless, SYMBYAX should be prescribed in a manner that is most likely to minimize the risk of tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear in a patient on SYMBYAX, drug discontinuation should be considered. However, some patients may require treatment with SYMBYAX despite the presence of the syndrome. The need for continued treatment should be reassessed periodically.

Thioridazine — In a study of 19 healthy male subjects, which included 6 slow and 13 rapid hydroxylators of debrisoquin, a single 25-mg oral dose of thioridazine produced a 2.4-fold higher C_{max} and a 4.5-fold higher AUC for thioridazine in the slow hydroxylators compared with the rapid hydroxylators. The rate of debrisoquin hydroxylation is felt to depend on the level of CYP2D6 isozyme activity. Thus, this study suggests that drugs that inhibit CYP2D6, such as certain SSRIs, including fluoxetine, will produce elevated plasma levels of thioridazine (*see* PRECAUTIONS).

Thioridazine administration produces a dose-related prolongation of the QT_c interval, which is associated with serious ventricular arrhythmias, such as torsades de pointes-type arrhythmias and sudden death. This risk is expected to increase with fluoxetine-induced inhibition of thioridazine metabolism (*see* CONTRAINDICATIONS, Thioridazine).

PRECAUTIONS

General

Concomitant Use of Olanzapine and Fluoxetine Products — SYMBYAX contains the same active ingredients that are in Zyprexa and Zyprexa Zydis (olanzapine) and in Prozac, Prozac Weekly, and Sarafem (fluoxetine HCl). Caution should be exercised when prescribing these medications concomitantly with SYMBYAX.

Abnormal Bleeding — Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have

demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding (*see* DRUG INTERACTIONS). Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of SYMBYAX with NSAIDs, aspirin, or other drugs that affect coagulation.

Mania/Hypomania — In the two controlled bipolar depression studies there was no statistically significant difference in the incidence of manic events (manic reaction or manic depressive reaction) between SYMBYAX- and placebo-treated patients. In one of the studies, the incidence of manic events was (7% [3/43]) in SYMBYAX-treated patients compared to (3% [5/184]) in placebo-treated patients. In the other study, the incidence of manic events was (2% [1/43]) in SYMBYAX-treated patients compared to (8% [15/193]) in placebo-treated patients. This limited controlled trial experience of SYMBYAX in the treatment of bipolar depression makes it difficult to interpret these findings until additional data is obtained. Because of this and the cyclical nature of bipolar disorder, patients should be monitored closely for the development of symptoms of mania/hypomania during treatment with SYMBYAX.

Body Temperature Regulation — Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic drugs. Appropriate care is advised when prescribing SYMBYAX for patients who will be experiencing conditions which may contribute to an elevation in core body temperature (e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration).

Cognitive and Motor Impairment — Somnolence was a commonly reported adverse event associated with SYMBYAX treatment, occurring at an incidence of 22% in SYMBYAX patients compared with 11% in placebo patients. Somnolence led to discontinuation in 2% (10/571) of patients in the premarketing controlled clinical studies.

As with any CNS-active drug, SYMBYAX has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that SYMBYAX therapy does not affect them adversely.

Discontinuation of Treatment with SYMBYAX

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

Dysphagia — Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's disease. Olanzapine and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Half-Life — Because of the long elimination half-lives of fluoxetine and its major active metabolite, changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment (*see* CLINICAL PHARMACOLOGY, Accumulation and slow elimination).

Hyperprolactinemia — As with other drugs that antagonize dopamine D₂ receptors, SYMBYAX elevates prolactin levels, and a modest elevation persists during administration; however, possibly associated clinical manifestations (e.g., galactorrhea and breast enlargement) were infrequently observed.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer of this type. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds that increase prolactin release, an increase in mammary gland neoplasia was observed in the olanzapine carcinogenicity studies conducted in mice and rats (*see* Carcinogenesis). However, neither clinical studies nor epidemiologic studies have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive.

Hyponatremia — Hyponatremia has been observed in SYMBYAX premarketing clinical studies. In controlled trials, no SYMBYAX-treated patients had a treatment-emergent serum sodium below 130 mmol/L; however, a lowering of serum sodium below the reference range occurred at an incidence of 2% (10/500) of SYMBYAX patients compared with 0.5% (2/380) of placebo patients. In open label studies, 0.3% (5/1889) of these SYMBYAX-treated patients had a treatment-emergent serum sodium below 130 mmol/L.

Cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been reported with fluoxetine. The hyponatremia appeared to be reversible when fluoxetine was discontinued. Although these cases were complex with varying possible etiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted. In two 6-week controlled studies in patients ≥ 60 years of age, 10 of 323 fluoxetine patients and 6 of 327 placebo recipients had a lowering of serum sodium below the reference range; this difference was not statistically significant. The lowest observed concentration was 129 mmol/L. The observed decreases were not clinically significant.

Seizures — Seizures occurred in 0.2% (4/2066) of SYMBYAX-treated patients during open-label premarketing clinical studies. No seizures occurred in the premarketing controlled SYMBYAX studies. Seizures have also been reported with both olanzapine and fluoxetine monotherapy. Therefore, SYMBYAX should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in a population of ≥ 65 years of age.

Transaminase Elevations — As with olanzapine, asymptomatic elevations of hepatic transaminases [ALT (SGPT), AST (SGOT), and GGT] and alkaline phosphatase have been observed with SYMBYAX. In the SYMBYAX-controlled database, ALT (SGPT) elevations (≥ 3 times the upper limit of the normal range) were observed in 6.3% (31/495) of patients exposed to SYMBYAX compared with 0.5% (2/384) of the placebo patients and 4.5% (25/560) of olanzapine-treated patients. The difference between SYMBYAX and placebo was statistically significant. None of these 31 SYMBYAX-treated patients experienced jaundice and three had transient elevations > 200 IU/L.

In olanzapine placebo-controlled studies, clinically significant ALT (SGPT) elevations (≥ 3 times the upper limit of the normal range) were observed in 2% (6/243) of patients exposed

to olanzapine compared with 0% (0/115) of the placebo patients. None of these patients experienced jaundice. In 2 of these patients, liver enzymes decreased toward normal despite continued treatment, and in 2 others, enzymes decreased upon discontinuation of olanzapine. In the remaining 2 patients, 1, seropositive for hepatitis C, had persistent enzyme elevations for 4 months after discontinuation, and the other had insufficient follow-up to determine if enzymes normalized.

Within the larger olanzapine premarketing database of about 2400 patients with baseline SGPT \leq 90 IU/L, the incidence of SGPT elevation to $>$ 200 IU/L was 2% (50/2381). Again, none of these patients experienced jaundice or other symptoms attributable to liver impairment and most had transient changes that tended to normalize while olanzapine treatment was continued. Among all 2500 patients in olanzapine clinical studies, approximately 1% (23/2500) discontinued treatment due to transaminase increases.

Rare postmarketing reports of hepatitis have been received. Very rare cases of cholestatic or mixed liver injury have also been reported in the postmarketing period.

Caution should be exercised in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic drugs. Periodic assessment of transaminases is recommended in patients with significant hepatic disease (*see* Laboratory Tests).

Weight Gain — In clinical studies, the mean weight increase for SYMBYAX-treated patients was statistically significantly greater than placebo-treated (3.6 kg vs -0.3 kg) and fluoxetine-treated (3.6 kg vs -0.7 kg) patients, but was not statistically significantly different from olanzapine-treated patients (3.6 kg vs 3.0 kg). Fourteen percent of SYMBYAX-treated patients met criterion for having gained $>$ 10% of their baseline weight. This was statistically significantly greater than placebo-treated ($<$ 1%) and fluoxetine-treated patients ($<$ 1%) but was not statistically significantly different than olanzapine-treated patients (11%).

Use in Patients with Concomitant Illness

Clinical experience with SYMBYAX in patients with concomitant systemic illnesses is limited (*see* CLINICAL PHARMACOLOGY, Renal Impairment *and* Hepatic Impairment). The following precautions for the individual components may be applicable to SYMBYAX.

Olanzapine exhibits in vitro muscarinic receptor affinity. In premarketing clinical studies, SYMBYAX was associated with constipation, dry mouth, and tachycardia, all adverse events possibly related to cholinergic antagonism. Such adverse events were not often the basis for study discontinuations; SYMBYAX should be used with caution in patients with clinically significant prostatic hypertrophy, narrow angle glaucoma, a history of paralytic ileus, or related conditions.

In five placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis (n=1184), the following treatment-emergent adverse events were reported in olanzapine-treated patients at an incidence of at least 2% and significantly greater than placebo-treated patients: falls, somnolence, peripheral edema, abnormal gait, urinary incontinence, lethargy, increased weight, asthenia, pyrexia, pneumonia, dry mouth and visual hallucinations. The rate of discontinuation due to adverse events was significantly greater with olanzapine than placebo (13% vs 7%). Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis. If the prescriber elects to treat elderly patients with dementia-related psychosis, vigilance should be exercised (*see* BOX WARNING *and* WARNINGS).

As with other CNS-active drugs, SYMBYAX should be used with caution in elderly patients with dementia. Olanzapine is not approved for the treatment of patients with dementia-related

psychosis. If the prescriber elects to treat elderly patients with dementia-related psychosis, vigilance should be exercised (*see* BOX WARNING *and* WARNINGS).

SYMBYAX 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 excluded from clinical studies during the premarket testing.

Caution is advised when using SYMBYAX in cardiac patients and in patients with diseases or conditions that could affect hemodynamic responses (*see* WARNINGS, Orthostatic Hypotension).

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower dose of the fluoxetine-component of SYMBYAX should be used in patients with cirrhosis. Caution is advised when using SYMBYAX in patients with diseases or conditions that could affect its metabolism (*see* CLINICAL PHARMACOLOGY, Hepatic Impairment *and* DOSING AND ADMINISTRATION, Special Populations).

Olanzapine and fluoxetine individual pharmacokinetics do not differ significantly in patients with renal impairment. SYMBYAX dosing adjustment based upon renal impairment is not routinely required (*see* CLINICAL PHARMACOLOGY, Renal Impairment).

Information for Patients

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with SYMBYAX and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for SYMBYAX. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

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

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

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

Abnormal Bleeding — Patients should be cautioned about the concomitant use of SYMBYAX and NSAIDs, aspirin, or other drugs that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding (*see* PRECAUTIONS, Abnormal Bleeding).

Alcohol — Patients should be advised to avoid alcohol while taking SYMBYAX.

Cognitive and Motor Impairment — As with any CNS-active drug, SYMBYAX has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about

operating hazardous machinery, including automobiles, until they are reasonably certain that SYMBYAX therapy does not affect them adversely.

Concomitant Medication — Patients should be advised to inform their physician if they are taking Prozac[®], Prozac Weekly[™], Sarafem[®], fluoxetine, Zyprexa[®], or Zyprexa Zydis[®]. Patients should also be advised to inform their physicians if they are taking or plan to take any prescription or over-the-counter drugs, including herbal supplements, since there is a potential for interactions.

Heat Exposure and Dehydration — Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Nursing — Patients, if taking SYMBYAX, should be advised not to breast-feed.

Orthostatic Hypotension — Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration and in association with the use of concomitant drugs that may potentiate the orthostatic effect of olanzapine, e.g., diazepam or alcohol (*see WARNINGS and Drug Interactions*).

Pregnancy — Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during SYMBYAX therapy.

Rash — Patients should be advised to notify their physician if they develop a rash or hives while taking SYMBYAX.

Treatment Adherence — Patients should be advised to take SYMBYAX exactly as prescribed, and to continue taking SYMBYAX as prescribed even after their mood symptoms improve. Patients should be advised that they should not alter their dosing regimen, or stop taking SYMBYAX, without consulting their physician.

Patient information is printed at the end of this insert. Physicians should discuss this information with their patients and instruct them to read the Medication Guide before starting therapy with SYMBYAX and each time their prescription is refilled.

Laboratory Tests

Periodic assessment of transaminases is recommended in patients with significant hepatic disease (*see Transaminase Elevations*).

Drug Interactions

The risks of using SYMBYAX in combination with other drugs have not been extensively evaluated in systematic studies. The drug-drug interactions of the individual components are applicable to SYMBYAX. As with all drugs, the potential for interaction by a variety of mechanisms (e.g., pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc.) is a possibility. Caution is advised if the concomitant administration of SYMBYAX and other CNS-active 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 CLINICAL PHARMACOLOGY, Accumulation and slow elimination*).

Antihypertensive agents — Because of the potential for olanzapine to induce hypotension, SYMBYAX may enhance the effects of certain antihypertensive agents (*see WARNINGS, Orthostatic Hypotension*).

Anti-Parkinsonian — The olanzapine component of SYMBYAX may antagonize the effects of levodopa and dopamine agonists.

Benzodiazepines — Multiple doses of olanzapine did not influence the pharmacokinetics of diazepam and its active metabolite N-desmethyldiazepam. However, the coadministration of diazepam with olanzapine potentiated the orthostatic hypotension observed with olanzapine.

When concurrently administered with fluoxetine, the half-life of diazepam may be prolonged in some patients (*see CLINICAL PHARMACOLOGY, Accumulation and slow elimination*).

Coadministration of alprazolam and fluoxetine has resulted in increased alprazolam plasma concentrations and in further psychomotor performance decrement due to increased alprazolam levels.

Biperiden — Multiple doses of olanzapine did not influence the pharmacokinetics of biperiden.

Carbamazepine — Carbamazepine therapy (200 mg BID) causes an approximate 50% increase in the clearance of olanzapine. This increase is likely due to the fact that carbamazepine is a potent inducer of CYP1A2 activity. Higher daily doses of carbamazepine may cause an even greater increase in olanzapine clearance.

Patients on stable doses of carbamazepine have developed elevated plasma anticonvulsant concentrations and clinical anticonvulsant toxicity following initiation of concomitant fluoxetine treatment.

Clozapine — Elevation of blood levels of clozapine has been observed in patients receiving concomitant fluoxetine.

Electroconvulsive therapy (ECT) — There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment (*see* Seizures).

Ethanol — Ethanol (45 mg/70 kg single dose) did not have an effect on olanzapine pharmacokinetics. The coadministration of ethanol with SYMBYAX may potentiate sedation and orthostatic hypotension.

Fluvoxamine — Fluvoxamine, a CYP1A2 inhibitor, decreases the clearance of olanzapine. This results in a mean increase in olanzapine C_{max} following fluvoxamine administration of 54% in female nonsmokers and 77% in male smokers. The mean increase in olanzapine AUC is 52% and 108%, respectively. Lower doses of the olanzapine component of SYMBYAX should be considered in patients receiving concomitant treatment with fluvoxamine.

