

**Pediatric Focused Safety Review
Xolair[®] (omalizumab)
Pediatric Advisory Committee Meeting
September 14, 2016**

**Amy M. Taylor, MD, MHS
Division of Pediatric and Maternal Health
Office of New Drugs/ ODE IV
Center for Drug Evaluation and Research
Food and Drug Administration**

Outline

- **Background Information**
- Pediatric Studies
- Labeling Changes
- Drug Use Trends
- Safety
- Summary

Background Drug Information

Xolair[®] (omalizumab)

- **Drug:** Xolair[®] (omalizumab)
- **Formulation:** injection for subcutaneous use
- **Sponsor:** Genentech
- **Original Market Approval:** June 20, 2003
- **Therapeutic Category:** Anti-IgE antibody

Background Drug Information, continued

Xolair[®] (omalizumab)

Indications

- Moderate to severe persistent asthma in patients 6 years of age and older with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids
- Chronic idiopathic urticaria (CIU) in adults and adolescents 12 years of age and older who remain symptomatic despite H1 antihistamine treatment
 - Approval of this indication necessitated the current PAC presentation.

Background Drug Information, continued

Xolair[®] (omalizumab)

4 Contraindications

Severe hypersensitivity reaction to Xolair[®] or any ingredient of Xolair[®]

5 Selected Warnings and Precautions

- Anaphylaxis
- Malignancy
- Acute Asthma Symptoms: Do not use for acute treatment
- Corticosteroid reduction: Do not abruptly discontinue corticosteroids upon initiation of Xolair[®] therapy
- Fever, Arthralgia, and Rash: Stop Xolair[®] if patients develop signs and symptoms similar to serum sickness
- Eosinophilic Conditions: Be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications and/or neuropathy, especially upon reduction of oral corticosteroids

Outline

- Background Information
- **Pediatric Studies**
- Labeling Changes
- Drug Use Trends
- Safety
- Summary

Pediatric Studies

Xolair[®] (omalizumab)

The safety and effectiveness of Xolair[®] for adolescent patients with CIU were evaluated in 39 patients 12 to 17 years of age (Xolair[®] 29, placebo 10) included in two randomized, placebo-controlled CIU studies of a total of 640 adult and adolescent patients. A numerical decrease in weekly itch score was observed, and adverse reactions in adolescent patients were similar to those reported in patients 18 years and older

Outline

- Background Information
- Pediatric Studies
- **Labeling Changes**
- Drug Use Trends
- Safety
- Summary

Pediatric Labeling Changes

Xolair[®] (omalizumab)

1 Indications and Usage

1.2 Chronic Idiopathic Urticaria (CIU)

Xolair is indicated for the treatment of adults and adolescents (12 years of age and above) with chronic idiopathic urticaria who remain symptomatic despite H1 antihistamine treatment

2 Dosage and Administration

2.3 Dose for Chronic Idiopathic Urticaria

Instructions for administration of Xolair were added

6 Adverse Reactions

6.2 Clinical Trials Experience in Chronic Idiopathic Urticaria

Information on adverse reactions observed during clinical trials with patients 12 years and older was added

Pediatric Labeling Changes

Xolair[®] (omalizumab)

8 Use in Specific Populations

8.4 Pediatric Use

Information on the clinical studies in patients with CIU was added. The original pediatric labeling for CIU included the following rationale for not studying patients less than 12 years of age.

“Clinical studies with Xolair have not been conducted in CIU patients below the age of 12 years. Considering the risk of anaphylaxis and malignancy seen in Xolair-treated patients ≥ 12 years old, the risk-benefit assessment does not support the use of Xolair in patients <12 years of age. Therefore, the use of Xolair in this patient population is not recommended.”

Pediatric Labeling Changes

Xolair[®] (omalizumab)

8 Use in Specific Populations

8.4 Pediatric Use continued

On July 6, 2016, the previous statement was removed after completion of studies in patients 6 to less than 12 years with asthma.

The following statements are now in labeling:

“Safety and efficacy in pediatric patients with asthma below 6 years of age have not been established.”

“Safety and efficacy in pediatric patients with CIU below 12 years of age have not been established.”



Pediatric Labeling Changes Xolair[®] (omalizumab)

14 Clinical Studies

14.2 Chronic Idiopathic Urticaria

Information on the clinical studies conducted in adult and adolescent patients with CIU was added.

