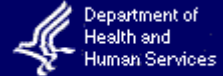




U.S. Food and Drug Administration



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Update of Safety Review

Follow-up to the March 27, 2008, Communication about the Ongoing Safety Review of Montelukast (Singulair)

This information reflects FDA's current analysis of available data concerning this drug.

On March 27, 2008, FDA announced that it was reviewing safety data that raised concerns about a possible association between the use of montelukast and behavior/mood changes, suicidality (suicidal thinking and behavior) and suicide.

FDA requested manufacturers of products indicated for the treatment of asthma and/or allergic rhinitis that act through the leukotriene pathway (montelukast, zafirlukast, zileuton) to submit adverse event data for suicidality adverse events as well as mood and behavioral-related adverse events from all available placebo-controlled clinical trials. (Early Communication About an Ongoing Safety Review of Montelukast (Singulair), http://www.fda.gov/cder/drug/early_comm/montelukast.htm). FDA stated at the time that it expected its preliminary review to take about 9 months and that it would communicate its conclusions and any resulting recommendations to the public at the completion of its review.

FDA requested that Merck, Astra Zeneca, and Cornerstone Therapeutics use the Columbia Classification Algorithm of Suicide Assessment (C-CASA) to classify suicidal events. Merck submitted results from 41 placebo-controlled clinical trials in patients 6 years of age and older, of which 9929 were treated with montelukast and 7780 were treated with a placebo. One adult patient (0.01%) out of 9929 patients treated with montelukast had suicidal ideation and there were no completed suicides. No patients in the placebo group had suicidal ideation or suicide. Astra Zeneca submitted results from 45 placebo-controlled clinical trials in patients 5 years of age and older, of which 7540 were treated with zafirlukast and 4659 were treated with a placebo. No patients treated with zafirlukast had suicidal ideation or completed suicide. Two patients in the placebo group (0.04%) had suicidality (one suicide attempt and one suicidal ideation). Cornerstone Therapeutics submitted results from 11 placebo-controlled clinical trials in patients 12 years of age and older, of which 1745 were treated with zileuton and 1063 were treated with a placebo. No patients treated with zileuton or placebo had suicidal ideation or completed suicide. Although these data do not suggest that montelukast, zafirlukast, or zileuton are associated with suicide or suicidal behavior, these clinical trials were not designed specifically to examine neuropsychiatric events. As a result, some events may not have been reported.

FDA is continuing to review *clinical trial data* to assess other neuropsychiatric events, (mood and behavioral adverse events) related to drugs that act through the leukotriene pathway (montelukast, zafirlukast, zileuton). As a result, FDA has not yet reached a definitive conclusion regarding the clinical trial data on mood and behavioral adverse events associated with montelukast, zafirlukast, and zileuton. We will communicate our conclusions and any resulting

recommendations to the public at the conclusion of the review, which may take months to complete.

Post-marketing reports of neuropsychiatric events associated with montelukast, zafirlukast and zileuton have been reported to FDA's Adverse Event Reporting System (AERS). Most of the reports of neuropsychiatric events are associated with montelukast, currently the most commonly prescribed drug that acts through the leukotriene pathway. The clinical details of some reports involving montelukast are consistent with a drug-induced effect. Because of the paucity of reports involving zafirlukast and zileuton, assessment of a drug-induced effect with these is limited. Accordingly, at this time, patients and prescribers should monitor for the possibility of neuropsychiatric events associated with these agents.

Singulair (montelukast) is a medicine in the drug class known as leukotriene receptor antagonists. Leukotriene receptor antagonists work by blocking substances in the body called leukotrienes. Leukotrienes are chemicals the body releases in response to an inflammatory stimulus, such as when a person breathes in an allergen. Singulair is used to treat asthma and the symptoms of allergic rhinitis (sneezing, stuffy nose, runny nose, itching of the nose) and to prevent exercise-induced asthma. Accolate (zafirlukast) is also a medicine in the drug class known as leukotriene receptor antagonists. Accolate is used to treat asthma. Zyflo and Zyflo CR (zileuton) are medicines in the drug class known as leukotriene synthesis inhibitors. Leukotriene synthesis inhibitors work by stopping the formation of certain natural substances that cause swelling, tightening, and mucus production in the airways. Zyflo and Zyflo CR are used to treat asthma.

The FDA urges both healthcare professionals and patients to report side effects from the use of Singulair, Accolate, Zyflo, and Zyflo CR to the FDA's MedWatch Adverse Event Reporting program

- online at www.fda.gov/medwatch/report.htm
- by returning the postage-paid FDA form 3500 available in PDF format at www.fda.gov/medwatch/getforms.htm to 5600 Fishers Lane, Rockville, MD 20852-9787
- faxing the form to 1-800-FDA-0178
- by phone at 1-800-332-1088

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