U.S. Food and Drug Administration
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Drug Safety Communications

FDA approves label changes for asthma drug Xolair (omalizumab), including describing slightly higher risk of heart and brain adverse events

This update is in follow-up to the Early Communication about an Ongoing Safety Review of Omalizumab (marketed as Xolair) issued on July 16, 2009.

Safety Announcement

[9-26-2014] A U.S. Food and Drug Administration (FDA) review of safety studies suggests a slightly increased risk of problems involving the heart and blood vessels supplying the brain among patients being treated with the asthma drug Xolair (omalizumab) than in those who were not treated with Xolair. As a result, we have added information about these potential risks to the drug label. Patients taking Xolair should continue to take the medication as prescribed and discuss any questions or concerns with their health care professionals.

FDA approved Xolair in 2003 to treat patients 12 years and older with moderate to severe persistent asthma who have a positive skin or blood test to year-round allergens in the air and whose symptoms are not well-controlled by asthma medicines called inhaled corticosteroids. Xolair has been shown to decrease the number of asthma attacks in these patients. Asthma is a chronic disease that affects the airways in the lungs and can cause serious trouble breathing, so it is important to take all asthma medicines exactly as they are prescribed. Xolair is also approved for patients 12 years and older with chronic hives without a known cause—a condition called chronic idiopathic urticaria or CIU—who continue to have hives that are not controlled by H1 antihistamine treatment.

Our review of a 5-year safety study found a slightly higher rate of heart and brain blood vessel problems occurred in patients being treated with Xolair compared to those patients not treated with Xolair. The heart and brain blood vessel problems included mini-strokes known as transient ischemic attacks or TIAs; heart attacks; sudden, unexpected chest pain; high blood pressure in the arteries of the lungs called pulmonary hypertension; and blood clots in the lungs and veins. Although the data are suggestive of a serious safety signal, due to weaknesses in how the safety study was designed and carried out, we are unable to definitively confirm or determine the exact increased level of these risks with Xolair.

To further evaluate the heart and brain risks noted in the 5-year safety study, we reviewed a combined analysis of 25 randomized double-blind clinical trials comparing Xolair to a

placebo, a treatment that does not contain any medicine. An increased risk of heart- and brain-related problems in patients treated with Xolair was not noted in this combined analysis, but the low number of these events, the young patient population, and the short duration of follow-up prevent us from making any definite conclusions about the absence of a risk. As a result of our review of the safety study and the combined clinical trials, we have added information about the potential risks of heart- and brain-related problems to the Adverse Reactions section of the drug label.

Some previous clinical trials have shown slightly higher rates of various cancers in patients treated with Xolair compared with non-Xolair-treated patients. Our review of the 5-year safety study found no difference in the rates of cancer between those patients being treated with Xolair and those who were not being treated with Xolair. However, due to limitations in the 5-year study, we cannot rule out a potential risk of cancer with Xolair, so we have added this information to the Warnings and Precautions section of the drug label.

Facts about Xolair (omalizumab)

- Xolair is an injectable medicine for patients 12 years and older with moderate to severe persistent asthma who have a positive skin or blood test to year-round allergens in the air and whose symptoms are not well-controlled by asthma medicines called inhaled corticosteroids.
- Xolair is only used in asthma patients who have elevated levels of a substance called IgE in their blood. A blood test must be performed prior to starting Xolair to determine the appropriate dose and dosing frequency. Xolair has been shown to reduce the number of asthma attacks in these patients.
- Xolair is also approved to treat patients 12 years and older with chronic hives without a known cause who continue to have hives that are not controlled by H1 antihistamine treatment.
- Xolair is administered by a health care professional by subcutaneous injection under the skin every 2-4 weeks.
- Xolair is not used to treat other allergic conditions, other forms of urticaria, acute bronchospasm, or status asthmaticus.

Additional Information for Patients

- FDA has added information to the drug label about the slightly increased risk of problems involving blood vessels supplying the heart and brain in Xolair-treated patients. We have also added information about uncertain cancer findings.
- Uncontrolled asthma can cause serious breathing problems, so it is important to take all the medicines your health care professionals prescribe exactly as they tell you.
- Do not change or stop taking Xolair or any of your other asthma medicines unless your health care professional tells you to do so.

- Read the patient Medication Guide for Xolair and talk to your health care professionals about any questions you may have about it or other asthma medicines.
- Report side effects from Xolair to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Additional Information for Health Care Professionals

- FDA has added information about the findings of a slightly elevated risk of cardiovascular and cerebrovascular serious adverse events in Xolair-treated patients to the Adverse Reactions section of the Xolair label. We have also added information about uncertain findings regarding a potential risk of cancer to the Warnings and Precautions section of the drug label.
- Periodically reassess the need for continued therapy with Xolair based on the patient's disease severity and level of asthma control.
- The appropriate duration of therapy for chronic idiopathic urticaria has not been evaluated. Periodically reassess the need for continued Xolair therapy.
- Instruct patients receiving Xolair not to decrease the dose or stop taking the drug or any other asthma medicines unless you instruct them to do otherwise.
- Provide and instruct patients to read the Xolair patient Medication Guide before starting treatment and before starting each new prescription.
- Report adverse events involving Xolair to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Data Summary

