U.S. Food and Drug Administration

Department of Health and Human Services

CENTER FOR DRUG EVALUATION AND RESEARCH

FDA Public Health Advisory

Deaths with Antipsychotics in Elderly Patients with Behavioral Disturbances

The Food and Drug Administration has determined that the treatment of behavioral disorders in elderly patients with dementia with atypical (second generation) antipsychotic medications is associated with increased mortality. Of a total of seventeen placebo controlled trials performed with **olanzapine** (Zyprexa), **aripiprazole** (Abilify), **risperidone** (Risperdal), or **quetiapine** (Seroquel) in elderly demented patients with behavioral disorders, fifteen showed numerical increases in mortality in the drug-treated group compared to the placebo-treated patients. These studies enrolled a total of 5106 patients, and several analyses have demonstrated an approximately 1.6-1.7 fold increase in mortality in these studies. Examination of the specific causes of these deaths revealed that most were either due to heart related events (e.g., heart failure, sudden death) or infections (mostly pneumonia).

The atypical antipsychotics fall into three drug classes based on their chemical structure. Because the increase in mortality was seen with atypical antipsychotic medications in all three chemical classes, the Agency has concluded that the effect is probably related to the common pharmacologic effects of all atypical antipsychotic medications, including those that have not been systematically studied in the dementia population. In addition to the drugs that were studied, the atypical antipsychotic medications include **clozapine** (Clozaril) and **ziprasidone** (Geodon). All of tvhe atypical antipsychotics are approved for the treatment of schizophrenia. None, however, is approved for the treatment of behavioral disorders in patients with dementia. Because of these findings, the Agency will ask the manufacturers of these drugs to include a Boxed Warning in their labeling describing this risk and noting that these drugs are not approved for this indication. **Symbyax**, a combination product containing olanzapine and fluoxetine, approved for the treatment of depressive episodes associated with bipolar disorder, will also be included in the request.

The Agency is also considering adding a similar warning to the labeling for older antipsychotic medications because the limited data available suggest a similar increase in mortality for these drugs.