Outline

- Background Information
- Pediatric Studies
- Labeling Changes
- **Drug Use Trends**
- Safety
- Summary

Xolair Pediatric Utilization

Estimates of patients who had a prescription or medical claim for Xolair®, stratified by patient age*, from a sample of U.S. outpatient retail, mail-order/specialty, and non-retail settings**, cumulative March 2014 through February 2016

	Cumulative 3/1/2014-2/29/2016	
	N	%
Total Xolair® patients	54,628	100.0%
0 - 16 years	3,834	7.0%
0 - 5 years	18	0.5%
6 - 11 years	789	20.6%
12 - 16 years	3,027	79.0%
17+ years	50,794	93.0%

Source: Symphony Health Solutions' Integrated Dataverse. March 2014 through February 2016. Data extracted June 2016. File: SHSIDV 2016-476 xolair BPCA 6-1-2016.xlsx

*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years old (16 years and 11 months).

**Patient data were obtained from a sample of 453 outpatient and mail-order/specialty pharmacies, and 2,156 non-retail settings which include hospitals, clinics, physician offices, etc.

Limitations of Drug Utilization Database

- Data are not nationally projected
 - The universe of mail-order/specialty and clinics contributing the use data are unknown.
 - Unable to identify national trends

Outline

- Background Information
- Pediatric Studies
- Labeling Changes
- Drug Use Trends
- **Safety**
- Summary



Number* of Adult and Pediatric FDA Adverse Event Reporting System (FAERS) reports with omalizumab (August 1, 2011 to January 31, 2016)

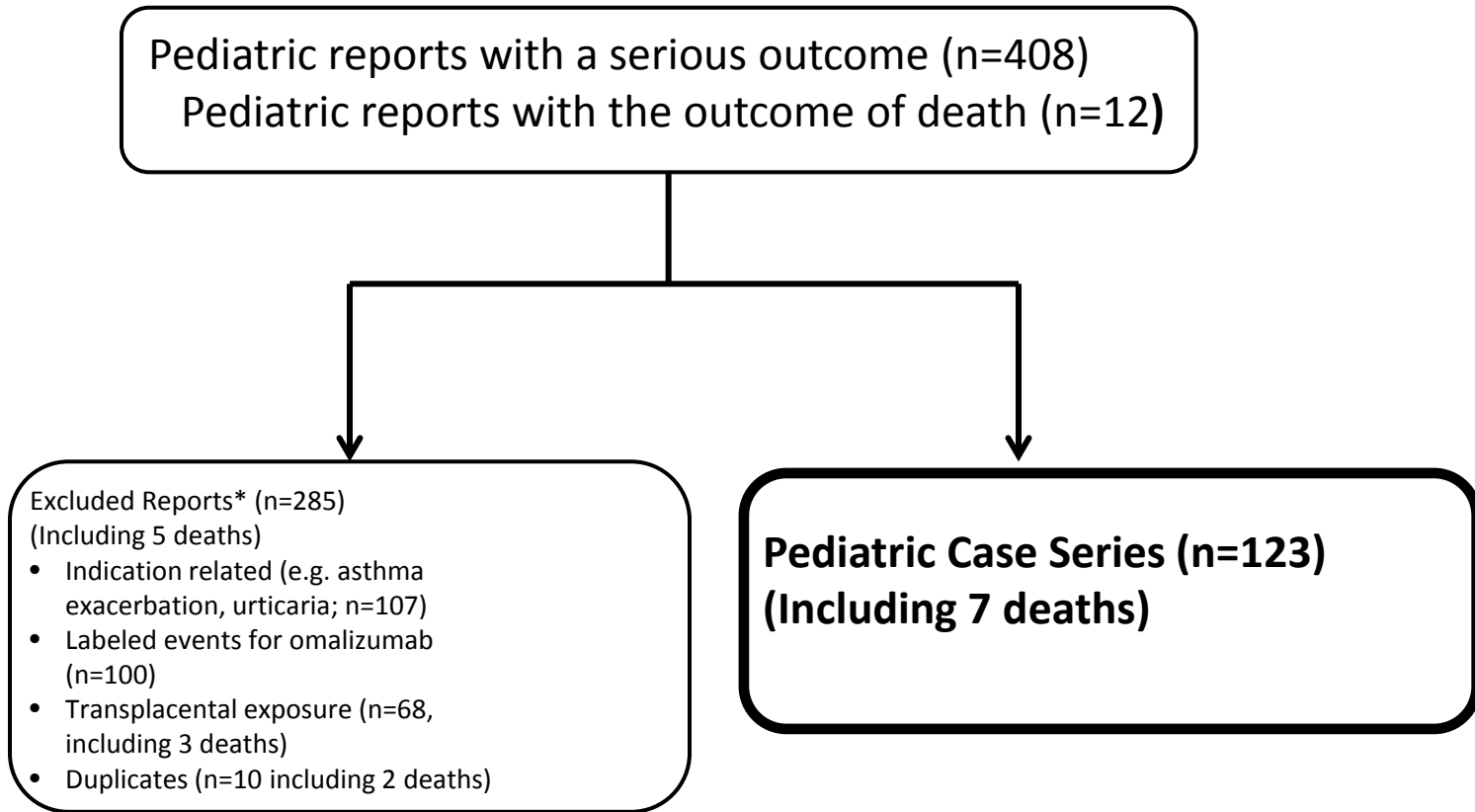
	All reports (US)	Serious[†] (US)	Deaths (US)
Adults (≥ 17 yrs.)	4344 (1462)	4249 (1405)	275 (118)
Pediatrics (0- <17 yrs.)	420 (149)	405 (143)	9[§](2)

