PV 5419 AMP

SYMBYAX®
(olanzapine and fluoxetine HCl capsules)

WARNING

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

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).

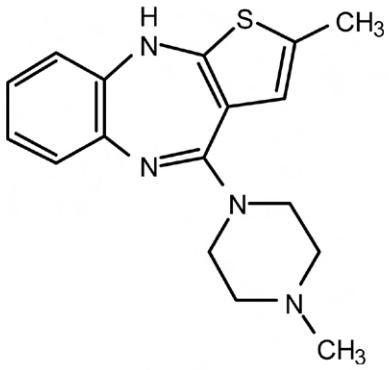
DESCRIPTION

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®).

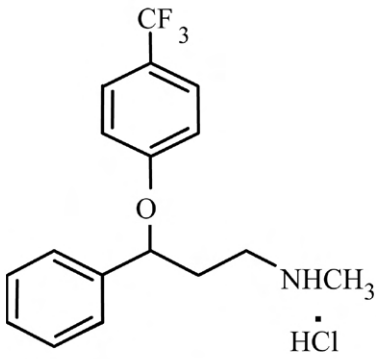
Olanzapine belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*] [1,5]benzodiazepine. The molecular formula is $C_{17}H_{20}N_4S$, which corresponds to a molecular weight of 312.44.

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 $C_{17}H_{18}F_3NO \cdot HCl$, 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:

	3 mg/25 mg	6 mg/25 mg	6 mg/50 mg	12 mg/25 mg	12 mg/50 mg
olanzapine equivalent	3	6	6	12	12
fluoxetine base equivalent	25	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 $5HT_{2A/2C}$, $5HT_6$, (K_i=4, 11, and 5 nM, respectively), dopamine $D_{1\text{-}4}$ (K_i=11 to 31 nM), histamine H_1 (K_i=7 nM), and adrenergic α_1 receptors (K_i=19 nM). Olanzapine is an antagonist with moderate affinity binding for serotonin $5HT_3$ (K_i=57 nM) and muscarinic $M_{1\text{-}5}$ (K_i=73, 96, 132, 32, and 48 nM, respectively). 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 $5HT_2$ may explain some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of muscarinic $M_{1\text{-}5}$ receptors

may explain its anticholinergic-like effects. The antagonism of histamine H_1 receptors by olanzapine may explain the somnolence observed with this drug. The antagonism of α_1-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 ^{14}C-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. In vivo studies have shown that exposures to olanzapine are similar among Japanese, Chinese and Caucasians, especially after normalization for body weight differences. 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 Mean[1]
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. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

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

Table 2

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo

25-64	1 fewer case
≥65	6 fewer cases

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

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

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

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

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

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

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

It should be noted that 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 — 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. While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics.

Mean increases in blood glucose have been observed in patients treated (median exposure of 9.2 months) with olanzapine in phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). The mean increase of serum glucose (fasting and nonfasting samples) from baseline to the average of the two highest serum concentrations was 15.0 mg/dL.

In an analysis of 7 controlled clinical studies, 2 of which were placebo-controlled, with treatment duration up to 12 weeks, SYMBYAX was associated with a statistically significantly greater mean change in random glucose compared to placebo (8.65 mg/dL versus -3.86 mg/dL). In patients with baseline normal random glucose levels (<140 mg/dL), 2.3% of those treated with SYMBYAX were found to have high glucose levels (≥200 mg/dL) during SYMBYAX treatment and were statistically significantly different compared to 0.3% of those treated with placebo. In patients with baseline borderline random glucose levels (≥140 mg/dL and <200 mg/dL), 34.1% of those treated with SYMBYAX were found to have high glucose levels (≥200 mg/dL) during SYMBYAX treatment and were statistically significantly different compared to 3.6% of those treated with placebo. The difference in mean changes between SYMBYAX and placebo was greater in patients with evidence of glucose dysregulation at baseline (including those patients

diagnosed with diabetes mellitus or related adverse events, patients treated with anti-diabetic agents, patients with a baseline random glucose level ≥200 mg/dL, or a baseline fasting glucose level ≥126 mg/dL). These patients had a greater mean increase in HbA_{1c}.

