Information for Healthcare Professionals

Omalizumab (for Subcutaneous Use)
(marketed as Xolair)

The full prescribing information (product labeling) for Xolair was updated on July 2, 2007 with important new safety information—see summary below.

FDA ALERT [2/2007, updated 7/2007]: This Alert highlights important revisions to the full prescribing information for Xolair. The updated full prescribing information for Xolair (July 2007) includes a new Boxed WARNING, updated WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS--Postmarketing Spontaneous Reports. A New Medication Guide about the risk of anaphylaxis following administration of Xolair is to be distributed with each dose of Xolair. These revisions address the risk of anaphylaxis following treatment with Xolair. The implications of this new labeling for healthcare professionals who administer Xolair are summarized below. Xolair is approved to treat adults and adolescents (12 years of age and above) with moderate to severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids.

This information reflects FDA's current analysis of data available to FDA concerning this drug. FDA intends to update this sheet when additional information or analyses become available.

To report any unexpected adverse or serious events associated with the use of this drug, please contact the FDA MedWatch program and complete a form on line at http://www.fda.gov/medwatch/report/hcp.htm or report by fax to 1-800-FDA-0178, by mail using the postage-paid address form provided on line, or by telephone to 1-800-FDA-1088.

The Xolair product label now includes a Boxed Warning, new Warnings and Precautions and an Adverse Reactions section that address the risk of anaphylaxis following administration of Xolair. Xolair also has a new Medication Guide for distribution with each Xolair prescription.

Recommendations and considerations for healthcare professionals:

- Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue has been reported to occur after administration of Xolair.
- Anaphylaxis has occurred as early as after the first dose of Xolair, but also has occurred beyond one year after beginning regular treatment with Xolair.
- Due to the risk of anaphylaxis, Xolair should only be administered to patients in a healthcare setting under direct medical supervision by providers who:
    - Are prepared to identify and treat anaphylaxis after Xolair treatment
    - Know anaphylaxis can occur after any dose of Xolair, even if past doses were well tolerated
    - Know the onset of anaphylaxis can be delayed after administration
    - Observe patients for an appropriate period of time following each Xolair injection

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- Have trained personnel, medications, and equipment for the treatment of life-threatening anaphylaxis available when administering Xolair. Medical personnel administering Xolair should be prepared to recognize and treat anaphylaxis

- Inform patients receiving Xolair treatment of their chance of developing anaphylaxis (including anaphylaxis delayed for 24 hours or more following Xolair treatment) and how to treat it if it occurs. The "Information for the patient" section below provides more detail.
  - Give patients the Medication Guide for Xolair and instruct them to read it before starting treatment with Xolair and before each subsequent dose
  - Inform patients of the signs and symptoms of anaphylaxis
  - Instruct patients to seek immediate care should such symptoms occur
- Discontinue Xolair in patients who experience a severe hypersensitivity reaction
- Report patients who have adverse events including anaphylaxis or hypersensitivity to the FDA's MedWatch program (see reporting information at the bottom of this page)
- Periodically reassess the need for continued Xolair therapy based upon the patient's disease severity and level of asthma control

Information for the patient: *Physicians who are prescribing Xolair should discuss with their patients:*

- Because of the chance of anaphylaxis with Xolair, patients should receive Xolair treatment in a doctor's office and be observed for an appropriate period of time after each treatment
- Anaphylaxis can be serious and life-threatening. Signs and symptoms of anaphylaxis include:
  - Wheezing, shortness of breath, cough, chest tightness, or trouble breathing
  - Low blood pressure, dizziness, fainting, rapid or weak heartbeat, anxiety, or feeling of "impending doom"
  - Swelling of the throat or tongue, throat tightness, hoarse voice, or trouble swallowing
  - Flushing, itching, hives, or feeling warm
- Anaphylaxis can occur with the first dose or after any dose of Xolair
- Anaphylaxis can begin 24 hours or more after Xolair treatment
- To tell your healthcare provider right away if you have symptoms of anaphylaxis after receiving Xolair, and
- To get emergency medical attention immediately if any symptoms of anaphylaxis appear after leaving the doctor's office

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- Carry medical contact information and be fully prepared to begin treatment for anaphylaxis
- You should not receive Xolair if you have ever had an allergic reaction to a Xolair injection
- Do not change or stop taking any of your other asthma medications unless otherwise instructed to do so by a healthcare provider
- Patients may not see immediate improvement in their asthma after beginning Xolair therapy

Background Information and Data

Clinical trial experience

Three cases of anaphylaxis were identified among the 3,507 subjects exposed to Xolair in premarketing clinical trials. Reports of anaphylaxis were based on investigator judgment in relationship to the study drug. The time to onset of anaphylaxis after administration of Xolair in these three patients was:

- 90 minutes in two patients
- 2 hours in one patient.

In addition to these three cases, there were two cases of dyspnea and/or wheezing with urticaria that were not reported as anaphylaxis, but met the diagnostic criteria for anaphylaxis that were used to define the postmarketing cases (see below). One of these patients developed localized urticaria, dyspnea, coughing, and wheezing after receiving the first dose of Xolair. The second patient experienced urticaria, dyspnea, and hot flushes the day after receiving the third dose of Xolair.

Postmarketing Cases

Based on a review of 124 spontaneous case reports and an estimated exposure of about 57,300 patients from June 2003 to December 2006, the frequency of anaphylaxis attributed to Xolair use was estimated to be at least 0.2% of treated patients. Because adverse reactions are reported voluntarily, the actual frequency of anaphylaxis and percent of patients with onset during specific time periods after administration of Xolair may differ from these estimates and this case series. The case definition of anaphylaxis used for this review included either skin or mucosal tissue involvement, and, either airway compromise, and/or reduced blood pressure with or without associated symptoms; and a temporal relationship with Xolair administration with no other identifiable cause.

Symptoms and signs of anaphylaxis in these reported cases included bronchospasm, hypotension, syncope, urticaria, angioedema of the throat or tongue, dyspnea, cough, chest tightness, cutaneous angioedema, and generalized pruritus. Some patients required oxygen and parenteral medications. Pulmonary involvement, including bronchospasm, dyspnea, cough, or chest tightness, was reported in

89% of the cases. Hypotension or syncope was reported in 14% of cases. Fifteen percent of patients required hospitalization. A previous history of anaphylaxis unrelated to Xolair was reported in 24% of the cases. The list below provides information about the time to onset of anaphylaxis following Xolair administration for these patients.

- 30 minutes or less 35%
- Greater than 30 to 60 minutes 16%
- Greater than 60 to 90 minutes 2%
- Greater than 90 to 120 minutes 6%
- Greater than 2 hours to 6 hours 5%
- Greater than 6 to 12 hours 14%
- Greater than 12 to 24 hours 8%
- Greater than 24 hours (up to 4 days) 5%
- Unknown 9%.

Of the reported cases of anaphylaxis, 39% occurred after the first dose of Xolair, 19% occurred with the second dose, 10% occurred with the third dose, and the rest after subsequent doses. One case occurred after 39 doses (after 19 months of continuous therapy, anaphylaxis occurred when treatment was restarted following a 3 month gap). Twenty-three patients who experienced anaphylaxis were re-challenged with Xolair; among them, 18 had a recurrence of similar symptoms of anaphylaxis. Four patients who experienced urticaria and not anaphylaxis were re-challenged with Xolair and developed anaphylaxis upon re-challenge.