* May include duplicates and transplacental exposures; cases have not been assessed for causality

†Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.

§Three additional reports of pediatric deaths were identified among reports not reporting age.

Selection of Pediatric FAERS Cases omalizumab



* These 285 reports were reviewed and excluded from the case series.

Fatal cases omalizumab (n=7)

- *Clostridium difficile* (n=1)
- Cardio-respiratory arrest (n=1)
- Asthmatic crisis (n=1)
- Non-Hodgkin's lymphoma (n=1)
- Gunshot wound while protecting others (n=1)
- House collapsed on patient (n=1)
- Death not otherwise specified (n=1)

The following factors (alone or in combination) negatively affected causality assessment; insufficient clinical information, underlying contributive disease, concomitant medications and lack of temporal relationship between omalizumab administration and event.

Serious Non-Fatal Unlabeled Adverse Events omalizumab (n=116)

Of the 116 reports, 92 had alternative plausible explanations for the events:

- related to underlying disease (such as diabetes, dengue fever, pertussis, meningitis or medical history of seizures, hypertension; n=60)
- lacked temporal relationship (for example, the adverse event occurred 3 years after starting treatment with omalizumab; n=4)
- lacked clinical information for proper assessment (n=15)
- on concomitant medications that contributed to the adverse event (n=13).

Remaining Serious Non-Fatal Unlabeled Adverse Events Omalizumab (n=24)

- Infections and Infestations (n=19)
 - Pneumonia (n=12)
 - Varicella (n=3)
 - Osteomyelitis (n=2)
 - Abscess (n=1)
 - Wound infection (n=1)

Remaining Serious Non-Fatal Unlabeled Adverse Events Omalizumab (n=24) Continued

- Investigations (n=2)
 - Body height increased (n=2)
- Skin and subcutaneous tissue disorders (n=1)
 - Stevens-Johnson Syndrome (n=1)
- Endocrine disorders (n=1)
 - Secondary adrenocortical insufficiency (n=1)
- Musculoskeletal and connective tissue disorders (n=1)
 - Pain in extremity (n=1)

Summary of Safety Review

Xolair[®] (omalizumab)

- This concludes the pediatric focused safety review of FAERS reports.
- No new safety signals were identified.
- FDA recommends continuing routine, ongoing post-marketing safety monitoring.
- Does the committee concur?

ACKNOWLEDGEMENTS

DPARP

CAPT Angela Ramsey, MPH, MSN, RN
Peter Starke, MD
Sally Seymour, MD

DPMH

Ethan D. Hausman, MD
Denise Pica-Branco, PhD
Hari Cheryl Sachs, MD
John Alexander, MD, MPH
Lynne Yao, MD

OSE

LCDR Dipti Kalra, RPh
Allen Brinker, MD
Tracy Pham, PharmD
Eileen Wu, PharmD
LT Travis Ready, PharmD
LCDR Grace Chai, PharmD
Robert Levin, MD

OPT

Judith Cope, MD, MPH
Robert “Skip” Nelson, MD, PhD
Amy Odegaard, MPH
Pam Weinel, MS, MBA, RN
LCDR Kenneth Quinto, MD, MPH