Controlled fasting glucose data is limited for SYMBYAX; however, in an analysis of 5 placebo-controlled olanzapine monotherapy studies with treatment duration up to 12 weeks, olanzapine was associated with a greater mean change in fasting glucose levels compared to placebo (2.76 mg/dL vs 0.17 mg/dL).

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine and olanzapine and fluoxetine in combination have not been established in patients under the age of 18 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, including those with schizophrenia (6 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), olanzapine was associated with a statistically significantly greater mean change in fasting glucose levels compared to placebo (2.68 mg/dL versus -2.59 mg/dL). In patients with baseline normal fasting glucose levels (<100 mg/dL), zero out of 124 (0%) of those treated with olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus 1 out of 53 (1.9%) of those treated with placebo. In patients with baseline borderline fasting glucose levels (≥100 mg/dL and <126 mg/dL), 2 out of 14 (14.3%) of those treated with olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus zero out of 13 (0%) of those treated with placebo.

Physicians should consider the risks and benefits when prescribing SYMBYAX to patients with an established diagnosis of diabetes mellitus, or having borderline increased blood glucose level (fasting 100-126 mg/dL, nonfasting 140-200 mg/dL). Patients taking SYMBYAX 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.

Hyperlipidemia — Undesirable alterations in lipids have been observed with SYMBYAX use. Clinical monitoring, including baseline and follow-up lipid evaluations in patients using SYMBYAX, is advised.

Significant, and sometimes very high (>500 mg/dL), elevations in triglyceride levels have been observed with SYMBYAX use. Significant increases in total cholesterol have also been seen with SYMBYAX use.

Controlled fasting lipid data is limited for SYMBYAX.

In an analysis of 7 controlled clinical studies, 2 of which were placebo-controlled, with treatment duration up to 12 weeks, SYMBYAX-treated patients had an increase from baseline in mean random total cholesterol of 12.1 mg/dL compared to a statistically significantly different increase from baseline in mean random total cholesterol of 4.8 mg/dL for olanzapine-treated patients and a decrease in mean random total cholesterol of 5.5 mg/dL for placebo-treated patients. Table 3 shows categorical changes in nonfasting lipid values.

Table 3: Changes in Nonfasting Lipids Values from Controlled Clinical Studies with Treatment Duration up to 12 Weeks

Laboratory Analyte	Category Change from Baseline	Treatment Arm	N	Patients
Nonfasting Triglycerides	Increase by ≥50 mg/dL	OFC	174	67.8%
		Olanzapine	172	72.7%
	Normal to High (<150 mg/dL to ≥500 mg/dL)	OFC	57	0%
		Olanzapine	58	0%
	Borderline to High (≥150 mg/dL and <500 mg/dL to ≥500 mg/dL)	OFC	106	15.1%
		Olanzapine	103	8.7%
Nonfasting Total Cholesterol	Increase by ≥40 mg/dL	OFC	685	35%[a,b]
		Olanzapine	749	22.7%
		Placebo	390	9%
	Normal to High (<200 mg/dL to ≥240 mg/dL)	OFC	256	8.2%[a,b]
		Olanzapine	279	2.9%
		Placebo	175	1.7%
	Borderline to High (≥200 mg/dL and <240 mg/dL to ≥240 mg/dL)	OFC	213	36.2%[a,b]
		Olanzapine	261	27.6%
		Placebo	111	9.9%

[a] Statistically significant compared to olanzapine.
[b] Statistically significant compared to placebo.

Controlled fasting lipid data is limited for SYMBYAX; however, in an analysis of 5 placebo-controlled olanzapine monotherapy studies with treatment duration up to 12 weeks, olanzapine-treated patients had statistically significant increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.3 mg/dL, 3.0 mg/dL, and 20.8 mg/dL respectively compared to decreases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 6.1 mg/dL, 4.3 mg/dL, and 10.7 mg/dL for placebo-treated patients. For fasting HDL cholesterol, no statistically significant differences were observed between olanzapine-treated patients and placebo-treated patients. Mean increases in fasting lipid values (total cholesterol, LDL cholesterol, and triglycerides) were greater in patients without evidence of lipid dysregulation at baseline, where lipid dysregulation was defined as patients diagnosed with dyslipidemia or related adverse events, patients treated with lipid lowering agents, patients with high baseline lipid levels. Table 4 shows categorical changes in fasting lipid values.