Haloperidol — Elevation of blood levels of haloperidol has been observed in patients receiving concomitant fluoxetine.

Lithium — Multiple doses of olanzapine did not influence the pharmacokinetics of lithium.

There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with fluoxetine. Cases of lithium toxicity and increased serotonergic effects have been reported. Lithium levels should be monitored in patients taking SYMBYAX concomitantly with lithium.

Monoamine oxidase inhibitors — *See* CONTRAINDICATIONS.

Phenytoin — Patients on stable doses of phenytoin have developed elevated plasma levels of phenytoin with clinical phenytoin toxicity following initiation of concomitant fluoxetine.

Pimozide — Clinical studies of pimozide with other antidepressants demonstrate an increase in drug interaction or QT_c prolongation. While a specific study with pimozide and fluoxetine has not been conducted, the potential for drug interactions or QT_c prolongation warrants restricting the concurrent use of pimozide and fluoxetine. Concomitant use of fluoxetine and pimozide is contraindicated (*see* CONTRAINDICATIONS).

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

Theophylline — Multiple doses of olanzapine did not affect the pharmacokinetics of theophylline or its metabolites.

Thioridazine — *See* CONTRAINDICATIONS and WARNINGS, Thioridazine.

Tricyclic antidepressants (TCAs) — Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active metabolite desipramine.

In two fluoxetine studies, previously stable plasma levels of imipramine and desipramine have increased >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 TCA may need to be reduced and plasma TCA concentrations may need to be monitored temporarily when SYMBYAX is coadministered or has been recently discontinued (*see* Drugs metabolized by CYP2D6 and CLINICAL PHARMACOLOGY, Accumulation and slow elimination).

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

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

Valproate — In vitro studies using human liver microsomes determined that olanzapine has little potential to inhibit the major metabolic pathway, glucuronidation, of valproate. Further, valproate has little effect on the metabolism of olanzapine in vitro. Thus, a clinically significant pharmacokinetic interaction between olanzapine and valproate is unlikely.

Warfarin — Warfarin (20-mg single dose) did not affect olanzapine pharmacokinetics. Single doses of olanzapine did not affect the pharmacokinetics of warfarin.

Altered anticoagulant effects, including increased bleeding, have been reported when fluoxetine is coadministered with warfarin (*see* PRECAUTIONS, Abnormal Bleeding). Patients receiving warfarin therapy should receive careful coagulation monitoring when SYMBYAX is initiated or stopped.

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

Drugs metabolized by CYP2D6 — In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP2D6. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by this enzyme.

Approximately 7% of the normal population has a genetic variation that leads to reduced levels of activity of CYP2D6. Such individuals have been referred to as poor metabolizers of drugs such as debrisoquin, dextromethorphan, and TCAs. Many drugs, such as most antidepressants, including fluoxetine and other selective uptake inhibitors of serotonin, are metabolized by this isoenzyme; thus, both the pharmacokinetic properties and relative proportion of metabolites are altered in poor metabolizers. However, for fluoxetine and its metabolite, the sum of the plasma concentrations of the 4 enantiomers is comparable between poor and extensive metabolizers (*see* CLINICAL PHARMACOLOGY, Variability in metabolism).

Fluoxetine, like other agents that are metabolized by CYP2D6, inhibits the activity of this isoenzyme, and thus may make normal metabolizers resemble poor metabolizers. Therapy with medications that are predominantly metabolized by the CYP2D6 system and that have a relatively narrow therapeutic index 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 five weeks. If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need for a decreased dose of the original medication should be considered. Drugs with a narrow therapeutic index represent the greatest concern (including but not limited to,

flecainide, vinblastine, and TCAs). Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated thioridazine plasma levels, thioridazine should not be administered with fluoxetine or within a minimum of five weeks after fluoxetine has been discontinued (*see* CONTRAINDICATIONS, Monoamine Oxidase Inhibitors (MAOI) *and* WARNINGS, Thioridazine).

Drugs metabolized by CYP3A — In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP3A. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

In an in vivo interaction study involving the coadministration of fluoxetine with single doses of terfenadine (a CYP3A substrate), no increase in plasma terfenadine concentrations occurred with concomitant fluoxetine. In addition, in vitro studies have shown ketoconazole, a potent inhibitor of CYP3A 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 CYP3A activity is not likely to be of clinical significance.

Effect of olanzapine on drugs metabolized by other CYP enzymes — In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP1A2, CYP2C9, and CYP2C19. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

The effect of other drugs on olanzapine — Fluoxetine, an inhibitor of CYP2D6, decreases olanzapine clearance a small amount (*see* CLINICAL PHARMACOLOGY, Pharmacokinetics). Agents that induce CYP1A2 or glucuronyl transferase enzymes, such as omeprazole and rifampin, may cause an increase in olanzapine clearance. Fluvoxamine, an inhibitor of CYP1A2, decreases olanzapine clearance (*see* Drug Interactions, Fluvoxamine). The effect of CYP1A2 inhibitors, such as fluvoxamine and some fluoroquinolone antibiotics, on SYMBYAX has not been evaluated. Although olanzapine is metabolized by multiple enzyme systems, induction or inhibition of a single enzyme may appreciably alter olanzapine clearance. Therefore, a dosage increase (for induction) or a dosage decrease (for inhibition) may need to be considered with specific drugs.

Drugs tightly bound to plasma proteins — The in vitro binding of SYMBYAX to human plasma proteins is similar to the individual components. The interaction between SYMBYAX and other highly protein-bound drugs has not been fully evaluated. Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (e.g., Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound fluoxetine by other tightly bound drugs (*see* CLINICAL PHARMACOLOGY, Distribution *and* PRECAUTIONS, Drug Interactions).

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity, mutagenicity, or fertility studies were conducted with SYMBYAX. The following data are based on findings in studies performed with the individual components.

Carcinogenesis

Olanzapine — Oral carcinogenicity studies were conducted in mice and rats. Olanzapine was administered to mice in two 78-week studies at doses of 3, 10, and 30/20 mg/kg/day [equivalent to 0.8 to 5 times the maximum recommended human daily dose (MRHD) on a mg/m² basis] and 0.25, 2, and 8 mg/kg/day (equivalent to 0.06 to 2 times the MRHD on a mg/m² basis). Rats were dosed for 2 years at doses of 0.25, 1, 2.5, and 4 mg/kg/day (males) and 0.25, 1, 4, and 8 mg/kg/day (females) (equivalent to 0.1 to 2 and 0.1 to 4 times the MRHD on a mg/m² basis, respectively). The incidence of liver hemangiomas and hemangiosarcomas was significantly increased in one mouse study in females dosed at 8 mg/kg/day (2 times the MRHD on a mg/m²

basis). These tumors were not increased in another mouse study in females dosed at 10 or 30/20 mg/kg/day (2 to 5 times the MRHD on a mg/m² basis); in this study, there was a high incidence of early mortalities in males of the 30/20 mg/kg/day group. The incidence of mammary gland adenomas and adenocarcinomas was significantly increased in female mice dosed at ≥2 mg/kg/day and in female rats dosed at ≥4 mg/kg/day (0.5 and 2 times the MRHD on a mg/m² basis, respectively). Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the olanzapine carcinogenicity studies; however, measurements during subchronic toxicity studies showed that olanzapine elevated serum prolactin levels up to 4-fold in rats at the same doses used in the carcinogenicity study. An increase in mammary gland neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin-mediated. The relevance for human risk of the finding of prolactin-mediated endocrine tumors in rodents is unknown (*see* PRECAUTIONS, Hyperprolactinemia).

Fluoxetine — The dietary administration of fluoxetine to rats and mice for two years at doses of up to 10 and 12 mg/kg/day, respectively (approximately 1.2 and 0.7 times, respectively, the MRHD on a mg/m² basis), produced no evidence of carcinogenicity.

Mutagenesis

Olanzapine — No evidence of mutagenic potential for olanzapine was found in the Ames reverse mutation test, in vivo micronucleus test in mice, the chromosomal aberration test in Chinese hamster ovary cells, unscheduled DNA synthesis test in rat hepatocytes, induction of forward mutation test in mouse lymphoma cells, or in vivo sister chromatid exchange test in bone marrow of Chinese hamsters.

Fluoxetine — Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Impairment of Fertility

SYMBYAX — Fertility studies were not conducted with SYMBYAX. However, in a repeat-dose rat toxicology study of three months duration, ovary weight was decreased in females treated with the low-dose [2 and 4 mg/kg/day (1 and 0.5 times the MRHD on a mg/m² basis), respectively] and high-dose [4 and 8 mg/kg/day (2 and 1 times the MRHD on a mg/m² basis), respectively] combinations of olanzapine and fluoxetine. Decreased ovary weight, and corpora luteal depletion and uterine atrophy were observed to a greater extent in the females receiving the high-dose combination than in females receiving either olanzapine or fluoxetine alone. In a 3-month repeat-dose dog toxicology study, reduced epididymal sperm and reduced testicular and prostate weights were observed with the high-dose combination of olanzapine and fluoxetine [5 and 5 mg/kg/day (9 and 2 times the MRHD on a mg/m² basis), respectively] and with olanzapine alone (5 mg/kg/day or 9 times the MRHD on a mg/m² basis).

Olanzapine — In a fertility and reproductive performance study in rats, male mating performance, but not fertility, was impaired at a dose of 22.4 mg/kg/day and female fertility was decreased at a dose of 3 mg/kg/day (11 and 1.5 times the MRHD on a mg/m² basis, respectively). Discontinuance of olanzapine treatment reversed the effects on male-mating performance. In female rats, the precoital period was increased and the mating index reduced at 5 mg/kg/day (2.5 times the MRHD on a mg/m² basis). Diestrus was prolonged and estrus was delayed at 1.1 mg/kg/day (0.6 times the MRHD on a mg/m² basis); therefore, olanzapine may produce a delay in ovulation.

Fluoxetine — Two fertility studies conducted in adult rats at doses of up to 7.5 and 12.5 mg/kg/day (approximately 0.9 and 1.5 times the MRHD on a mg/m² basis) indicated that fluoxetine had no adverse effects on fertility (*see* Pediatric Use).

Pregnancy — Pregnancy Category C

SYMBYAX

Embryo fetal development studies were conducted in rats and rabbits with olanzapine and fluoxetine in low-dose and high-dose combinations. In rats, the doses were: 2 and 4 mg/kg/day (low-dose) [1 and 0.5 times the MRHD on a mg/m² basis, respectively], and 4 and 8 mg/kg/day (high-dose) [2 and 1 times the MRHD on a mg/m² basis, respectively]. In rabbits, the doses were 4 and 4 mg/kg/day (low-dose) [4 and 1 times the MRHD on a mg/m² basis, respectively], and 8 and 8 mg/kg/day (high-dose) [9 and 2 times the MRHD on a mg/m² basis, respectively]. In these studies, olanzapine and fluoxetine were also administered alone at the high-doses (4 and 8 mg/kg/day, respectively, in the rat; 8 and 8 mg/kg/day, respectively, in the rabbit). In the rabbit, there was no evidence of teratogenicity; however, the high-dose combination produced decreases in fetal weight and retarded skeletal ossification in conjunction with maternal toxicity. Similarly, in the rat there was no evidence of teratogenicity; however, a decrease in fetal weight was observed with the high-dose combination.

In a pre- and postnatal study conducted in rats, olanzapine and fluoxetine were administered during pregnancy and throughout lactation in combination (low-dose: 2 and 4 mg/kg/day [1 and 0.5 times the MRHD on a mg/m² basis], respectively, high-dose: 4 and 8 mg/kg/day [2 and 1 times the MRHD on a mg/m² basis], respectively, and alone: 4 and 8 mg/kg/day [2 and 1 times the MRHD on a mg/m² basis], respectively). Administration of the high-dose combination resulted in a marked elevation in offspring mortality and growth retardation in comparison to the same doses of olanzapine and fluoxetine administered alone. These effects were not observed with the low-dose combination; however, there were a few cases of testicular degeneration and atrophy, depletion of epididymal sperm and infertility in the male progeny. The effects of the high-dose combination on postnatal endpoints could not be assessed due to high progeny mortality.

There are no adequate and well-controlled studies with SYMBYAX in pregnant women.

SYMBYAX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Olanzapine

In reproduction studies in rats at doses up to 18 mg/kg/day and in rabbits at doses up to 30 mg/kg/day (9 and 30 times the MRHD on a mg/m² basis, respectively), no evidence of teratogenicity was observed. In a rat teratology study, early resorptions and increased numbers of nonviable fetuses were observed at a dose of 18 mg/kg/day (9 times the MRHD on a mg/m² basis). Gestation was prolonged at 10 mg/kg/day (5 times the MRHD on a mg/m² basis). In a rabbit teratology study, fetal toxicity (manifested as increased resorptions and decreased fetal weight) occurred at a maternally toxic dose of 30 mg/kg/day (30 times the MRHD on a mg/m² basis).

Placental transfer of olanzapine occurs in rat pups.

There are no adequate and well-controlled clinical studies with olanzapine in pregnant women. Seven pregnancies were observed during premarketing clinical studies with olanzapine, including two resulting in normal births, one resulting in neonatal death due to a cardiovascular defect, three therapeutic abortions, and one spontaneous abortion.

Fluoxetine

In embryo fetal development studies in rats and rabbits, there was no evidence of teratogenicity following administration of up to 12.5 and 15 mg/kg/day, respectively (1.5 and 3.6 times the MRHD on a mg/m² basis, respectively) throughout organogenesis. However, in rat reproduction studies, an increase in stillborn pups, a decrease in pup weight, and an increase in pup deaths during the first 7 days postpartum occurred following maternal exposure to 12 mg/kg/day (1.5 times the MRHD on a mg/m² basis) during gestation or 7.5 mg/kg/day

(0.9 times the MRHD on a mg/m² basis) during gestation and lactation. There was no evidence of developmental neurotoxicity in the surviving offspring of rats treated with 12 mg/kg/day during gestation. The no-effect dose for rat pup mortality was 5 mg/kg/day (0.6 times the MRHD on a mg/m² basis).

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

Labor and Delivery

SYMBYAX

The effect of SYMBYAX on labor and delivery in humans is unknown. Parturition in rats was not affected by SYMBYAX. SYMBYAX should be used during labor and delivery only if the potential benefit justifies the potential risk.

Olanzapine

Parturition in rats was not affected by olanzapine. The effect of olanzapine on labor and delivery in humans is unknown.

