

January 15, 2004

Re: Safety data on Zyprexa[®] (olanzapine) and Symbyax[™] (olanzapine and fluoxetine HCl):
Elderly Patients with Dementia-Related Psychosis

Dear Doctor,

In the interest of improving patient care, Eli Lilly and Company is communicating proactively with you to provide some important safety information regarding olanzapine and its use in *elderly patients with dementia-related psychosis*. Olanzapine is not approved for the treatment of dementia-related psychosis. The following information should be carefully considered by prescribers electing to treat elderly patients who have dementia-related psychosis with olanzapine.

This information is based upon an integrated review of 5 placebo-controlled studies (N=1662; olanzapine n=1184, placebo n=478) conducted by Lilly with olanzapine in elderly patients with dementia (Alzheimer's, vascular, and mixed). The efficacy of olanzapine in elderly patients with dementia-related psychosis has not been established in clinical trials.

There are two components of this safety information relevant to elderly patients with dementia being treated with olanzapine:

- 1) Increased incidence of cerebrovascular adverse events versus placebo and
- 2) Increased incidence of mortality versus placebo.

Cerebrovascular Adverse Events

Olanzapine prescribing information was updated in January 2004 as follows:

WARNINGS

Cerebrovascular adverse events (CVAE), including stroke, in elderly patients with dementia –

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.

This information is also included in the prescribing information for Symbyax[™] (olanzapine and fluoxetine HCl), approved December 24, 2003 for the treatment of bipolar depression.

Mortality

The following data are not included in the prescribing information for Zyprexa® or Symbyax™, but have been proactively communicated to the FDA.

In the integrated review described above, the incidence of mortality in elderly patients with dementia-related psychosis was 3.5% in the olanzapine treatment group versus 1.5% in the placebo treatment group ($p=.024$). Exposure-adjusted incidence of mortality (per 10 patient-years) was not significantly different between olanzapine- (1.095; 95% CI=0.789–1.481) and placebo-treated patients (0.477; 95% CI=0.192–0.983). The incidence of mortality was not associated with olanzapine dose or duration of exposure.

Risk factors for mortality, irrespective of treatment, in this integrated review of placebo-controlled studies included: age >80, lower baseline Mini-Mental State Examination score, benzodiazepine use, weight change (loss or gain $\geq 7\%$), treatment-emergent sedation, treatment-emergent malnutrition/dehydration, treatment-emergent dysphagia, and treatment-emergent pulmonary conditions. Risk factors associated with a higher incidence of mortality in olanzapine-treated patients compared with placebo-treated patients included: age >80, concurrent benzodiazepine use, treatment-emergent sedation, or treatment-emergent pulmonary conditions (e.g., pneumonia, with or without aspiration).

Please note that the efficacy of olanzapine in elderly patients with dementia-related psychosis has not been established in clinical trials and is not approved for use in this patient population. This information reconfirms the need for careful patient assessment and consideration of risk in the treatment of elderly patients with dementia-related psychosis.

Should you have any questions or concerns regarding this important safety information, please contact your Eli Lilly and Company sales representative or contact the Lilly medical department at 1-800-Lilly-Rx. Full prescribing information for Zyprexa® and Symbyax™ is included with this letter.

Sincerely,

Alan Breier, MD
Vice President, Medical
Chief Medical Officer
Eli Lilly and Company

Zyprexa® (olanzapine) is indicated for the short-term and maintenance treatment of schizophrenia. Zyprexa® is also indicated as monotherapy or in combination with lithium or valproate for the short-term treatment of acute mixed or manic episodes associated with Bipolar I Disorder and as maintenance treatment in bipolar disorder. Symbyax™ (olanzapine and fluoxetine HCl) is indicated for the treatment of depressive episodes associated with bipolar disorder.