Table 4: Changes in Fasting Lipids Values from Adult Placebo-Controlled Olanzapine Monotherapy Studies with Treatment Duration up to 12 Weeks

Laboratory Analyte	Category Change from Baseline	Treatment Arm	N	Patients
Fasting Triglycerides	Increase by ≥50 mg/dL	Olanzapine	745	39.6%[a]
		Placebo	402	26.1%
	Normal to High	Olanzapine	457	9.2%[a]

	(<150 mg/dL to ≥200 mg/dL)	Placebo	251	4.4%
	Borderline to High (≥150 mg/dL and <200 mg/dL to ≥200 mg/dL)	Olanzapine	135	39.3%[a]
		Placebo	65	20.0%
Fasting Total Cholesterol	Increase by ≥40 mg/dL	Olanzapine	745	21.6%[a]
		Placebo	402	9.5%
	Normal to High (<200 mg/dL to ≥240 mg/dL)	Olanzapine	392	2.8%
		Placebo	207	2.4%
	Borderline to High (≥200 mg/dL and <240 mg/dL to ≥240 mg/dL)	Olanzapine	222	23.0%[a]
		Placebo	112	12.5%
Fasting LDL Cholesterol	Increase by ≥30 mg/dL	Olanzapine	536	23.7%[a]
		Placebo	304	14.1%
	Normal to High (<100 mg/dL to ≥160 mg/dL)	Olanzapine	154	0%
		Placebo	82	1.2%
	Borderline to High (≥100 mg/dL and <160 mg/dL to ≥160 mg/dL)	Olanzapine	302	10.6%
		Placebo	173	8.1%

[a] Statistically significant compared to placebo.

In phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), over a median exposure of 9.2 months, the mean increase in triglycerides in patients taking olanzapine was 40.5 mg/dL. In phase 1 of CATIE, the median increase in total cholesterol was 9.4 mg/dL.

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine and olanzapine and fluoxetine in combination have not been established in patients under the age of 18 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, including those with schizophrenia (6 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), for fasting HDL cholesterol, no statistically significant differences were observed between olanzapine-treated patients and placebo-treated patients. Table 5 shows categorical changes in fasting lipid values in adolescent patients.

Table 5: Changes in Fasting Lipids Values from Adolescent Placebo-Controlled Olanzapine Monotherapy Studies

Laboratory Analyte	Category Change from Baseline	Treatment Arm	N	Patients
Fasting Triglycerides	Increase by ≥50 mg/dL	Olanzapine	138	37%[a]
		Placebo	66	15.2%
	Normal to High (<90 mg/dL to ≥130 mg/dL)	Olanzapine	67	26.9%
		Placebo	28	10.7%
	Borderline to High (≥90 mg/dL and <130 mg/dL to ≥130 mg/dL)	Olanzapine	37	59.5%
		Placebo	17	35.3%

Fasting Total Cholesterol	Increase by ≥40 mg/dL	Olanzapine	138	14.5%[a]
		Placebo	66	4.5%
	Normal to High (<170 mg/dL to ≥200 mg/dL)	Olanzapine	87	6.9%
		Placebo	43	2.3%
	Borderline to High (≥170 mg/dL and <200 mg/dL to ≥200 mg/dL)	Olanzapine	36	38.9%[a]
		Placebo	13	7.7%
Fasting LDL Cholesterol	Increase by ≥30 mg/dL	Olanzapine	137	17.5%
		Placebo	63	11.1%
	Normal to High (<110 mg/dL to ≥130 mg/dL)	Olanzapine	98	5.1%
		Placebo	44	4.5%
	Borderline to High (≥110 mg/dL and <130 mg/dL to ≥130 mg/dL)	Olanzapine	29	48.3%[a]
		Placebo	9	0%

[a] Statistically significant compared to placebo.

Weight Gain — Potential consequences of weight gain should be considered prior to starting SYMBYAX. Patients receiving SYMBYAX should receive regular monitoring of weight.

In an analysis of 7 controlled clinical studies, 2 of which were placebo-controlled, the mean weight increase for SYMBYAX-treated patients was statistically significantly greater than placebo-treated patients (4 kg vs -0.3 kg). Twenty-two percent of SYMBYAX-treated patients gained at least 7% of their baseline weight, with a median exposure of 6 weeks. This was statistically significantly greater than in placebo-treated patients (1.8%). Approximately three percent of SYMBYAX-treated patients gained at least 15% of their baseline weight, with a median exposure of 8 weeks. This was statistically significantly greater than in placebo-treated patients (0%). Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories. Discontinuation due to weight gain occurred in 2.5% of SYMBYAX-treated patients and zero placebo-treated patients.