Fluoxetine

The effect of fluoxetine on labor and delivery in humans is unknown. Fluoxetine crosses the placenta; therefore, there is a possibility that fluoxetine may have adverse effects on the newborn.

Nursing Mothers

SYMBYAX

There are no adequate and well-controlled studies with SYMBYAX in nursing mothers or infants. No studies have been conducted to examine the excretion of olanzapine or fluoxetine in breast milk following SYMBYAX treatment. It is recommended that women not breast-feed when receiving SYMBYAX.

Olanzapine

Olanzapine was excreted in milk of treated rats during lactation.

Fluoxetine

Fluoxetine is excreted in human breast milk. In one breast milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng/mL. The concentration in the mother's plasma was 295.0 ng/mL. No adverse effects on the infant were reported. In another case, an infant nursed by a mother on fluoxetine developed crying, sleep disturbance, vomiting, and watery stools. The infant's plasma drug levels were 340 ng/mL of fluoxetine and 208 ng/mL of norfluoxetine on the 2nd day of feeding.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established (*see* BOX WARNING and WARNINGS, Clinical Worsening and Suicide Risk). Anyone considering the

use of SYMBYAX in a child or adolescent must balance the potential risks with the clinical need.

Fluoxetine

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

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

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

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

Geriatric Use

SYMBYAX

Clinical studies of SYMBYAX did not include sufficient numbers of patients ≥ 65 years of age to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (*see* DOSAGE AND ADMINISTRATION).

Olanzapine

Of the 2500 patients in premarketing clinical studies with olanzapine, 11% (263 patients) were ≥ 65 years of age. In patients with schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared with younger patients. Studies in patients with dementia-related psychosis have suggested that there may be a different tolerability profile in this population compared with younger patients with schizophrenia. In placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis, there was a significantly higher incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis. If the prescriber elects to treat elderly patients with dementia-related psychosis, vigilance should be exercised (*see* BOX WARNING, WARNINGS, PRECAUTIONS, Use in Patients with Concomitant Illness and DOSAGE AND ADMINISTRATION, Special Populations).

As with other CNS-active drugs, olanzapine should be used with caution in elderly patients with dementia. Also, the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine should lead to consideration of a lower starting dose for any geriatric patient.

Fluoxetine

US fluoxetine clinical studies (10,782 patients) included 687 patients ≥ 65 years of age and 93 patients ≥ 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with other SSRIs, fluoxetine has been associated with cases of clinically significant hyponatremia in elderly patients.

ADVERSE REACTIONS

The information below is derived from a premarketing clinical study database for SYMBYAX consisting of 2066 patients with various diagnoses with approximately 1061 patient-years of exposure. The conditions and duration of treatment with SYMBYAX varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or long-term exposure.

Adverse events were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a limited (i.e., reduced) number of standardized event categories.

In the tables and tabulations that follow, COSTART Dictionary terminology has been used to classify reported adverse events. The data in the tables 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 possible that events reported during therapy were not necessarily related to drug exposure.

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 studies. 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 clinician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

Incidence in Controlled Clinical Studies

The following findings are based on the short-term, controlled premarketing studies in various diagnoses including bipolar depression.

Adverse events associated with discontinuation of treatment — Overall, 10% of the patients in the SYMBYAX group discontinued due to adverse events compared with 4.6% for placebo. Table 2 enumerates the adverse events leading to discontinuation associated with the use of SYMBYAX (incidence of at least 1% for SYMBYAX and greater than that for placebo). The bipolar depression column shows the incidence of adverse events with SYMBYAX in the bipolar depression studies and the “SYMBYAX-Controlled” column shows the incidence in the controlled SYMBYAX studies; the placebo column shows the incidence in the pooled controlled studies that included a placebo arm.

Table 2: Adverse Events Associated with Discontinuation*

Adverse Event	Percentage of Patients Reporting Event		
	SYMBYAX		Placebo
	Bipolar Depression (N=86)	SYMBYAX-Controlled (N=571)	(N=477)
Asthenia	0	1	0
Somnolence	0	2	0
Weight gain	0	2	0
Chest pain	1	0	0

* Table includes events associated with discontinuation of at least 1% and greater than placebo

Commonly observed adverse events in controlled clinical studies — The most commonly observed adverse events associated with the use of SYMBYAX (incidence of $\geq 5\%$ and at least twice that for placebo in the SYMBYAX-controlled database) were: asthenia, edema, increased appetite, peripheral edema, pharyngitis, somnolence, thinking abnormal, tremor, and weight gain.

Adverse events occurring at an incidence of 2% or more in controlled clinical studies — Table 3 enumerates the treatment-emergent adverse events associated with the use of SYMBYAX (incidence of at least 2% for SYMBYAX and twice or more that for placebo).

**Table 3: Treatment-Emergent Adverse Events:
Incidence in Controlled Clinical Studies**

Body System/ Adverse Event ¹	Percentage of Patients Reporting Event		
	SYMBYAX		Placebo
	Bipolar Depression (N=86)	SYMBYAX-Controlled (N=571)	(N=477)
Body as a Whole			
Asthenia	13	15	3
Accidental injury	5	3	2
Fever	4	3	1
Cardiovascular System			
Hypertension	2	2	1
Tachycardia	2	2	0

Digestive System			
Diarrhea	19	8	7
Dry mouth	16	11	6
Increased appetite	13	16	4
Tooth disorder	1	2	1
Metabolic and Nutritional Disorders			
Weight gain	17	21	3
Peripheral edema	4	8	1
Edema	0	5	0
Musculoskeletal System			
Joint disorder	1	2	1
Twitching	6	2	1
Arthralgia	5	3	1
Nervous System			
Somnolence	21	22	11
Tremor	9	8	3
Thinking abnormal	6	6	3
Libido decreased	4	2	1
Hyperkinesia	2	1	1
Personality disorder	2	1	1
Sleep disorder	2	1	1
Amnesia	1	3	0
Respiratory System			
Pharyngitis	4	6	3
Dyspnea	1	2	1
Special Senses			
Amblyopia	5	4	2
Ear pain	2	1	1
Otitis media	2	0	0
Speech disorder	0	2	0
Urogenital System			
Abnormal ejaculation ²	7	2	1
Impotence ²	4	2	1
Anorgasmia	3	1	0

¹ Included are events reported by at least 2% of patients taking SYMBYAX except the following events, which had an incidence on placebo \geq SYMBYAX: abdominal pain, abnormal dreams, agitation, akathisia, anorexia, anxiety, apathy, back pain, chest pain, constipation, cough increased, depression, dizziness, dysmenorrhea (adjusted for gender), dyspepsia, flatulence, flu syndrome, headache, hypertonia, insomnia, manic reaction, myalgia, nausea, nervousness, pain, palpitation, paresthesia, rash, rhinitis, sinusitis, sweating, vomiting.

² Adjusted for gender.

Additional Findings Observed in Clinical Studies

The following findings are based on clinical studies.

Effect on cardiac repolarization — The mean increase in QT_c interval for SYMBYAX-treated patients (4.9 msec) in clinical studies was significantly greater than that for placebo-treated (-0.9 msec) and olanzapine-treated (0.6 msec) patients, but was not significantly different from fluoxetine-treated (3.7 msec) patients. There were no differences between patients treated with SYMBYAX, placebo, olanzapine, or fluoxetine in the incidence of QT_c outliers (>500 msec).

Laboratory changes — In SYMBYAX clinical studies, SYMBYAX was associated with asymptomatic mean increases in alkaline phosphatase, cholesterol, GGT, and uric acid compared with placebo (*see* PRECAUTIONS, Transaminase Elevations).

SYMBYAX was associated with a slight decrease in hemoglobin that was statistically significantly greater than that seen with placebo, olanzapine, and fluoxetine.

An elevation in serum prolactin was observed with SYMBYAX. This elevation was not statistically different than that seen with olanzapine (*see* PRECAUTIONS, Hyperprolactinemia).

In olanzapine clinical studies among olanzapine-treated patients with random triglyceride levels of <150 mg/dL at baseline (N=659), 0.5% of patients experienced triglyceride levels of ≥500 mg/dL anytime during the trials. In these same trials, olanzapine-treated patients (N=1185) had a mean increase of 20 mg/dL in triglycerides from a mean baseline value of 175 mg/dL.

In olanzapine placebo-controlled trials, olanzapine-treated patients with random cholesterol levels of <200 mg/dL at baseline (N=1034) experienced cholesterol levels of ≥240 mg/dL anytime during the trials more often than placebo-treated patients (N=602) (3.6% vs 2.2%, respectively). In these same trials, olanzapine-treated patients (N=2528) had a mean increase of 0.4 mg/dL in cholesterol from a mean baseline value of 203 mg/dL, which was significantly different compared to placebo-treated patients (N=1415) with a mean decrease of 4.6 mg/dL from a mean baseline value of 203 mg/dL.

Sexual dysfunction — In the pool of controlled SYMBYAX studies, there were higher rates of the treatment-emergent adverse events decreased libido, anorgasmia, impotence and abnormal ejaculation in the SYMBYAX group than in the placebo group. One case of decreased libido led to discontinuation in the SYMBYAX group. In the controlled studies that contained a fluoxetine arm, the rates of decreased libido and abnormal ejaculation in the SYMBYAX group were less than the rates in the fluoxetine group. None of the differences were statistically significant.

Sexual dysfunction, including 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.

Vital signs — Tachycardia, bradycardia, and orthostatic hypotension have occurred in SYMBYAX-treated patients (*see* WARNINGS, Orthostatic Hypotension). The mean pulse of SYMBYAX-treated patients was reduced by 1.6 beats/min.

Other Events Observed in Clinical Studies

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

Events are classified within body system categories using the following definitions: frequent adverse events are defined as those occurring on 1 or more occasions in at least 1/100 patients, infrequent adverse events are those occurring in 1/100 to 1/1000 patients, and rare events are those occurring in <1/1000 patients.

Body as a Whole — *Frequent*: chills, infection, neck pain, neck rigidity, photosensitivity reaction; *Infrequent*: cellulitis, cyst, hernia, intentional injury, intentional overdose, malaise, moniliasis, overdose, pelvic pain, suicide attempt; *Rare*: death, tolerance decreased.

Cardiovascular System — *Frequent*: migraine, vasodilatation; *Infrequent*: arrhythmia, bradycardia, cerebral ischemia, electrocardiogram abnormal, hypotension, QT-interval prolonged; *Rare*: angina pectoris, atrial arrhythmia, atrial fibrillation, bundle branch block, congestive heart failure, myocardial infarct, peripheral vascular disorder, T-wave inverted.

Digestive System — *Frequent*: increased salivation, thirst; *Infrequent*: cholelithiasis, colitis, eructation, esophagitis, gastritis, gastroenteritis, gingivitis, hepatomegaly, nausea and vomiting, peptic ulcer, periodontal abscess, stomatitis, tooth caries; *Rare*: aphthous stomatitis, fecal incontinence, gastrointestinal hemorrhage, gum hemorrhage, intestinal obstruction, liver fatty deposit, pancreatitis.

Endocrine System — *Infrequent*: hypothyroidism.

Hemic and Lymphatic System — *Frequent*: ecchymosis; *Infrequent*: anemia, leukocytosis, lymphadenopathy; *Rare*: coagulation disorder, leukopenia, purpura, thrombocytopenia.

Metabolic and Nutritional — *Frequent*: generalized edema, weight loss; *Infrequent*: alcohol intolerance, dehydration, glycosuria, hyperlipemia, hypoglycemia, hypokalemia, obesity; *Rare*: acidosis, bilirubinemia, creatinine increased, gout, hyperkalemia, hypoglycemic reaction.

Musculoskeletal System — *Infrequent*: arthritis, bone disorder, generalized spasm, leg cramps, tendinous contracture, tenosynovitis; *Rare*: arthrosis, bursitis, myasthenia, myopathy, osteoporosis, rheumatoid arthritis.

Nervous System — *Infrequent*: abnormal gait, ataxia, buccoglossal syndrome, cogwheel rigidity, coma, confusion, depersonalization, dysarthria, emotional lability, euphoria, extrapyramidal syndrome, hostility, hypesthesia, hypokinesia, incoordination, movement disorder, myoclonus, neuralgia, neurosis, vertigo; *Rare*: acute brain syndrome, aphasia, dystonia, libido increased, subarachnoid hemorrhage, withdrawal syndrome.

Respiratory System — *Frequent*: bronchitis, lung disorder; *Infrequent*: apnea, asthma, epistaxis, hiccup, hyperventilation, laryngitis, pneumonia, voice alteration, yawn; *Rare*: emphysema, hemoptysis, laryngismus.

Skin and Appendages — *Infrequent*: acne, alopecia, contact dermatitis, dry skin, eczema, pruritis, psoriasis, skin discoloration, vesiculobullous rash; *Rare*: exfoliative dermatitis, maculopapular rash, seborrhea, skin ulcer.

Special Senses — *Frequent*: abnormal vision, taste perversion, tinnitus; *Infrequent*: abnormality of accommodation, conjunctivitis, deafness, diplopia, dry eyes, eye pain, miosis; *Rare*: eye hemorrhage.

Urogenital System — *Frequent*: breast pain, menorrhagia¹, urinary frequency, urinary incontinence, urinary tract infection; *Infrequent*: amenorrhea¹, breast enlargement, breast neoplasm, cystitis, dysuria, female lactation¹, fibrocystic breast¹, hematuria, hypomenorrhea¹, leukorrhea¹, menopause¹, metrorrhagia¹, oliguria, ovarian disorder¹, polyuria, urinary retention, urinary urgency, urination impaired, vaginal hemorrhage¹, vaginal moniliasis¹, vaginitis¹; *Rare*: breast carcinoma, breast engorgement, endometrial disorder¹, gynecomastia¹, kidney calculus, uterine fibroids enlarged¹.

¹ Adjusted for gender.

Other Events Observed with Olanzapine or Fluoxetine Monotherapy

The following adverse events were not observed in SYMBYAX-treated patients during premarketing clinical studies but have been reported with olanzapine or fluoxetine monotherapy: aplastic anemia, cholestatic jaundice, diabetic coma, dyskinesia, eosinophilic pneumonia, erythema multiforme, hepatitis, idiosyncratic hepatitis, jaundice, priapism, pulmonary embolism, rhabdomyolysis, serotonin syndrome, serum sickness-like reaction, sudden unexpected death,

suicidal ideation, vasculitis, venous thromboembolic events (including pulmonary embolism and deep venous thrombosis), violent behaviors. Random cholesterol levels of ≥ 240 mg/dL and random triglyceride levels of ≥ 1000 mg/dL have been rarely reported.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class — SYMBYAX is not a controlled substance.

