Important Safety Information about Symbyax® (olanzapine and fluoxetine HCl)

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.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis--Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotics, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death 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 (eg, heart failure or sudden death) or infectious (eg, pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patient is not clear. SYMBYAX is not approved for the treatment of patients with dementia-related psychosis.

Contraindications

- SYMBYAX should not be used with an MAOI or within at least 14 days of discontinuing an MAOI. At least 5 weeks should be allowed after stopping fluoxetine before starting an MAOI.
- Thioridazine should not be given with SYMBYAX or within at least 5 weeks after stopping SYMBYAX.
- Concomitant use of SYMBYAX in patients taking pimozide is contraindicated.

Warnings and Precautions

- **Clinical Worsening and Suicide Risk--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 within the first few months of treatment and when changing the dose.** Consider changing the therapeutic regimen, including possibly discontinuing the medication in patients whose depression is persistently worse or includes symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, or suicidality that are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Prescriptions for SYMBYAX should be written for the smallest quantity necessary for good management and to reduce the risk of overdose. If discontinuing treatment, the medication should be tapered. **Families and caregivers or patients being treated with antidepressants for any indication should be alerted about the need to monitor**

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

- Cerebrovascular adverse events including fatalities were reported significantly more commonly with olanzapine than placebo in trials of elderly patients with dementia-related psychosis. Olanzapine and SYMBYAX are not approved for the treatment of patients with dementia-related psychosis.
- As with all antipsychotic medications, a rare and potentially fatal condition known as Neuroleptic Malignant Syndrome (NMS) has been reported with olanzapine. If signs and symptoms appear, immediate discontinuation is recommended. 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.
- Hyperglycemia, in some cases associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics, including olanzapine alone, as well as olanzapine taken concomitantly with fluoxetine. 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. 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 levels. Patients taking SYMBYAX should be monitored regularly for worsening of glucose control. Patients starting treatment with SYMBYAX 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 should undergo fasting blood glucose testing.
- Undesirable alterations in lipids have been observed with SYMBYAX use. Clinical monitoring, including baseline and follow-up lipid evaluations in patients using SYMBYAX, is recommended. Clinically significant, and sometimes very high, elevations in triglyceride levels have been observed with SYMBYAX use. Clinically meaningful increases in total cholesterol have also been seen with SYMBYAX use.
- Potential consequences of weight gain should be considered prior to starting SYMBYAX. Patients receiving SYMBYAX should receive regular monitoring of weight.
- Development of a potentially life-threatening serotonin syndrome or NMS-like reactions have been reported with SNRIs and SSRIs alone, including SYMBYAX treatment, but particularly with concomitant use of serotonergic drugs, including triptans, with drugs which impair serotonin metabolism, including MAOIs, or with antipsychotics or other dopamine antagonists. If these events occur, treatment with SYMBYAX and any concomitant serotonergic or antidopaminergic agents should be discontinued immediately and supportive symptomatic treatment should be initiated.
- If rash or other possibly allergic phenomena appear during SYMBYAX treatment for which an alternative etiology cannot be determined, immediate discontinuation is recommended.
- Patients being treated with SYMBYAX should be screened for bipolar disorder and monitored for mania/hypomania.
- As with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of Tardive Dyskinesia (TD). The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic increase. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

- SYMBYAX may induce orthostatic hypotension associated with dizziness, tachycardia, bradycardia, and in some patients, syncope, especially during the initial dose-titration period. SYMBYAX should be used with particular caution in patients with known cardiovascular disease, cerebrovascular disease, or those predisposed to hypotension.
- Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Olanzapine and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.
- SYMBYAX should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold.
- Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of SYMBYAX with NSAIDs, aspirin, warfarin or other drugs that affect coagulation.
- As with other antidepressants, SYMBYAX has been associated with cases of clinically significant hyponatremia that appeared to be reversible when SYMBYAX was discontinued.
- As with any CNS-active drug, SYMBYAX has the potential to impair judgment, thinking or motor skills.
- Body temperature dysregulation may occur with antipsychotic agents. Appropriate care is advised when prescribing SYMBYAX for patients who will be experiencing conditions which may contribute to elevation in core body temperature.
- 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 5 studies in elderly patients with dementia-related psychosis, adverse events reported more commonly with olanzapine than with placebo were falls, somnolence, peripheral edema, abnormal gait, urinary incontinence, lethargy, increased weight, asthenia, pyrexia, pneumonia, dry mouth, and visual hallucinations. SYMBYAX should be used with caution in elderly patients with dementia. Olanzapine and SYMBYAX are not approved for treatment of patients with dementia-related psychosis.
- As with other drugs that antagonize dopamine receptors, SYMBYAX elevates prolactin levels, and a modest elevation persists during administration.
- Caution should be used when prescribing other medications that contain olanzapine or fluoxetine.
- Because of the long elimination half-lives of fluoxetine and its major metabolite, changes in dose will not be fully reflected in plasma for several weeks.
- Symptoms associated with discontinuation of fluoxetine have been reported (e.g., dysphoric mood, irritability, agitation, dizziness, sensory disturbances). While these events are generally self-limiting, some have been serious. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible.

Use in Specific Populations

- Pregnancy: Use only if the potential benefit justifies the potential risk to the fetus.
- Nursing mothers: Breast feeding is not recommended.
- Pediatric: Symbyax is not approved for children and adolescents.
- Hepatic Impairment: Use a lower or less frequent dose in patients with cirrhosis.

Adverse Events

The most common treatment-emergent adverse events (≥5% and at least twice that for placebo) associated with SYMBYAX (vs placebo) in clinical trials were weight gain (25% vs 3%), increased appetite (20% vs 4%), dry mouth (15% vs 6%), somnolence (14% vs 6%), fatigue (12% vs 2%), peripheral edema (9% vs 0%), tremor (9% vs 3%), sedation (8% vs 4%), hypersomnia (5% vs 1%), disturbance in attention (5% vs 1%), and blurred vision (5% vs 2%).

For complete safety profile, see the full Prescribing Information.