Table 6 includes data on weight gain with olanzapine pooled from 68 clinical trials. The data in each column represent data for those patients who completed treatment periods of the durations specified.

Table 6: Weight Gain with Olanzapine Use

Amount Gained kg (lb)	6 Weeks (N=2976) (%)	6 Months (N=1536) (%)	12 Months (N=778) (%)	24 Months (N=422) (%)
≤0	27	21	20	22
0-5 (0-11 lb)	57	34	25	22
5-10 (11-22 lb)	15	26	25	22
10-15 (22-33 lb)	2	12	16	18
>15 (>33 lb)	0	6	14	16

During long-term continuation therapy with olanzapine monotherapy (238 median days of exposure), 56% of olanzapine patients met the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 5.4 kg.

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine and olanzapine and fluoxetine in combination have not been established in patients under the age of 18 years. In an analysis of 4 placebo-controlled olanzapine monotherapy studies of adolescent patients (ages 13 to 17 years), including those with schizophrenia (6 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), olanzapine-treated patients gained an average of 4.6 kg, which was statistically significantly different compared to an average of 0.3 kg in placebo-treated patients, with a median exposure of 3 weeks; 40.6% of olanzapine-treated patients gained at least 7% of their baseline body weight, which was statistically significantly different compared to 9.8% of placebo-treated patients, with a median exposure of 4 weeks; 7.1% of olanzapine-treated patients gained at least 15% of their baseline weight, compared to 2.7% of placebo-treated patients, with a median exposure of 19 weeks. Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories, but mean changes in weight were greater in adolescents with BMI categories above normal at baseline. Discontinuation due to weight gain occurred in 1% of olanzapine-treated patients, compared to zero placebo-treated patients.

During long-term continuation therapy with olanzapine, 65% of olanzapine-treated patients met the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 7.4 kg.

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 SNRIs and SSRIs, including 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 D_2 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 may occur as a result of treatment with SSRIs and SNRIs, including SYMBYAX. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported and appeared to be reversible when SYMBYAX was

discontinued. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk (*see* Geriatric Use). Discontinuation of SYMBYAX should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

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

Seizures — 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 ≤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).

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 “Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions” 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 look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Hyperglycemia — Patients should be advised of the potential risk of hyperglycemia-related adverse events. Patients should be monitored regularly for worsening of glucose control.

Weight Gain — Patients should be counseled that SYMBYAX is associated with weight gain. Patients should have their weight monitored regularly.

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 SNRIs and SSRIs, including 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.

Fluoxetine inhibits the activity of CYP2D6, and may make individuals with normal CYP2D6 metabolic activity resemble a poor metabolizer. Coadministration of fluoxetine with other drugs that are metabolized by CYP2D6, including certain antidepressants (e.g., TCAs), antipsychotics (e.g., phenothiazines and most atypicals), and antiarrhythmics (e.g., propafenone, flecainide, and others) should be approached with caution. Therapy with medications that are predominantly metabolized by the CYP2D6 system and that have a relatively narrow therapeutic index 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, propafenone, 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/m^2 basis] and 0.25, 2, and 8 mg/kg/day (equivalent to 0.06 to 2 times the MRHD on a mg/m^2 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/m^2 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/m^2 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/m^2 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/m^2 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/m^2 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/m^2 basis), respectively] and high-dose [4 and 8 mg/kg/day (2 and 1 times the MRHD on a mg/m^2 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/m^2 basis), respectively] and with olanzapine alone (5 mg/kg/day or 9 times the MRHD on a mg/m^2 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/m^2 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/m^2 basis). Diestrous was prolonged and estrous was delayed at 1.1 mg/kg/day (0.6 times the MRHD on a mg/m^2 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/m^2 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/m^2 basis, respectively], and 4 and 8 mg/kg/day (high-dose) [2 and 1 times the MRHD on a mg/m^2 basis, respectively]. In rabbits, the doses were 4 and 4 mg/kg/day (low-dose) [4 and 1 times the MRHD on a mg/m^2 basis, respectively], and 8 and 8 mg/kg/day (high-dose) [9 and 2 times the MRHD on a mg/m^2 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/m^2 basis], respectively, high-dose: 4 and 8 mg/kg/day [2 and 1 times the MRHD on a mg/m^2 basis], respectively, and alone: 4 and 8 mg/kg/day [2 and 1 times the MRHD on a mg/m^2 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/m^2 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/m^2 basis). Gestation was prolonged at 10 mg/kg/day (5 times the MRHD on a mg/m^2 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/m^2 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/m^2 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/m^2 basis) during gestation or 7.5 mg/kg/day (0.9 times the MRHD on a mg/m^2 basis) during gestation and lactation. There was no evidence of developmental