Physical and Psychological Dependence — SYMBYAX, as with fluoxetine and olanzapine, has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. While the clinical studies did not reveal any tendency for any drug-seeking behavior, these observations were not systematic, and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of SYMBYAX (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

In studies in rats and rhesus monkeys designed to assess abuse and dependence potential, olanzapine alone was shown to have acute depressive CNS effects but little or no potential of abuse or physical dependence at oral doses up to 15 (rat) and 8 (monkey) times the MRHD (20 mg) on a mg/m^2 basis.

OVERDOSAGE

SYMBYAX

During premarketing clinical studies of the olanzapine/fluoxetine combination, overdose of both fluoxetine and olanzapine were reported in five study subjects. Four of the five subjects experienced loss of consciousness (3) or coma (1). No fatalities occurred.

Since the market introduction of olanzapine in October 1996, adverse event cases involving combination use of fluoxetine and olanzapine have been reported to Eli Lilly and Company. An overdose of combination therapy is defined as confirmed or suspected ingestion of a dose of olanzapine 20 mg or greater in combination with a dose of fluoxetine 80 mg or greater. As of 1 February 2002, 12 cases of combination therapy overdose were reported, most of which involved additional substances. Adverse events associated with these reports included somnolence; impaired consciousness (coma, lethargy); impaired neurologic function (ataxia, confusion, convulsions, dysarthria); arrhythmias; and fatality. Fatalities have been confounded by exposure to additional substances including alcohol, thioridazine, oxycodone, and propoxyphene.

Olanzapine

In postmarketing reports of overdose with olanzapine alone, symptoms have been reported in the majority of cases. In symptomatic patients, symptoms with $\geq 10\%$ incidence included agitation/aggressiveness, dysarthria, tachycardia, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma. Among less commonly reported symptoms were the following potentially medically serious events: aspiration, cardiopulmonary arrest, cardiac arrhythmias (such as supraventricular tachycardia as well as a patient that experienced sinus pause with spontaneous resumption of normal rhythm), delirium, possible neuroleptic malignant syndrome, respiratory depression/arrest, convulsion, hypertension, and hypotension. Eli Lilly and Company has received reports of fatality in association with overdose of olanzapine alone. In 1 case of death, the amount of acutely ingested olanzapine was reported to be possibly as low as 450 mg; however, in another case, a patient was reported to survive an acute olanzapine ingestion of 1500 mg.

Fluoxetine

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

Among 633 adult patients who overdosed on fluoxetine alone, 34 resulted in a fatal outcome, 378 completely recovered, and 15 patients experienced sequelae after overdose, 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 overdose were seizures, somnolence, nausea, tachycardia, and vomiting. The largest known ingestion of fluoxetine 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 6 fatalities was a 9-year-old boy who had a history of OCD, Tourette's Syndrome with tics, attention deficit disorder, and fetal alcohol syndrome. He had been receiving 100 mg of fluoxetine daily for 6 months in addition to clonidine, methylphenidate, and promethazine. Mixed-drug ingestion or other methods of suicide complicated all 6 overdoses in children that resulted in fatalities. The largest ingestion in pediatric patients was 3 grams, which was non-lethal.

Other important adverse events reported with fluoxetine overdose (single or multiple drugs) included 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.

Management of Overdose — In managing overdose, the possibility of multiple drug involvement should be considered. In case of acute overdose, establish and maintain an airway and ensure adequate ventilation, which may include intubation. Induction of emesis is not recommended as the possibility of obtundation, seizures, or dystonic reactions of the head and neck following overdose may create a risk for aspiration. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

A specific precaution involves patients who are taking or have recently taken SYMBYAX and may have ingested excessive quantities of a TCA (tricyclic antidepressant). In such cases, accumulation of the parent TCA and/or an active metabolite may increase the possibility of serious sequelae and extend the time needed for close medical observation.

Due to the large volume of distribution of olanzapine and fluoxetine, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidote for either fluoxetine or olanzapine overdose is known. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. Do not use epinephrine, dopamine, or other sympathomimetics with β -agonist activity, since beta stimulation may worsen hypotension in the setting of olanzapine-induced alpha blockade.

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

DOSAGE AND ADMINISTRATION

SYMBYAX should be administered once daily in the evening, generally beginning with the 6-mg/25-mg capsule. While food has no appreciable effect on the absorption of olanzapine and fluoxetine given individually, the effect of food on the absorption of SYMBYAX has not been studied. Dosage adjustments, if indicated, can be made according to efficacy and tolerability. Antidepressant efficacy was demonstrated with SYMBYAX in a dose range of olanzapine 6 to 12 mg and fluoxetine 25 to 50 mg (*see* CLINICAL STUDIES).

The safety of doses above 18 mg/75 mg has not been evaluated in clinical studies.

Special Populations

The starting dose of SYMBYAX 6 mg/25 mg should be used for patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of SYMBYAX (female gender, geriatric age, nonsmoking status). When indicated, dose escalation should be performed with caution in these patients. SYMBYAX has not been systematically studied in patients over 65 years of age or in patients <18 years of age (*see* WARNINGS, Orthostatic Hypotension, PRECAUTIONS, Pediatric Use, and Geriatric Use, and CLINICAL PHARMACOLOGY, Pharmacokinetics).

Treatment of Pregnant Women During the Third Trimester

Neonates exposed to fluoxetine, a component of SYMBYAX, and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (*see* PRECAUTIONS). When treating pregnant women with fluoxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering fluoxetine in the third trimester.

Discontinuation of Treatment with SYMBYAX

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

HOW SUPPLIED

SYMBYAX capsules are supplied in 6/25-, 6/50-, 12/25-, and 12/50-mg (mg equivalent olanzapine/mg equivalent fluoxetine^a) strengths.

SYMBYAX	CAPSULE STRENGTH			
	6 mg/25 mg	6 mg/50 mg	12 mg/25 mg	12 mg/50 mg
Color	Mustard Yellow & Light Yellow	Mustard Yellow & Light Grey	Red & Light Yellow	Red & Light Grey
Capsule No.	PU3231	PU3233	PU3232	PU3234
Identification	Lilly 3231 6/25	Lilly 3233 6/50	Lilly 3232 12/25	Lilly 3234 12/50
NDC Codes				
Bottles 30	0002-3231-30	0002-3233-30	0002-3232-30	0002-3234-30
Bottles 100	0002-3231-02	0002-3233-02	0002-3232-02	0002-3234-02

Bottles 1000	0002-3231-04	0002-3233-04	0002-3232-04	0002-3234-04
Blisters ID ^b 100	0002-3231-33	0002-3233-33	0002-3232-33	0002-3234-33

^a Fluoxetine base equivalent.

^b IDENTI-DOSE[®], Unit Dose Medication, Lilly.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Keep tightly closed and protect from moisture.

Medication Guide

About Using Antidepressants in Children and Teenagers

What is the most important information I should know if my child is being prescribed an antidepressant?

Parents or guardians need to think about 4 important things when their child is prescribed an antidepressant:

1. There is a risk of suicidal thoughts or actions
2. How to try to prevent suicidal thoughts or actions in your child
3. You should watch for certain signs if your child is taking an antidepressant
4. There are benefits and risks when using antidepressants

1. There is a Risk of Suicidal Thoughts or Actions

Children and teenagers sometimes think about suicide, and many report trying to kill themselves.

Antidepressants increase suicidal thoughts and actions in some children and teenagers. But suicidal thoughts and actions can also be caused by depression, a serious medical condition that is commonly treated with antidepressants. Thinking about killing yourself or trying to kill yourself is called *suicidality* or *being suicidal*.

A large study combined the results of 24 different studies of children and teenagers with depression or other illnesses. In these studies, patients took either a placebo (sugar pill) or an antidepressant for 1 to 4 months. ***No one committed suicide in these studies***, but some patients became suicidal. On sugar pills, 2 out of every 100 became suicidal. On the antidepressants, 4 out of every 100 patients became suicidal.

For some children and teenagers, the risks of suicidal actions may be especially high. These include patients with

- Bipolar illness (sometimes called manic-depressive illness)
- A family history of bipolar illness
- A personal or family history of attempting suicide

If any of these are present, make sure you tell your health care provider before your child takes an antidepressant.

2. How to Try to Prevent Suicidal Thoughts and Actions

To try to prevent suicidal thoughts and actions in your child, pay close attention to changes in her or his moods or actions, especially if the changes occur suddenly. Other important people in your child's life can help by paying attention as well (e.g., your child, brothers and sisters, teachers, and other important people). The changes to look out for are listed in Section 3, on what to watch for.

Whenever an antidepressant is started or its dose is changed, pay close attention to your child.

After starting an antidepressant, your child should generally see his or her health care provider

- Once a week for the first 4 weeks
- Every 2 weeks for the next 4 weeks
- After taking the antidepressant for 12 weeks
- After 12 weeks, follow your health care provider's advice about how often to come back
- More often if problems or questions arise (see Section 3)

You should call your child's health care provider between visits if needed.

3. You Should Watch for Certain Signs If Your Child is Taking an Antidepressant

Contact your child's health care provider *right away* if your child exhibits any of the following signs for the first time, or if they seem worse, or worry you, your child, or your child's teacher:

- Thoughts about suicide or dying
- Attempts to commit suicide
- New or worse depression
- New or worse anxiety
- Feeling very agitated or restless
- Panic attacks
- Difficulty sleeping (insomnia)
- New or worse irritability
- Acting aggressive, being angry, or violent
- Acting on dangerous impulses
- An extreme increase in activity and talking
- Other unusual changes in behavior or mood

Never let your child stop taking an antidepressant without first talking to his or her health care provider. Stopping an antidepressant suddenly can cause other symptoms.

4. There are Benefits and Risks When Using Antidepressants

Antidepressants are used to treat depression and other illnesses. Depression and other illnesses can lead to suicide. In some children and teenagers, treatment with an antidepressant increases suicidal thinking or actions. It is important to discuss all the risks of treating depression and also

the risks of not treating it. You and your child should discuss all treatment choices with your health care provider, not just the use of antidepressants.

Other side effects can occur with antidepressants (see section below).

Of all the antidepressants, only fluoxetine (Prozac[®]) has been FDA approved to treat pediatric depression.

For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine (Prozac[®]), sertraline (Zoloft[®]), fluvoxamine, and clomipramine (Anafranil[®]).

Your health care provider may suggest other antidepressants based on the past experience of your child or other family members.

Is this all I need to know if my child is being prescribed an antidepressant?

No. This is a warning about the risk for suicidality. Other side effects can occur with antidepressants. Be sure to ask your health care provider to explain all the side effects of the particular drug he or she is prescribing. Also ask about drugs to avoid when taking an antidepressant. Ask your health care provider or pharmacist where to find more information.

Prozac[®] is a registered trademark of Eli Lilly and Company.

Zoloft[®] is a registered trademark of Pfizer Pharmaceuticals.

Anafranil[®] is a registered trademark of Mallinckrodt Inc.

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

Rx only

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CYMBALTA[®] (duloxetine hydrochloride) Delayed-release Capsules

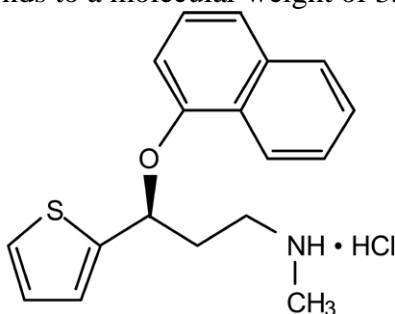
WARNING

Suicidality in Children and Adolescents — Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Cymbalta or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Cymbalta is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS, Pediatric Use.)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

Cymbalta[®] (duloxetine hydrochloride) is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) for oral administration. Its chemical designation is (+)-(S)-N-methyl-γ-(1-naphthoxy)-2-thiophenepropylamine hydrochloride. The empirical formula is C₁₈H₁₉NOS•HCl, which corresponds to a molecular weight of 333.88. The structural formula is:



Duloxetine hydrochloride is a white to slightly brownish white solid, which is slightly soluble in water.

Each capsule contains enteric-coated pellets of 22.4, 33.7, or 67.3 mg of duloxetine hydrochloride equivalent to 20, 30, or 60 mg of duloxetine, respectively. These enteric-coated pellets are designed to prevent degradation of the drug in the acidic environment of the stomach. Inactive ingredients include FD&C Blue No. 2, gelatin, hypromellose, hydroxypropyl methylcellulose acetate succinate, sodium lauryl sulfate, sucrose, sugar spheres, talc, titanium dioxide, and triethyl citrate. The 20 and 60 mg capsules also contain iron oxide yellow.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Although the exact mechanisms of the antidepressant and central pain inhibitory action of duloxetine in humans are unknown, the antidepressant and pain inhibitory actions are believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS. Preclinical studies have shown that duloxetine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a less potent inhibitor of dopamine reuptake. Duloxetine has no significant affinity for dopaminergic, adrenergic, cholinergic, histaminergic, opioid, glutamate, and GABA receptors *in vitro*. Duloxetine does not inhibit monoamine oxidase (MAO). Duloxetine undergoes extensive metabolism, but the major circulating metabolites have not been shown to contribute significantly to the pharmacologic activity of duloxetine.

Pharmacokinetics

Duloxetine has an elimination half-life of about 12 hours (range 8 to 17 hours) and its pharmacokinetics are dose proportional over the therapeutic range. Steady-state plasma concentrations are typically achieved after 3 days of dosing. Elimination of duloxetine is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP1A2.

Absorption and Distribution — Orally administered duloxetine hydrochloride is well absorbed. There is a median 2-hour lag until absorption begins (T_{lag}), with maximal plasma concentrations (C_{max}) of duloxetine occurring 6 hours post dose. Food does not affect the C_{max} of duloxetine, but delays the time to reach peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (AUC) by about 10%. There is a 3-hour delay in absorption and a one-third increase in apparent clearance of duloxetine after an evening dose as compared to a morning dose.

The apparent volume of distribution averages about 1640 L. Duloxetine is highly bound (>90%) to proteins in human plasma, binding primarily to albumin and α_1 -acid glycoprotein. The interaction between duloxetine and other highly protein bound drugs has not been fully evaluated. Plasma protein binding of duloxetine is not affected by renal or hepatic impairment.