The manufacturer of Xolair, Genentech, initiated the postmarketing commitment study titled An **E**pidemiologic Study of **X**olair (omalizumab): Evaluating **C**linical **E**ffectiveness and **L**ong-Term **S**afety in Patients with Moderate to Severe Asthma *(*EXCELS) in June 2004 to assess the long-term safety of Xolair. EXCELS was a 5-year observational cohort study conducted in patients 12 years of age and older with moderate to severe persistent asthma and a positive skin test reaction to a perennial aeroallergen. A total of 5,007 Xolair-treated and 2,829 non-Xolair-treated patients were enrolled. Similar percentages of patients in both cohorts were current (5 percent) or former smokers (29 percent). Patients had a mean age of 45 years and were followed for a mean of 3.7 years. More Xolair-treated patients were diagnosed with severe asthma (50 percent) compared to the non-Xolair-treated patients (23 percent). Additionally, 88 percent of patients in the Xolair-treated cohort had been previously exposed to Xolair for a mean of 8 months (prevalent users). Forty-six percent and 40 percent of patients in the Xolair-treated and non-Xolair-treated cohorts, respectively, prematurely discontinued the study.

A higher incidence rate per 1,000 patient years of overall cardiovascular and cerebrovascular serious adverse events was observed in Xolair-treated patients compared to non-Xolair-treated patients, as well as for myocardial infarction, unstable angina, transient ischemic attack, pulmonary embolism/venous thrombosis, and pulmonary hypertension. No increases in the rates of ischemic stroke or cardiovascular death were

observed in patients treated with Xolair compared to non-Xolair-treated patients. Incidence rates of study-emergent cardiovascular and cerebrovascular serious adverse events are shown in the table below.

EXCELS Observational Cohort Study: Incidence rates per 1,000 patient years of study-emergent cardiovascular and cerebrovascular serious adverse events*

	Xolair cohort (n=5,007)	Non-Xolair cohort (n=2,829)
Overall cardiovascular and cerebrovascular events	13.4	8.1
Myocardial infarction	2.1	0.8
Unstable angina	2.2	1.4
Transient ischemic attack	0.7	0.1
Pulmonary embolism/ venous thrombosis	3.2	1.5
Pulmonary hypertension	0.5	0
Ischemic stroke	0.5	0.7
Cardiovascular death	2.4	2.0

*Estimates are reflective of the number of patients rather than the number of occurrences of each event, and on the patient-years at risk for each individual event rather than overall patient-years at risk for any event during the study.

These results suggest a potential increased risk of serious cardiovascular and cerebrovascular events in patients treated with Xolair. However, our ability to quantify the magnitude of the risk was limited by unmeasured/uncontrolled confounding due to the observational nature of the study, the inclusion of patients previously exposed to Xolair, higher baseline cardiovascular risk among Xolair users, an inability to adjust for unmeasured risk factors, and the high study discontinuation rate.

To further evaluate the cardiovascular and cerebrovascular risks of Xolair, we reviewed a pooled analysis of 25 randomized double-blind, placebo-controlled clinical trials of 8 to 52 weeks in duration completed by December 31, 2010. A total of 3,342 Xolair-treated patients and 2,895 placebo-treated patients were included in this pooled analysis. The primary outcomes of interest included cardiovascular death, myocardial infarction, arrhythmias, heart failure, stroke, transient ischemic attack, pulmonary hypertension, pulmonary embolism, and unstable angina. Across all the studies, a total of eight events occurred in the Xolair-treated patients compared with 15 in the placebo patients, and no notable differences were observed in the rates of specific cardiovascular events. Although no association was found in this pooled analysis, the results were based on a low number of events, relatively young patients (i.e., mean age 38 years and only 5.5 percent elderly), shorter duration of follow-up (mean 6.8 months) than the EXCELS study, and low incidence of baseline cardiovascular disease. Therefore, the results of the pooled analysis are insufficient to confirm or reject the findings noted in the EXCELS study.

We also evaluated the EXCELS study for the risk of malignancy, which was the original intent of this postmarketing commitment study. In the clinical trials that supported approval of Xolair, higher numbers of various malignant neoplasms were observed in Xolair-treated patients compared with control patients. The majority of the patients in these clinical trials were observed for less than 1 year. In the EXCELS study, the incidence rates of primary malignancies per 1,000 patient years were similar among Xolair-treated (12.3) and non-Xolair-treated patients (13.0). However, study limitations prevented us from definitively ruling out a malignancy risk with Xolair. These limitations include the potential for unmeasured/uncontrolled confounding, the bias introduced by allowing enrollment of patients previously exposed to Xolair (prevalent users), an initial enrollment criterion that excluded patients with a history of cancer or a premalignant condition (56 percent), and a high study discontinuation rate.