

Asthma Drugs Get 'Precaution' Labeling for Possible Psychiatric Side Effects

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FRIDAY, June 12 (HealthDay News) -- The U.S. Food and Drug Administration on Friday requested that the makers of a class of asthma drugs called leukotriene receptor agonists place a "precaution" on the drugs' labeling, warning of the potential for neuropsychiatric events.

The drugs in question include the blockbuster medication Singulair (montelukast), as well as Accolate (zafirlukast). Zflo and Zflo CR (zileuton), drugs in a class known as leukotriene synthesis inhibitors, are also included in the labeling change.

"The reported neuropsychiatric events include postmarket cases of agitation, aggression, anxiousness, dream abnormalities and hallucinations, depression, insomnia, irritability, restlessness, suicidal thinking and behavior [including suicide], and tremor," the agency said in a statement posted on its Web site Friday.

In its advice to patients, the FDA said that patients taking these medications should be aware of the potential hazard and talk to their doctor if some sort of neuropsychiatric problem occurs. Doctors may then decide to discontinue the medication, the agency said.

The move follows an ongoing FDA safety review of possible suicidal behavior among those taking asthma drugs. In early January, FDA officials said they had found no evidence of a link.

The agency, which began its review of the data in March 2008, said clinical trial data submitted by the manufacturers of Singulair, Accolate and Zflo suggested the products are not associated with an increased risk of mood changes or suicidal behavior.

But, the agency also noted at the time that the trials were not designed to examine such behavior, and that the safety review would continue, probably for several more months.

That review ended last April, the FDA said. "The postmarket reports of patients on these medications included cases of neuropsychiatric events," according to the agency statement. "Some reports included clinical details consistent with a drug-induced effect. In the clinical trial data submitted by manufacturers, neuropsychiatric events were not commonly observed. However, the available data were limited because the trials were not designed to look for neuropsychiatric events. Sleep disorders [primarily insomnia] were reported more frequently with all three products compared to placebo."

According to *Bloomberg News*, Merck & Co submitted results from 41 placebo-controlled trials involving 9,929 patients treated with Singulair, which is the top-selling drug for people under 17

years old. One adult patient treated with Singulair had suicidal thoughts, and there were no suicides, according to the FDA report.

A spokeswoman for Merck told the *AP* Friday that the precaution is already included in Singulair's labeling; it will simply be moved from a section on side effects to a higher section on "precautions."

AstraZeneca submitted results from 45 placebo-controlled trials in which 7,540 patients were treated with Accolate. The FDA said one patient in an accompanying placebo group attempted suicide, and another thought about it. No Accolate patients reported any suicidal behavior. The FDA also said Cornerstone submitted information showing no suicidal behavior among Zylflo users.

A Merck executive told the *AP* in January that the company had turned over extensive records to the FDA.

"We still believe, after a thorough review of our clinical trial data and postmarketing event reports that the safety profile of Singulair hasn't changed," Dr. Scott Korn, vice president for clinical risk management, said at the time. "We look forward to discussions with the FDA after they've completed their work."

Before last year's review began, Merck had updated prescribing information for Singulair to include information on several adverse events including tremor, depression, suicidality (suicidal thinking and behavior) and anxiousness, according to the FDA.

When the review began, experts pointed out that while it was under way, asthma sufferers needed to determine with their doctors whether Singulair is the best treatment for them.

"[Patients need] to define what they're taking it for," said Dr. David Weldon, director of the Allergy and Pulmonary Lab Services at Scott & White in College Station, Texas. "In some instances, patients may be prescribed Singulair by itself for management of their asthma, and the expert panel guidelines recommend inhaled steroids as the drug of choice for management of asthma as the first line. So if they're still having problems with asthma, they should check with their prescribing physician regarding this."

Weldon said that he has not seen any increase in psychiatric problems with the drug, but that some patients had complained of nightmares after starting on Singulair.

"The physician really needs to review whether there are symptoms that have developed since patients started taking the medication, if there's an underlying depression that was there before medication started," added Dr. Rauno Joks, chief of the division of allergy and immunology at SUNY (State University of New York) Downstate in New York City. "Also, seasonal allergies in and of themselves can cause fatigue and lethargy, which makes it harder to assess, because those are some of the symptoms you have with depression."

Joks said he had seen headaches develop as a side effect of Singulair, but not psychiatric problems.

Leukotriene receptor antagonists target part of the body's inflammatory process. They are prescribed to treat asthma and the symptoms of allergic rhinitis, as well as to prevent exercise-induced asthma.

More information

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