Metabolism and Elimination — Biotransformation and disposition of duloxetine in humans have been determined following oral administration of ^{14}C -labeled duloxetine. Duloxetine comprises about 3% of the total radiolabeled material in the plasma, indicating that it undergoes extensive metabolism to numerous metabolites. The major biotransformation pathways for duloxetine involve oxidation of the naphthyl ring followed by conjugation and further oxidation. Both CYP2D6 and CYP1A2 catalyze the oxidation of the naphthyl ring *in vitro*. Metabolites found in plasma include 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate. Many additional metabolites have been identified in urine, some representing only minor pathways of elimination. Only trace (<1% of the dose) amounts of unchanged duloxetine are present in the urine. Most (about 70%) of the duloxetine dose appears in the urine as metabolites of duloxetine; about 20% is excreted in the feces.

Special Populations

Gender — Duloxetine's half-life is similar in men and women. Dosage adjustment based on gender is not necessary.

Age — The pharmacokinetics of duloxetine after a single dose of 40 mg were compared in healthy elderly females (65 to 77 years) and healthy middle-age females (32 to 50 years). There was no difference in the C_{max} , but the AUC of duloxetine was somewhat (about 25%) higher and

the half-life about 4 hours longer in the elderly females. Population pharmacokinetic analyses suggest that the typical values for clearance decrease by approximately 1% for each year of age between 25 to 75 years of age; but age as a predictive factor only accounts for a small percentage of between-patient variability. Dosage adjustment based on the age of the patient is not necessary (*see* DOSAGE AND ADMINISTRATION).

Smoking Status — Duloxetine bioavailability (AUC) appears to be reduced by about one-third in smokers. Dosage modifications are not recommended for smokers.

Race — No specific pharmacokinetic study was conducted to investigate the effects of race.

Renal Insufficiency — Limited data are available on the effects of duloxetine in patients with end-stage renal disease (ESRD). After a single 60-mg dose of duloxetine, C_{max} and AUC values were approximately 100% greater in patients with end-stage renal disease receiving chronic intermittent hemodialysis than in subjects with normal renal function. The elimination half-life, however, was similar in both groups. The AUCs of the major circulating metabolites, 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate, largely excreted in urine, were approximately 7- to 9-fold higher and would be expected to increase further with multiple dosing. For this reason, Cymbalta is not recommended for patients with end-stage renal disease (requiring dialysis) or severe renal impairment (estimated creatinine clearance [CrCl] <30 mL/min) (*see* DOSAGE AND ADMINISTRATION). Population PK analyses suggest that mild to moderate degrees of renal dysfunction (estimated CrCl 30-80 mL/min) have no significant effect on duloxetine apparent clearance.

Hepatic Insufficiency — Patients with clinically evident hepatic insufficiency have decreased duloxetine metabolism and elimination. After a single 20-mg dose of Cymbalta, 6 cirrhotic patients with moderate liver impairment (Child-Pugh Class B) had a mean plasma duloxetine clearance about 15% that of age- and gender-matched healthy subjects, with a 5-fold increase in mean exposure (AUC). Although C_{max} was similar to normals in the cirrhotic patients, the half-life was about 3 times longer (*see* PRECAUTIONS). It is recommended that duloxetine not be administered to patients with any hepatic insufficiency (*see* DOSAGE AND ADMINISTRATION).

Nursing Mothers — The disposition of duloxetine was studied in 6 lactating women who were at least 12-weeks postpartum. Duloxetine 40 mg BID was given for 3.5 days. Like many other drugs, duloxetine is detected in breast milk, and steady-state concentrations in breast milk are about one-fourth those in plasma. The amount of duloxetine in breast milk is approximately 7 µg/day while on 40 mg BID dosing. Lactation did not influence duloxetine pharmacokinetics. Because the safety of duloxetine in infants is not known, nursing while on Cymbalta is not recommended. However, if the physician determines that the benefit of duloxetine therapy for the mother outweighs any potential risk to the infant, no dosage adjustment is required as lactation did not influence duloxetine pharmacokinetics (*see* DOSAGE AND ADMINISTRATION).

Drug-Drug Interactions (also see PRECAUTIONS, Drug Interactions)

Potential for Other Drugs to Affect Duloxetine

Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

Inhibitors of CYP1A2 — When duloxetine was co-administered with fluvoxamine, a potent CYP1A2 inhibitor, to male subjects (n=14) the AUC was increased approximately 6-fold, the C_{max} was increased about 2.5-fold, and duloxetine $t_{1/2}$ was increased approximately 3-fold. Other drugs that inhibit CYP1A2 metabolism include cimetidine and quinolone antimicrobials such as ciprofloxacin and enoxacin.

Inhibitors of CYP2D6 — Because CYP2D6 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP2D6 would be expected to, and does, result in higher concentrations of duloxetine (*see* PRECAUTIONS, Drug Interactions).

Studies with Benzodiazepines

Lorazepam — Under steady-state conditions for duloxetine (60 mg Q 12 hours) and lorazepam (2 mg Q 12 hours), the pharmacokinetics of duloxetine were not affected by co-administration.

Temazepam — Under steady-state conditions for duloxetine (20 mg qhs) and temazepam (30 mg qhs), the pharmacokinetics of duloxetine were not affected by co-administration.

Potential for Duloxetine to Affect Other Drugs

Drugs Metabolized by CYP1A2 — *In vitro* drug interaction studies demonstrate that duloxetine does not induce CYP1A2 activity. Therefore, an increase in the metabolism of CYP1A2 substrates (e.g., theophylline, caffeine) resulting from induction is not anticipated, although clinical studies of induction have not been performed. Although duloxetine is an inhibitor of the CYP1A2 isoform in *in vitro* studies, the pharmacokinetics of theophylline, a CYP1A2 substrate, were not significantly affected by co-administration with duloxetine (60 mg BID). Duloxetine is thus unlikely to have a clinically significant effect on the metabolism of CYP1A2 substrates.

Drugs Metabolized by CYP2D6 — Duloxetine is a moderate inhibitor of CYP2D6 and increases the AUC and C_{max} of drugs metabolized by CYP2D6 (*see* PRECAUTIONS). Therefore, co-administration of Cymbalta with other drugs that are extensively metabolized by this isozyme and that have a narrow therapeutic index should be approached with caution (*see* PRECAUTIONS, Drug Interactions).

Drugs Metabolized by CYP2C9 — Duloxetine does not inhibit the *in vitro* enzyme activity of CYP2C9. Inhibition of the metabolism of CYP2C9 substrates is therefore not anticipated, although clinical studies have not been performed.

Drugs Metabolized by CYP3A — Results of *in vitro* studies demonstrate that duloxetine does not inhibit or induce CYP3A activity. Therefore, an increase or decrease in the metabolism of CYP3A substrates (e.g., oral contraceptives and other steroidal agents) resulting from induction or inhibition is not anticipated, although clinical studies have not been performed.

Drugs Metabolized by CYP2C19 — Results of *in vitro* studies demonstrate that duloxetine does not inhibit CYP2C19 activity at therapeutic concentrations. Inhibition of the metabolism of CYP2C19 substrates is therefore not anticipated, although clinical studies have not been performed.

Studies with Benzodiazepines

Lorazepam — Under steady-state conditions for duloxetine (60 mg Q 12 hours) and lorazepam (2 mg Q 12 hours), the pharmacokinetics of lorazepam were not affected by co-administration.

Temazepam — Under steady-state conditions for duloxetine (20 mg qhs) and temazepam (30 mg qhs), the pharmacokinetics of temazepam were not affected by co-administration.

Drugs Highly Bound to Plasma Protein — Because duloxetine is highly bound to plasma protein, administration of Cymbalta to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse events.

CLINICAL STUDIES

Major Depressive Disorder

The efficacy of Cymbalta as a treatment for depression was established in 4 randomized, double-blind, placebo-controlled, fixed-dose studies in adult outpatients (18 to 83 years) meeting

DSM-IV criteria for major depression. In 2 studies, patients were randomized to Cymbalta 60 mg once daily (N=123 and N=128, respectively) or placebo (N=122 and N=139, respectively) for 9 weeks; in the third study, patients were randomized to Cymbalta 20 or 40 mg twice daily (N=86 and N=91, respectively) or placebo (N=89) for 8 weeks; in the fourth study, patients were randomized to Cymbalta 40 or 60 mg twice daily (N=95 and N=93, respectively) or placebo (N=93) for 8 weeks. There is no evidence that doses greater than 60 mg/day confer any additional benefit.

In all 4 studies, Cymbalta demonstrated superiority over placebo as measured by improvement in the 17-item Hamilton Depression Rating Scale (HAM-D-17) total score.

Analyses of the relationship between treatment outcome and age, gender, and race did not suggest any differential responsiveness on the basis of these patient characteristics.

Diabetic Peripheral Neuropathic Pain

The efficacy of Cymbalta for the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN) was established in 2 randomized, 12-week, double-blind, placebo-controlled, fixed-dose studies in adult patients having diabetic peripheral neuropathy for at least 6 months. Study 1 and 2 enrolled a total of 791 patients of whom 592 (75%) completed the studies. Patients enrolled had Type I or II diabetes mellitus with a diagnosis of painful distal symmetrical sensorimotor polyneuropathy for at least 6 months. The patients had a baseline pain score of ≥ 4 on an 11-point scale ranging from 0 (no pain) to 10 (worst possible pain). Patients were permitted up to 4 g of acetaminophen per day as needed for pain, in addition to Cymbalta. Patients recorded their pain daily in a diary.

Both studies compared Cymbalta 60 mg once daily or 60 mg twice daily with placebo. Study 1 additionally compared Cymbalta 20 mg with placebo. A total of 457 patients (342 Cymbalta, 115 placebo) were enrolled in Study 1 and a total of 334 patients (226 Cymbalta, 108 placebo) were enrolled in Study 2. Treatment with Cymbalta 60 mg one or two times a day statistically significantly improved the endpoint mean pain scores from baseline and increased the proportion of patients with at least a 50% reduction in pain score from baseline. For various degrees of improvement in pain from baseline to study endpoint, Figures 1 and 2 show the fraction of patients achieving that degree of improvement. The figures are cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

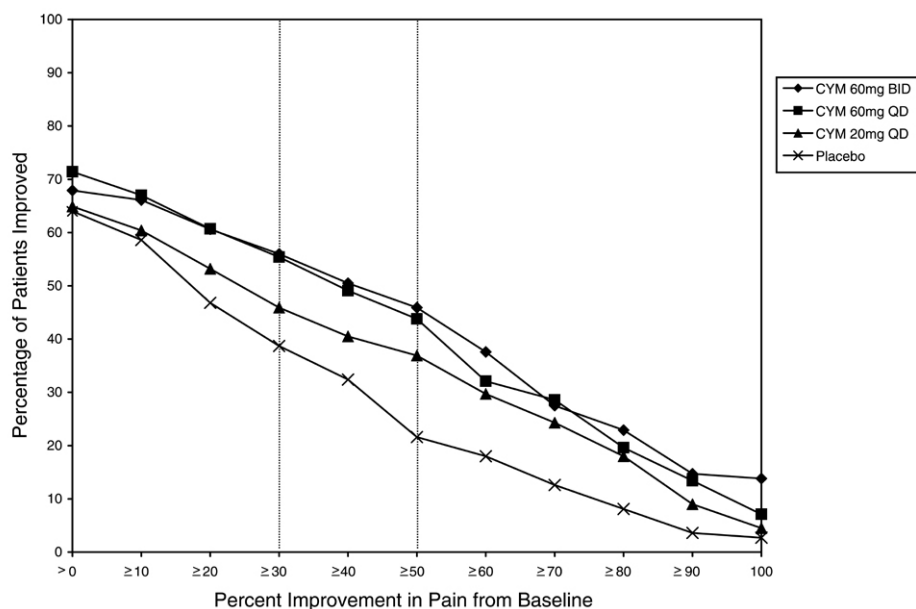


Figure 1: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity - Study 1

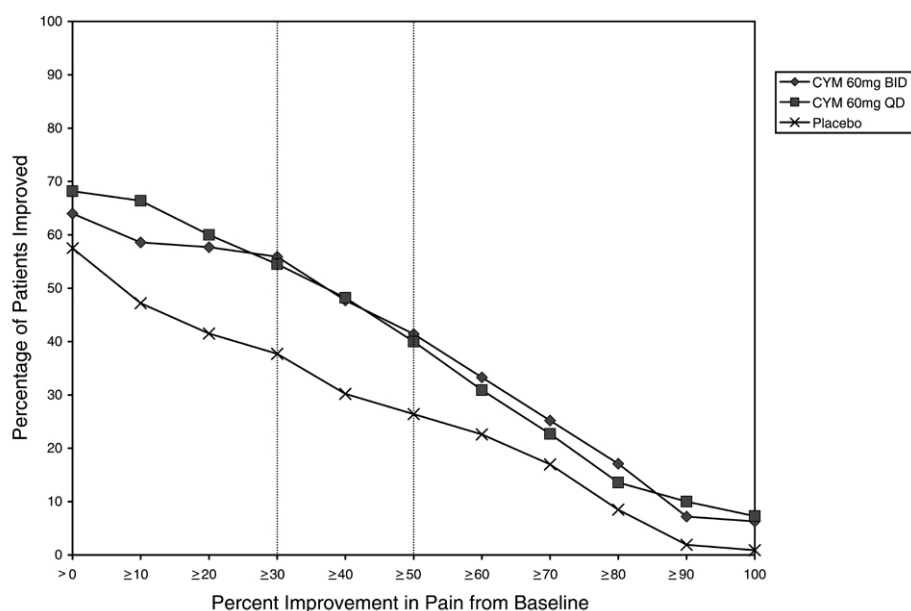


Figure 2: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity - Study 2

INDICATIONS AND USAGE

Major Depressive Disorder

Cymbalta is indicated for the treatment of major depressive disorder (MDD).

The efficacy of Cymbalta has been established in 8- and 9-week placebo-controlled trials of outpatients who met DSM-IV diagnostic criteria for major depressive disorder (*see CLINICAL STUDIES*).

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 in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, or a suicide attempt or suicidal ideation.

The effectiveness of Cymbalta in hospitalized patients with major depressive disorder has not been studied.

The effectiveness of Cymbalta in long-term use for major depressive disorder, that is, for more than 9 weeks, has not been systematically evaluated in controlled trials. The physician who elects to use Cymbalta for extended periods should periodically evaluate the long-term usefulness of the drug for the individual patient.

Diabetic Peripheral Neuropathic Pain

Cymbalta is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy (*see* CLINICAL STUDIES).

CONTRAINDICATIONS

Hypersensitivity

Cymbalta is contraindicated in patients with a known hypersensitivity to duloxetine or any of the inactive ingredients.

Monoamine Oxidase Inhibitors

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (*see* WARNINGS).