neurotoxicity in the surviving offspring of rats treated with 12 mg/kg/day during gestation. The no-effect dose for rat pup mortality was 5 mg/kg/day (0.6 times the MRHD on a mg/m^2 basis).

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).

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

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

Labor and Delivery

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

In a study in lactating, healthy women, olanzapine was excreted in breast milk. Mean infant dose at steady state was estimated to be 1.8% of the maternal olanzapine dose.

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 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. SSRIs and SNRIs, including SYMBYAX, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event (*see* PRECAUTIONS, Hyponatremia).

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 7 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 7: 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 ≥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 8 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 8: 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 ≥ 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).

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.

Additional findings — In a single 8-week randomized, double-blind, fixed-dose, study comparing 10 (N=199), 20 (N=200) and 40 (N=200) mg/day of olanzapine in patients with schizophrenia or schizoaffective disorder, statistically significant differences among 3 dose groups were observed for the following safety outcomes: weight gain, prolactin elevation, fatigue and dizziness. Mean baseline to endpoint increase in weight (10 mg/day: 1.9 kg; 20 mg/day: 2.3 kg; 40 mg/day: 3 kg) was observed with significant differences between 10 vs 40 mg/day. Incidence of treatment-emergent prolactin elevation >24.2 ng/mL (female) or >18.77 ng/mL (male) at any time during the trial (10 mg/day: 31.2%; 20 mg/day: 42.7%; 40 mg/day: 61.1%) with significant differences between 10 vs 40 mg/day and 20 vs 40 mg/day; fatigue (10 mg/day: 1.5%; 20 mg/day: 2.1%; 40 mg/day: 6.6%) with significant differences between 10 vs 40 and 20 vs 40 mg/day; and dizziness (10 mg/day: 2.6%; 20 mg/day: 1.6%; 40 mg/day: 6.6%) with significant differences between 20 vs 40 mg, was observed.

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 7 and 8 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, thrombocythemia.

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, menorrhagia[1], urinary frequency, urinary incontinence, urinary tract infection; *Infrequent:* amenorrhea[1], breast enlargement, breast neoplasm, cystitis, dysuria, female lactation[1], fibrocystic breast[1], hematuria, hypomenorrhea[1], leukorrhea[1], menopause[1], metrorrhagia[1], oliguria, ovarian disorder[1], polyuria, urinary retention, urinary urgency, urination impaired, vaginal hemorrhage[1], vaginal moniliasis[1], vaginitis[1]; *Rare:* breast carcinoma, breast engorgement, endometrial disorder[1], gynecomastia[1], kidney calculus, uterine fibroids enlarged[1].

[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, neutropenia, 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 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 ≥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 3 mg/25 mg - 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) or those patients who may be pharmacodynamically sensitive to olanzapine. 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 3/25-, 6/25-, 6/50-, 12/25-, and 12/50-mg (mg equivalent olanzapine/mg equivalent fluoxetine[a]) strengths.

SYMBYAX	CAPSULE STRENGTH				
	3 mg/25 mg	6 mg/25 mg	6 mg/50 mg	12 mg/25 mg	12 mg/50 mg
Color	Peach & Light Yellow	Mustard Yellow & Light Yellow	Mustard Yellow & Light Grey	Red & Light Yellow	Red & Light Grey
Capsule No.	PU3230	PU3231	PU3233	PU3232	PU3234
Identification	Lilly 3230 3/25	Lilly 3231 6/25	Lilly 3233 6/50	Lilly 3232 12/25	Lilly 3234 12/50
NDC Codes					
Bottles 30	0002-3230-30	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.

Literature revised December 17, 2007

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