Uncontrolled Narrow-Angle Glaucoma

In clinical trials, Cymbalta use was associated with an increased risk of mydriasis; therefore, its use should be avoided in patients with uncontrolled narrow-angle glaucoma.

WARNINGS

Clinical Worsening and Suicide Risk — Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well.

No suicides occurred in any of these trials. It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

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

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

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

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

Screening Patients for Bipolar Disorder — A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately

screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Cymbalta is not approved for use in treating bipolar depression.

Monoamine Oxidase Inhibitors (MAOI) — In patients receiving a serotonin reuptake inhibitor in combination with a monoamine oxidase inhibitor, 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. These reactions have also been reported in patients who have recently discontinued serotonin reuptake inhibitors and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. The effects of combined use of Cymbalta and MAOIs have not been evaluated in humans or animals. Therefore, because Cymbalta is an inhibitor of both serotonin and norepinephrine reuptake, it is recommended that Cymbalta not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of Cymbalta, at least 5 days should be allowed after stopping Cymbalta before starting an MAOI.

Serotonin Syndrome: The development of a potentially life-threatening serotonin syndrome may occur with Cymbalta treatment, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs which impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

The concomitant use of Cymbalta with MAOIs intended to treat depression is contraindicated (*see* CONTRAINDICATIONS and WARNINGS, Potential for Interaction with Monoamine Oxidase Inhibitors)

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

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

PRECAUTIONS

General

Hepatotoxicity — Cymbalta increases the risk of elevation of serum transaminase levels. Liver transaminase elevations resulted in the discontinuation of 0.4% (31/8454) of Cymbalta-treated patients. In these patients, the median time to detection of the transaminase elevation was about two months. In controlled trials in MDD, elevations of alanine transaminase (ALT) to >3 times the upper limit of normal occurred in 0.9% (8/930) of Cymbalta-treated patients and in 0.3% (2/652) of placebo-treated patients. In controlled trials in DPN, elevations of ALT to >3 times the upper limit of normal occurred in 1.68% (8/477) of Cymbalta-treated patients and in 0% (0/187) of placebo-treated patients. In the full cohort of placebo-controlled trials in any indication, 1% (39/3732) of Cymbalta-treated patients had a >3 times the upper limit of normal elevation of ALT compared to 0.2% (6/2568) of placebo-treated patients. In placebo-controlled studies using a fixed-dose design, there was evidence of a dose-response relationship for ALT and AST elevation of >3 times the upper limit of normal and >5 times the upper limit of normal,

respectively. Postmarketing reports have described cases of hepatitis with abdominal pain, hepatomegaly and elevation of transaminase levels to more than twenty times the upper limit of normal with or without jaundice, reflecting a mixed or hepatocellular pattern of liver injury. Cases of cholestatic jaundice with minimal elevation of transaminase levels have also been reported.

The combination of transaminase elevations and elevated bilirubin, without evidence of obstruction, is generally recognized as an important predictor of severe liver injury. In clinical trials, three Cymbalta patients had elevations of transaminases and bilirubin, but also had elevation of alkaline phosphatase, suggesting an obstructive process; in these patients, there was evidence of heavy alcohol use and this may have contributed to the abnormalities seen. Two placebo-treated patients also had transaminase elevations with elevated bilirubin. Postmarketing reports indicate that elevated transaminases, bilirubin and alkaline phosphatase have occurred in patients with chronic liver disease or cirrhosis. Because it is possible that duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate pre-existing liver disease, Cymbalta should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

Effect on Blood Pressure — In MDD clinical trials, Cymbalta treatment was associated with mean increases in blood pressure, averaging 2 mm Hg systolic and 0.5 mm Hg diastolic and an increase in the incidence of at least one measurement of systolic blood pressure over 140 mm Hg compared to placebo.

Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment (*see* ADVERSE REACTIONS, Vital Sign Changes).

Activation of Mania/Hypomania — In placebo-controlled trials in patients with major depressive disorder, activation of mania or hypomania was reported in 0.1% (1/1139) of Cymbalta-treated patients and 0.1% (1/777) of placebo-treated patients. Activation of mania/hypomania has been reported in a small proportion of patients with mood disorders who were treated with other marketed drugs effective in the treatment of major depressive disorder. As with these other agents, Cymbalta should be used cautiously in patients with a history of mania.

Seizures — Cymbalta has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. In placebo-controlled clinical trials in patients with major depressive disorder, seizures occurred in 0.1% (1/1139) of patients treated with Cymbalta and 0% (0/777) of patients treated with placebo. In placebo-controlled clinical trials in patients with diabetic peripheral neuropathy, seizures did not occur in any patients treated with either Cymbalta or placebo. Cymbalta should be prescribed with care in patients with a history of a seizure disorder.

Controlled Narrow-Angle Glaucoma — In clinical trials, Cymbalta was associated with an increased risk of mydriasis; therefore, it should be used cautiously in patients with controlled narrow-angle glaucoma (*see* CONTRAINDICATIONS, Uncontrolled Narrow-Angle Glaucoma).

Discontinuation of Treatment with Cymbalta — Discontinuation symptoms have been systematically evaluated in patients taking Cymbalta. Following abrupt discontinuation in MDD placebo-controlled clinical trials of up to 9-weeks duration, the following symptoms occurred at a rate greater than or equal to 2% and at a significantly higher rate in Cymbalta-treated patients compared to those discontinuing from placebo: dizziness; nausea; headache; paresthesia; vomiting; irritability; and nightmare.

During marketing of other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Although these events are generally self-limiting, some have been reported to be severe.

Patients should be monitored for these symptoms when discontinuing treatment with Cymbalta. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (*see* DOSAGE AND ADMINISTRATION).

Use in Patients with Concomitant Illness — Clinical experience with Cymbalta in patients with concomitant systemic illnesses is limited. There is no information on the effect that alterations in gastric motility may have on the stability of Cymbalta's enteric coating. As duloxetine is rapidly hydrolyzed in acidic media to naphthol, caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (e.g., some diabetics).

Cymbalta has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable coronary artery disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing. However, the electrocardiograms of 321 patients who received Cymbalta in MDD placebo-controlled clinical trials and had qualitatively normal ECGs at baseline were evaluated; Cymbalta was not associated with the development of clinically significant ECG abnormalities (*see* ADVERSE REACTIONS, Electrocardiogram Changes).

In DPN placebo-controlled clinical trials, Cymbalta-treated patients did not develop abnormal ECGs at a rate different from that in placebo-treated patients (*see* ADVERSE REACTIONS, Electrocardiogram Changes).

In three clinical trials of Cymbalta for the management of neuropathic pain associated with diabetic peripheral neuropathy, the mean duration of diabetes was approximately 12 years, the mean baseline fasting blood glucose was 176 mg/dL, and the mean baseline hemoglobin A_{1c} (HbA_{1c}) was 7.8%. In the 12-week acute treatment phase of these studies, small increases in fasting blood glucose were observed in Cymbalta-treated patients. HbA_{1c} was stable in both Cymbalta-treated and placebo-treated patients. In the extension phase of these studies, which lasted up to 52 weeks, there was an increase in HbA_{1c} in both the Cymbalta and the routine care groups, but the mean increase was 0.3% greater in the Cymbalta-treated group. There was also a small increase in fasting blood glucose in the Cymbalta-treated group. Total cholesterol was increased in Cymbalta-treated patients (2 mg/dL) and decreased in the routine care group (6 mg/dL).

Increased plasma concentrations of duloxetine, and especially of its metabolites, occur in patients with end-stage renal disease (requiring dialysis). For this reason, Cymbalta is not recommended for patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min) (*see* CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Markedly increased exposure to duloxetine occurs in patients with hepatic insufficiency and Cymbalta should not be administered to these patients (*see* CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Information for Patients

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Cymbalta and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for Cymbalta. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

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

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

Cymbalta should be swallowed whole and should not be chewed or crushed, nor should the contents be sprinkled on food or mixed with liquids. All of these might affect the enteric coating.

Any psychoactive drug may impair judgment, thinking, or motor skills. Although in controlled studies Cymbalta has not been shown to impair psychomotor performance, cognitive function, or memory, it may be associated with sedation and dizziness. Therefore, patients should be cautioned about operating hazardous machinery including automobiles, until they are reasonably certain that Cymbalta therapy does not affect their ability to engage in such activities.

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter medications, since there is a potential for interactions.

Although Cymbalta does not increase the impairment of mental and motor skills caused by alcohol, use of Cymbalta concomitantly with heavy alcohol intake may be associated with severe liver injury. For this reason, Cymbalta should ordinarily not be prescribed for patients with substantial alcohol use.

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

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast-feeding.

While patients with MDD may notice improvement with Cymbalta therapy in 1 to 4 weeks, they should be advised to continue therapy as directed.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions (also see CLINICAL PHARMACOLOGY, Drug-Drug Interactions)

Potential for Other Drugs to Affect Cymbalta

Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

Inhibitors of CYP1A2 — Concomitant use of duloxetine with fluvoxamine, an inhibitor of CYP1A2, results in approximately a 6-fold increase in AUC and about a 2.5-fold increase in C_{max} of duloxetine. Some quinolone antibiotics would be expected to have similar effects and these combinations should be avoided.

Inhibitors of CYP2D6 — Because CYP2D6 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP2D6 may result in higher concentrations of duloxetine. Paroxetine (20 mg QD) increased the concentration of duloxetine (40 mg QD) by about 60%, and greater degrees of inhibition are expected with higher doses of paroxetine. Similar effects would be expected with other potent CYP2D6 inhibitors (e.g., fluoxetine, quinidine).

Potential for Duloxetine to Affect Other Drugs

Drugs Metabolized by CYP1A2 — *In vitro* drug interaction studies demonstrate that duloxetine does not induce CYP1A2 activity, and it is unlikely to have a clinically significant effect on the metabolism of CYP1A2 substrates (see CLINICAL PHARMACOLOGY, Drug Interactions).

Drugs Metabolized by CYP2D6 — Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered (at a dose of 60 mg BID) in conjunction with a single 50-mg dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold. Therefore, co-administration of Cymbalta with other drugs that are extensively metabolized by this isozyme and which have a narrow therapeutic index, including certain antidepressants (tricyclic antidepressants [TCAs], such as nortriptyline, amitriptyline, and imipramine), phenothiazines and Type 1C antiarrhythmics (e.g., propafenone, flecainide), should be approached with caution. Plasma TCA concentrations may need to be monitored and the dose of the TCA may need to be reduced if a TCA is co-administered with Cymbalta. Because of the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, Cymbalta and thioridazine should not be co-administered.

Drugs Metabolized by CYP3A — Results of *in vitro* studies demonstrate that duloxetine does not inhibit or induce CYP3A activity (see CLINICAL PHARMACOLOGY, Drug Interactions).

Cymbalta May Have a Clinically Important Interaction with the Following Other Drugs:

Alcohol — When Cymbalta and ethanol were administered several hours apart so that peak concentrations of each would coincide, Cymbalta did not increase the impairment of mental and motor skills caused by alcohol.

In the Cymbalta clinical trials database, three Cymbalta-treated patients had liver injury as manifested by ALT and total bilirubin elevations, with evidence of obstruction. Substantial intercurrent ethanol use was present in each of these cases, and this may have contributed to the abnormalities seen (see PRECAUTIONS, Hepatotoxicity).

CNS Acting Drugs — Given the primary CNS effects of Cymbalta, it should be used with caution when it is taken in combination with or substituted for other centrally acting drugs, including those with a similar mechanism of action.

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

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

Potential for Interaction with Drugs that Affect Gastric Acidity — Cymbalta has an enteric coating that resists dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. In extremely acidic conditions, Cymbalta, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (e.g., some diabetics). Drugs that raise the gastrointestinal pH may lead to an earlier release of duloxetine. However, co-administration of Cymbalta with aluminum- and magnesium-containing antacids (51 mEq) or Cymbalta with famotidine, had no significant effect on the rate or extent of duloxetine absorption after administration of a 40-mg oral dose. It is unknown whether the concomitant administration of proton pump inhibitors affects duloxetine absorption.

Monoamine Oxidase Inhibitors — *See* CONTRAINDICATIONS and WARNINGS.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis — Duloxetine was administered in the diet to mice and rats for 2 years.

In female mice receiving duloxetine at 140 mg/kg/day (11 times the maximum recommended human dose [MRHD, 60 mg/day] and 6 times the human dose of 120 mg/day on a mg/m² basis), there was an increased incidence of hepatocellular adenomas and carcinomas. The no-effect dose was 50 mg/kg/day (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m² basis). Tumor incidence was not increased in male mice receiving duloxetine at doses up to 100 mg/kg/day (8 times the MRHD and 4 times the human dose of 120 mg/day on a mg/m² basis).

In rats, dietary doses of duloxetine up to 27 mg/kg/day in females (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m² basis) and up to 36 mg/kg/day in males (6 times the MRHD and 3 times the human dose of 120 mg/day on a mg/m² basis) did not increase the incidence of tumors.

Mutagenesis — Duloxetine was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) and was not clastogenic in an *in vivo* chromosomal aberration test in mouse bone marrow cells. Additionally, duloxetine was not genotoxic in an *in vitro* mammalian forward gene mutation assay in mouse lymphoma cells or in an *in vitro* unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes, and did not induce sister chromatid exchange in Chinese hamster bone marrow *in vivo*.

Impairment of Fertility — Duloxetine administered orally to either male or female rats prior to and throughout mating at doses up to 45 mg/kg/day (7 times the maximum recommended human dose of 60 mg/day and 4 times the human dose of 120 mg/day on a mg/m² basis) did not alter mating or fertility.

Pregnancy

Pregnancy Category C — In animal reproduction studies, duloxetine has been shown to have adverse effects on embryo/fetal and postnatal development.

When duloxetine was administered orally to pregnant rats and rabbits during the period of organogenesis, there was no evidence of teratogenicity at doses up to 45 mg/kg/day (7 times the maximum recommended human dose [MRHD, 60 mg/day] and 4 times the human dose of 120 mg/day on a mg/m² basis, in rat; 15 times the MRHD and 7 times the human dose of 120 mg/day on a mg/m² basis in rabbit). However, fetal weights were decreased at this dose, with a no-effect dose of 10 mg/kg/day (2 times the MRHD and ≈1 times the human dose of 120 mg/day on a mg/m² basis in rat; 3 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m² basis in rabbits).

When duloxetine was administered orally to pregnant rats throughout gestation and lactation, the survival of pups to 1 day postpartum and pup body weights at birth and during the lactation period were decreased at a dose of 30 mg/kg/day (5 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m² basis); the no-effect dose was 10 mg/kg/day. Furthermore, behaviors consistent with increased reactivity, such as increased startle response to noise and decreased habituation of locomotor activity, were observed in pups following maternal exposure to 30 mg/kg/day. Post-weaning growth and reproductive performance of the progeny were not affected adversely by maternal duloxetine treatment.

There are no adequate and well-controlled studies in pregnant women; therefore, duloxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

Labor and Delivery

The effect of duloxetine on labor and delivery in humans is unknown. Duloxetine should be used during labor and delivery only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Duloxetine is excreted into the milk of lactating women. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose. Because the safety of duloxetine in infants is not known, nursing while on Cymbalta is not recommended. However, if the physician determines that the benefit of duloxetine therapy for the mother outweighs any potential risk to the infant, no dosage adjustment is required as lactation did not influence duloxetine pharmacokinetics.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established (*see* BOX WARNING and WARNINGS, Clinical Worsening and Suicide Risk). Anyone considering the use of Cymbalta in a child or adolescent must balance the potential risks with the clinical need.

Geriatric Use

Of the 2418 patients in clinical studies of Cymbalta for MDD, 5.9% (143) were 65 years of age or over. Of the 1074 patients in the DPN studies, 33% (357) were 65 years of age or over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Cymbalta has been evaluated for safety in 2418 patients diagnosed with major depressive disorder who participated in multiple-dose premarketing trials, representing 1099 patient-years of exposure. Among these 2418 Cymbalta-treated patients, 1139 patients participated in eight 8- or 9-week, placebo-controlled trials at doses ranging from 40 to 120 mg/day, while the remaining 1279 patients were followed for up to 1 year in an open-label safety study using flexible doses from 80 to 120 mg/day. Two placebo-controlled studies with doses of 80 and 120 mg/day had 6-month maintenance extensions. Of these 2418 patients, 993 Cymbalta-treated patients were exposed for at least 180 days and 445 Cymbalta-treated patients were exposed for at least 1 year.

Cymbalta has also been evaluated for safety in 1074 patients with diabetic peripheral neuropathy representing 472 patient-years of exposure. Among these 1074 Cymbalta-treated patients, 568 patients participated in two 12- to 13-week, placebo-controlled trials at doses ranging from 20 to 120 mg/day. An additional 449 patients were enrolled in an open-label safety study using 120 mg/day for a duration of 6 months. Another 57 patients, originally treated with placebo, were exposed to Cymbalta for up to 12 months at 60 mg twice daily in an extension phase. Among these 1074 patients, 484 had 6 months of exposure to Cymbalta, and 220 had 12 months of exposure.

For both MDD and DPN clinical trials, adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Clinical investigators recorded adverse events using descriptive terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals experiencing adverse events, grouping similar types of events into a smaller number of standardized event categories is necessary. In the tables and tabulations that follow, MedDRA terminology has been used to classify reported adverse events.

The stated frequencies of adverse events 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. Events reported during the studies were not necessarily caused by the therapy, and the frequencies do not reflect investigator impression (assessment) of causality.

The cited figures provide the prescriber with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied. The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of adverse events 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.

Adverse Events Reported as Reasons for Discontinuation of Treatment in Placebo-Controlled Trials

Major Depressive Disorder

Approximately 10% of the 1139 patients who received Cymbalta in the MDD placebo-controlled trials discontinued treatment due to an adverse event, compared with 4% of the 777 patients receiving placebo. Nausea (Cymbalta 1.4%, placebo 0.1%) was the only common adverse event reported as reason for discontinuation and considered to be drug-related (i.e., discontinuation occurring in at least 1% of the Cymbalta-treated patients and at a rate of at least twice that of placebo).

Diabetic Peripheral Neuropathic Pain

Approximately 14% of the 568 patients who received Cymbalta in the DPN placebo-controlled trials discontinued treatment due to an adverse event, compared with 7% of the 223 patients receiving placebo. Nausea (Cymbalta 3.5%, placebo 0.4%), dizziness (Cymbalta 1.6%, placebo 0.4%), somnolence (Cymbalta 1.6%, placebo 0%) and fatigue (Cymbalta 1.1%, placebo 0%) were the common adverse events reported as reasons for discontinuation and considered to be drug-related (i.e., discontinuation occurring in at least 1% of the Cymbalta-treated patients and at a rate of at least twice that of placebo).

Adverse Events Occurring at an Incidence of 2% or More Among Cymbalta-Treated Patients in Placebo-Controlled Trials

Major Depressive Disorder

Table 1 gives the incidence of treatment-emergent adverse events that occurred in 2% or more of patients treated with Cymbalta in the premarketing acute phase of MDD placebo-controlled trials and with an incidence greater than placebo. The most commonly observed adverse events in Cymbalta-treated MDD patients (incidence of 5% or greater and at least twice the incidence in placebo patients) were: nausea; dry mouth; constipation; decreased appetite; fatigue; somnolence; and increased sweating (*see* Table 1).

Table 1: Treatment-Emergent Adverse Events Incidence in MDD Placebo-Controlled Trials¹

System Organ Class / Adverse Event	Percentage of Patients Reporting Event	
	Cymbalta (N=1139)	Placebo (N=777)
Gastrointestinal Disorders		
Nausea	20	7
Dry mouth	15	6
Constipation	11	4
Diarrhea	8	6
Vomiting	5	3
Metabolism and Nutrition Disorders		
Appetite decreased ²	8	2
Investigations		
Weight decreased	2	1
General Disorders and Administration Site Conditions		

Fatigue	8	4
Nervous System Disorders		
Dizziness	9	5
Somnolence	7	3
Tremor	3	1
Skin and Subcutaneous Tissue Disorders		
Sweating increased	6	2
Vascular Disorders		
Hot flushes	2	1
Eye Disorders		
Vision blurred	4	1
Psychiatric Disorders		
Insomnia ³	11	6
Anxiety	3	2
Libido decreased	3	1
Orgasm abnormal ⁴	3	1
Reproductive System and Breast Disorders		
Erectile dysfunction ⁵	4	1
Ejaculation delayed ⁵	3	1
Ejaculatory dysfunction ^{5,6}	3	1

¹ Events reported by at least 2% of patients treated with Cymbalta and more often with placebo. The following events were reported by at least 2% of patients treated with Cymbalta for MDD and had an incidence equal to or less than placebo: upper abdominal pain, palpitations, dyspepsia, back pain, arthralgia, headache, pharyngitis, cough, nasopharyngitis, and upper respiratory tract infection.

² Term includes anorexia.

³ Term includes middle insomnia.

⁴ Term includes anorgasmia.

⁵ Male patients only.

⁶ Term includes ejaculation disorder and ejaculation failure.

Diabetic Peripheral Neuropathic Pain

Table 2 gives the incidence of treatment-emergent adverse events that occurred in 2% or more of patients treated with Cymbalta in the premarketing acute phase of DPN placebo-controlled trials (doses of 20 to 120 mg/day) and with an incidence greater than placebo. The most commonly observed adverse events in Cymbalta-treated DPN patients (incidence of 5% or greater and at least twice the incidence in placebo patients) were: nausea; somnolence; dizziness; constipation; dry mouth; hyperhidrosis; decreased appetite; and asthenia (*see* Table 2).

Table 2: Treatment-Emergent Adverse Events Incidence in DPN Placebo-Controlled Trials¹

System Organ Class / Adverse Event	Percentage of Patients Reporting Event			
	Cymbalta 60 mg BID (N=225)	Cymbalta 60 mg QD (N=228)	Cymbalta 20 mg QD (N=115)	Placebo (N=223)
Gastrointestinal Disorders				
Nausea	30	22	14	9
Constipation	15	11	5	3
Diarrhea	7	11	13	6
Dry mouth	12	7	5	4
Vomiting	5	5	6	4
Dyspepsia	4	4	4	3
Loose stools	2	3	2	1

General Disorders and Administration Site Conditions				
Fatigue	12	10	2	5
Asthenia	8	4	2	1
Pyrexia	3	1	2	1
Infections and Infestations				
Nasopharyngitis	9	7	9	5
Metabolism and Nutrition Disorders				
Decreased appetite	11	4	3	<1
Anorexia	5	3	3	<1
Musculoskeletal and Connective Tissue Disorders				
Muscle cramp	4	4	5	3
Myalgia	4	1	3	<1
Nervous System Disorders				
Somnolence	21	15	7	5
Headache	15	13	13	10
Dizziness	17	14	6	6
Tremor	5	1	0	0
Psychiatric Disorders				
Insomnia	13	8	9	7
Renal and Urinary Disorders				
Pollakiuria	5	1	3	2
Reproductive System and Breast Disorders				
Erectile dysfunction ²	4	1	0	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	5	3	6	4
Pharyngolaryngeal pain	6	1	3	1
Skin and Subcutaneous Tissue Disorders				
Hyperhidrosis	8	6	6	2

¹ Events reported by at least 2% of patients treated with Cymbalta and more often than placebo. The following events were reported by at least 2% of patients treated with Cymbalta for DPN and had an incidence equal to or less than placebo: edema peripheral, influenza, upper respiratory tract infection, back pain, arthralgia, pain in extremity, and pruritus.

² Male patients only.

Adverse events seen in men and women were generally similar except for effects on sexual function (described below). Clinical studies of Cymbalta did not suggest a difference in adverse event rates in people over or under 65 years of age. There were too few non-Caucasian patients studied to determine if these patients responded differently from Caucasian patients.

Effects on Male and Female Sexual Function

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. 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. Table 3 displays the incidence of sexual side effects

spontaneously reported by at least 2% of either male or female patients taking Cymbalta in MDD placebo-controlled trials.

Table 3: Treatment-Emergent Sexual Dysfunction-Related Adverse Events Incidence in MDD Placebo-Controlled Trials¹

Adverse Event	Percentage of Patients Reporting Event			
	% Male Patients		% Female Patients	
	Cymbalta (N=378)	Placebo (N=247)	Cymbalta (N=761)	Placebo (N=530)
Orgasm abnormal ²	4	1	2	0
Ejaculatory dysfunction ³	3	1	NA	NA
Libido decreased	6	2	1	0
Erectile dysfunction	4	1	NA	NA
Ejaculation delayed	3	1	NA	NA

¹ Events reported by at least 2% of patients treated with Cymbalta and more often than with placebo.

² Term includes anorgasmia.

³ Term includes ejaculation disorder and ejaculation failure.

NA=Not applicable.

Because adverse sexual events are presumed to be voluntarily underreported, the Arizona Sexual Experience Scale (ASEX), a validated measure designed to identify sexual side effects, was used prospectively in 4 MDD placebo-controlled trials. In these trials, as shown in Table 4 below, patients treated with Cymbalta experienced significantly more sexual dysfunction, as measured by the total score on the ASEX, than did patients treated with placebo. Gender analysis showed that this difference occurred only in males. Males treated with Cymbalta experienced more difficulty with ability to reach orgasm (ASEX Item 4) than males treated with placebo. Females did not experience more sexual dysfunction on Cymbalta than on placebo as measured by ASEX total score. These studies did not, however, include an active control drug with known effects on female sexual dysfunction, so that there is no evidence that its effects differ from other antidepressants. Negative numbers signify an improvement from a baseline level of dysfunction, which is commonly seen in depressed patients. Physicians should routinely inquire about possible sexual side effects.

Table 4: Mean Change in ASEX Scores by Gender in MDD Placebo-Controlled Trials

	Male Patients		Female Patients	
	Cymbalta (n=175)	Placebo (n=83)	Cymbalta (n=241)	Placebo (n=126)
ASEX Total (Items 1-5)	0.56*	-1.07	-1.15	-1.07
Item 1 — Sex drive	-0.07	-0.12	-0.32	-0.24
Item 2 — Arousal	0.01	-0.26	-0.21	-0.18
Item 3 — Ability to achieve erection (men); Lubrication (women)	0.03	-0.25	-0.17	-0.18
Item 4 — Ease of reaching orgasm	0.40**	-0.24	-0.09	-0.13
Item 5 — Orgasm satisfaction	0.09	-0.13	-0.11	-0.17

n=Number of patients with non-missing change score for ASEX total.

* p=0.013 versus placebo.

** p<0.001 versus placebo.

Urinary Hesitation

Cymbalta is in a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during treatment with Cymbalta, consideration should be given to the possibility that they might be drug-related.

Laboratory Changes

Cymbalta treatment, for up to 9-weeks in MDD or 13-weeks in DPN placebo-controlled clinical trials, was associated with small mean increases from baseline to endpoint in ALT, AST, CPK, and alkaline phosphatase; infrequent, modest, transient, abnormal values were observed for these analytes in Cymbalta-treated patients when compared with placebo-treated patients (*see* PRECAUTIONS).

Vital Sign Changes

Cymbalta treatment, for up to 9-weeks in MDD placebo-controlled clinical trials of 40 to 120 mg daily doses caused increases in blood pressure, averaging 2 mm Hg systolic and 0.5 mm Hg diastolic compared to placebo and an increase in the incidence of at least one measurement of systolic blood pressure over 140 mm Hg (*see* PRECAUTIONS).

Cymbalta treatment, for up to 9-weeks in MDD placebo-controlled clinical trials and for up to 13-weeks in DPN placebo-controlled trials caused a small increase in heart rate compared to placebo of about 2 beats per minute.

Weight Changes

In MDD placebo-controlled clinical trials, patients treated with Cymbalta for up to 9-weeks experienced a mean weight loss of approximately 0.5 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients.

In DPN placebo-controlled clinical trials, patients treated with Cymbalta for up to 13-weeks experienced a mean weight loss of approximately 1.1 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients.

Electrocardiogram Changes

Electrocardiograms were obtained from 321 Cymbalta-treated patients with major depressive disorder and 169 placebo-treated patients in clinical trials lasting up to 8-weeks. The rate-corrected QT (QTc) interval in Cymbalta-treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for QT, PR, and QRS intervals between Cymbalta-treated and placebo-treated patients.

Electrocardiograms were obtained from 528 Cymbalta-treated patients with DPN and 205 placebo-treated patients in clinical trials lasting up to 13-weeks. The rate-corrected QT (QTc) interval in Cymbalta-treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for QT, PR, QRS, or QTc measurements between Cymbalta-treated and placebo-treated patients.

Other Adverse Events Observed During the Premarketing and Postmarketing Clinical Trial Evaluation of Cymbalta for MDD and the Pain of DPN

Following is a list of modified MedDRA terms that reflect treatment-emergent adverse events as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with Cymbalta at multiple doses throughout the dose range studied during any phase of a trial within the premarketing and postmarketing database. The events included are those not already listed in both Table 1 and Table 2 and not considered in the WARNINGS and PRECAUTIONS sections. The events were reported with an incidence of greater than or equal to 0.05% and by more than one patient, are not common as background events and were

considered possibly drug related (e.g., because of the drug's pharmacology) or potentially important.

It is important to emphasize that, although the events reported occurred during treatment with Cymbalta, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Blood and Lymphatic System Disorders — *Infrequent*: anemia, leukopenia, increased white blood cell count, lymphadenopathy, and thrombocytopenia.

Cardiac Disorders — *Frequent*: palpitations; *Infrequent*: atrial fibrillation, bundle branch block right, cardiac failure, cardiac failure congestive, coronary artery disease, myocardial infarction, and tachycardia.

Ear and Labyrinth Disorders — *Frequent*: vertigo.

Eye Disorders — *Frequent*: vision blurred; *Infrequent*: diplopia, glaucoma, keratoconjunctivitis sicca, macular degeneration, maculopathy, photopsia, retinal detachment, and visual disturbance.

Gastrointestinal Disorders — *Frequent*: dyspepsia and gastritis; *Infrequent*: aphthous stomatitis, blood in stool, colitis, diverticulitis, dysphagia, eructation, esophageal stenosis acquired, gastric irritation, gastric ulcer, gastroenteritis, gingivitis, impaired gastric emptying, irritable bowel syndrome, lower abdominal pain, melena, and stomatitis.

General Disorders and Administration Site Conditions — *Frequent*: asthenia; *Infrequent*: edema, feeling abnormal, feeling hot and/or cold, feeling jittery, influenza-like illness, malaise, rigors, and thirst.

Hepato-biliary Disorders — *Infrequent*: hepatic steatosis.

Investigations — *Frequent*: weight decreased; *Infrequent*: blood cholesterol increased, blood creatinine increased, urine output decreased, and weight increased.

Metabolism and Nutrition Disorders — *Frequent*: hypoglycemia and increased appetite; *Infrequent*: dehydration, dyslipidemia, hypercholesterolemia, hyperlipidemia, and hypertriglyceridemia.

Musculoskeletal and Connective Tissue Disorders — *Frequent*: muscle tightness and muscle twitching; *Infrequent*: muscular weakness.

Nervous System Disorders — *Frequent*: dysgeusia and hypoesthesia; *Infrequent*: ataxia and dysarthria.

Psychiatric Disorders — *Frequent*: anorgasmia, anxiety, hypersomnia, initial insomnia, irritability, lethargy, libido decreased, middle insomnia, nervousness, nightmare, restlessness, and sleep disorder; *Infrequent*: agitation, bruxism, completed suicide, disorientation, loss of libido, mania, mood swings, orgasm abnormal, pressure of speech, sluggishness, suicide attempt, and tension.

Renal and Urinary Disorders — *Frequent*: dysuria and urinary hesitation; *Infrequent*: micturition urgency, nephropathy, nocturia, urinary incontinence, urinary retention, and urine flow decreased.

Reproductive System and Breast Disorders — *Frequent*: ejaculation delayed and ejaculation disorder.

Respiratory, Thoracic and Mediastinal Disorders — *Frequent*: yawning; *Infrequent*: oropharyngeal swelling.

Skin and Subcutaneous Tissue Disorders — *Frequent*: night sweats, pruritus, rash, and skin ulcer; *Infrequent*: acne, alopecia, cold sweat, ecchymosis, eczema, erythema, erythematous rash, exfoliative dermatitis, face edema, hyperkeratosis, increased tendency to bruise, photosensitivity reaction, and pruritic rash.

Vascular Disorders — *Frequent*: hot flush; *Infrequent*: flushing, hypertensive crisis, peripheral coldness, peripheral edema, and phlebitis.

Postmarketing Spontaneous Reports

Adverse events reported rarely since market introduction that were temporally related to Cymbalta therapy include: hallucinations, rash, and urinary retention. The following adverse events were reported very rarely: alanine aminotransferase increased, alkaline phosphatase increased, anaphylactic reaction, angioneurotic edema, aspartate aminotransferase increased, bilirubin increased, extrapyramidal disorder, glaucoma, hepatitis, hyponatremia, jaundice, orthostatic hypotension (especially at the initiation of treatment), serotonin syndrome, Stevens-Johnson Syndrome, syncope (especially at initiation of treatment), syndrome of inappropriate antidiuretic hormone secretion (SIADH), and urticaria.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Duloxetine is not a controlled substance.

Physical and Psychological Dependence

In animal studies, duloxetine did not demonstrate barbiturate-like (depressant) abuse potential. In drug dependence studies, duloxetine did not demonstrate dependence-producing potential in rats.

While Cymbalta has not been systematically studied in humans for its potential for abuse, there was no indication of drug-seeking behavior in the clinical trials. However, it is not possible to predict on the basis of premarketing experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of Cymbalta (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

There is limited clinical experience with Cymbalta overdose in humans. In premarketing clinical trials, cases of acute ingestions up to 1400 mg, alone or in combination with other drugs, were reported with none being fatal. Postmarketing experience includes reports of overdoses, alone or in combination with other drugs, with duloxetine doses of almost 2000 mg. Fatalities have been very rarely reported, primarily with mixed overdoses, but also with duloxetine alone at a dose of approximately 1000 mg. Signs and symptoms of overdose (mostly with mixed drugs) included serotonin syndrome, somnolence, vomiting, and seizures.

Management of Overdose

There is no specific antidote to Cymbalta, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. In case of acute overdose, treatment should consist of those general measures employed in the management of overdose with any drug.

An adequate airway, oxygenation, and ventilation should be assured, and cardiac rhythm and vital signs should be monitored. 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 may be useful in limiting absorption of duloxetine from the gastrointestinal tract. Administration of activated charcoal has been shown to decrease AUC and C_{max} by an average of one-third, although some subjects had a limited effect of activated charcoal. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be beneficial.

In managing overdose, the possibility of multiple drug involvement should be considered. A specific caution involves patients who are taking or have recently taken Cymbalta and might ingest excessive quantities of a TCA. In such a case, decreased clearance of the parent tricyclic and/or its active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (*see* PRECAUTIONS, Drug Interactions). The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

DOSAGE AND ADMINISTRATION

Initial Treatment

Major Depressive Disorder

Cymbalta should be administered at a total dose of 40 mg/day (given as 20 mg BID) to 60 mg/day (given either once a day or as 30 mg BID) without regard to meals.

There is no evidence that doses greater than 60 mg/day confer any additional benefits.

Diabetic Peripheral Neuropathic Pain

Cymbalta should be administered at a total dose of 60 mg/day given once a day, without regard to meals.

While a 120 mg/day dose was shown to be safe and effective, there is no evidence that doses higher than 60 mg confer additional significant benefit, and the higher dose is clearly less well tolerated. For patients for whom tolerability is a concern, a lower starting dose may be considered. Since diabetes is frequently complicated by renal disease, a lower starting dose and gradual increase in dose should be considered for patients with renal impairment (*see* CLINICAL PHARMACOLOGY, Special Populations *and* below).

Maintenance/Continuation/Extended Treatment

Major Depressive Disorder

It is generally agreed that acute episodes of major depression require several months or longer of sustained pharmacologic therapy. There is insufficient evidence available to answer the question of how long a patient should continue to be treated with Cymbalta. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

Diabetic Peripheral Neuropathic Pain

As the progression of diabetic peripheral neuropathy is highly variable and management of pain is empirical, the effectiveness of Cymbalta must be assessed individually. Efficacy beyond 12 weeks has not been systematically studied in placebo-controlled trials, but a one-year open-label safety study was conducted.

Special Populations

Dosage for Renally Impaired Patients — Cymbalta is not recommended for patients with end-stage renal disease (requiring dialysis) or in severe renal impairment (estimated creatinine clearance <30 mL/min) (*see* CLINICAL PHARMACOLOGY).

Dosage for Hepatically Impaired Patients — It is recommended that Cymbalta not be administered to patients with any hepatic insufficiency (*see* CLINICAL PHARMACOLOGY and PRECAUTIONS).

Dosage for Elderly Patients — No dose adjustment is recommended for elderly patients on the basis of age. As with any drug, caution should be exercised in treating the elderly. When individualizing the dosage in elderly patients, extra care should be taken when increasing the dose.

Treatment of Pregnant Women During the Third Trimester — Neonates exposed to SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (*see* PRECAUTIONS). When treating pregnant women with Cymbalta during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Cymbalta in the third trimester.

Dosage for Nursing Mothers — Because the safety of duloxetine in infants is not known, nursing while on Cymbalta is not recommended. However, if the physician determines that the benefit of duloxetine therapy for the mother outweighs any potential risk to the infant, no dosage adjustment is required as lactation did not influence duloxetine pharmacokinetics (*see* CLINICAL PHARMACOLOGY).

Discontinuing Cymbalta

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

Switching Patients to or from a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Cymbalta. In addition, at least 5 days should be allowed after stopping Cymbalta before starting an MAOI (*see* CONTRAINDICATIONS and WARNINGS).

HOW SUPPLIED

Cymbalta® (duloxetine hydrochloride) Delayed-release Capsules are available in 20, 30, and 60 mg strengths.

The 20 mg* capsule has an opaque green body and cap, and is imprinted with “20 mg” on the body and “LILLY 3235” on the cap:

NDC 0002-3235-60 (PU3235) — Bottles of 60

NDC 0002-3235-33 (PU3235) — (ID[†]100) Blisters

The 30 mg* capsule has an opaque white body and opaque blue cap, and is imprinted with “30 mg” on the body and “LILLY 3240” on the cap:

NDC 0002-3240-30 (PU3240) — Bottles of 30

NDC 0002-3240-90 (PU3240) — Bottles of 90
 NDC 0002-3240-04 (PU3240) — Bottles of 1000
 NDC 0002-3240-33 (PU3240) — (ID[†]100) Blisters

The 60 mg* capsule has an opaque green body and opaque blue cap, and is imprinted with “60 mg” on the body and “LILLY 3237” on the cap:

NDC 0002-3237-30 (PU3237) — Bottles of 30
 NDC 0002-3237-90 (PU3237) — Bottles of 90
 NDC 0002-3237-04 (PU3237) — Bottles of 1000
 NDC 0002-3237-33 (PU3237) — (ID[†]100) Blisters

* equivalent to duloxetine base.

[†] Identi-Dose[®] (unit dose medication, Lilly).

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

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Medication Guide

About Using Antidepressants in Children and Teenagers

What is the most important information I should know if my child is being prescribed an antidepressant?

Parents or guardians need to think about 4 important things when their child is prescribed an antidepressant:

1. There is a risk of suicidal thoughts or actions
2. How to try to prevent suicidal thoughts or actions in your child
3. You should watch for certain signs if your child is taking an antidepressant
4. There are benefits and risks when using antidepressants

1. There is a Risk of Suicidal Thoughts or Actions

Children and teenagers sometimes think about suicide, and many report trying to kill themselves.

Antidepressants increase suicidal thoughts and actions in some children and teenagers. But suicidal thoughts and actions can also be caused by depression, a serious medical condition that

is commonly treated with antidepressants. Thinking about killing yourself or trying to kill yourself is called *suicidality* or *being suicidal*.

A large study combined the results of 24 different studies of children and teenagers with depression or other illnesses. In these studies, patients took either a placebo (sugar pill) or an antidepressant for 1 to 4 months. ***No one committed suicide in these studies***, but some patients became suicidal. On sugar pills, 2 out of every 100 became suicidal. On the antidepressants, 4 out of every 100 patients became suicidal.

For some children and teenagers, the risks of suicidal actions may be especially high. These include patients with

- Bipolar illness (sometimes called manic-depressive illness)
- A family history of bipolar illness
- A personal or family history of attempting suicide

If any of these are present, make sure you tell your health care provider before your child takes an antidepressant.

2. How to Try to Prevent Suicidal Thoughts and Actions

To try to prevent suicidal thoughts and actions in your child, pay close attention to changes in her or his moods or actions, especially if the changes occur suddenly. Other important people in your child's life can help by paying attention as well (e.g., your child, brothers and sisters, teachers, and other important people). The changes to look out for are listed in Section 3, on what to watch for.

Whenever an antidepressant is started or its dose is changed, pay close attention to your child.

After starting an antidepressant, your child should generally see his or her health care provider

- Once a week for the first 4 weeks
- Every 2 weeks for the next 4 weeks
- After taking the antidepressant for 12 weeks
- After 12 weeks, follow your health care provider's advice about how often to come back
- More often if problems or questions arise (see Section 3)

You should call your child's health care provider between visits if needed.

3. You Should Watch for Certain Signs If Your Child is Taking an Antidepressant

Contact your child's health care provider ***right away*** if your child exhibits any of the following signs for the first time, or if they seem worse, or worry you, your child, or your child's teacher:

- Thoughts about suicide or dying
- Attempts to commit suicide
- New or worse depression

- New or worse anxiety
- Feeling very agitated or restless
- Panic attacks
- Difficulty sleeping (insomnia)
- New or worse irritability
- Acting aggressive, being angry, or violent
- Acting on dangerous impulses
- An extreme increase in activity and talking
- Other unusual changes in behavior or mood

Never let your child stop taking an antidepressant without first talking to his or her health care provider. Stopping an antidepressant suddenly can cause other symptoms.

4. There are Benefits and Risks When Using Antidepressants

Antidepressants are used to treat depression and other illnesses. Depression and other illnesses can lead to suicide. In some children and teenagers, treatment with an antidepressant increases suicidal thinking or actions. It is important to discuss all the risks of treating depression and also the risks of not treating it. You and your child should discuss all treatment choices with your health care provider, not just the use of antidepressants.

Other side effects can occur with antidepressants (see section below).

Of all the antidepressants, only fluoxetine (Prozac[®]) has been FDA approved to treat pediatric depression.

For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine (Prozac[®]), sertraline (Zoloft[®]), fluvoxamine, and clomipramine (Anafranil[®]).

Your health care provider may suggest other antidepressants based on the past experience of your child or other family members.

Is this all I need to know if my child is being prescribed an antidepressant?

No. This is a warning about the risk for suicidality. Other side effects can occur with antidepressants. Be sure to ask your health care provider to explain all the side effects of the particular drug he or she is prescribing. Also ask about drugs to avoid when taking an antidepressant. Ask your health care provider or pharmacist where to find more information.

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Zoloft[®] is a registered trademark of Pfizer Pharmaceuticals.

Anafranil[®] is a registered trademark of Mallinckrodt Inc.

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

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