Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

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Product Names:	Xolair (omalizumab)
Pediatric Labeling Approval Dates:	July 6, 2016; September 28, 2018
Application Type/Number:	BLA 103976
Applicant:	Genentech, Inc.
OSE RCM #:	2021-2314

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for omalizumab in pediatric patients through age 17 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) and the Pediatric Research Equity Act (PREA). This review focuses on U.S. serious, unlabeled adverse events associated with omalizumab in pediatric patients.

FDA approved omalizumab on June 20, 2003, and it is currently indicated for 1) moderate to severe persistent asthma in patients 12 years of age and above with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids, 2) chronic idiopathic urticaria in adults and adolescents (12 years of age and above) who remain symptomatic despite H1 antihistamine treatment, and 3) add-on maintenance treatment of nasal polyps in adult patients 18 years of age and older with inadequate response to nasal corticosteroids. On July 6, 2016, omalizumab was approved for moderate to severe persistent asthma in pediatric patients 6 to 11 years of age. On September 28, 2018, FDA approved omalizumab 75 mg and 150 mg liquid prefilled syringes for the treatment of patients 6 years and older with moderate to severe asthma and to treat patients 12 years and older with chronic idiopathic urticaria. OSE previously conducted pediatric postmarketing pharmacovigilance and drug utilization reviews for omalizumab for the Pediatric Advisory Committee (PAC) in 2012 and 2016. OSE's evaluations did not identify any new safety concerns and both evaluations resulted in recommendations to return to routine monitoring for adverse events with omalizumab.

We reviewed all serious, U.S. FAERS pediatric reports with omalizumab for the period of February 1, 2016, to September 30, 2021. We identified 191 U.S., serious pediatric reports with omalizumab and we excluded 189 reports from the case series for various reasons, such as duplicate reports, labeled adverse events, reports of transplacental exposure, adverse event was more likely due to concomitant medications or comorbidities, unassessable reports, reports describing no adverse events, or miscoded reports.

We identified singular cases reporting unlabeled events of left ventricular failure and scrotal edema. The cases lacked clinical information and additional FAERS searches did not identify sufficient evidence to support a signal for either adverse event. We identified no new safety signals, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with omalizumab.

DPV did not identify any new pediatric safety concerns for omalizumab during this review. DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of omalizumab.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for omalizumab in pediatric patients through age 17 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) and the Pediatric Research Equity Act (PREA). This review focuses on U.S. serious, unlabeled adverse events associated with omalizumab in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Omalizumab is an anti-IgE monoclonal antibody that was first approved on June 20, 2003, for use in 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 ("asthma"). On January 4, 2010, omalizumab labeling was updated to include a risk-benefit statement to the Pediatric Use section that efficacy was shown in the clinical trials, but the lingering safety issue of malignancies noted did not provide a favorable risk-benefit balance to support the use of omalizumab in patients 6 to 11 years of age with asthma.[1] In response to a postmarking commitment, a large, long-term observational cohort safety study (known by the acronym of "EXCELS") found the risk of primary malignancy to be similar between the omalizumab and non-omalizumab treated groups in patients 12 year and older.[2] On March 21, 2014, the omalizumab labeling was updated to include the results of the EXCELS study and was approved for use in adults and adolescents 12 years of age and older with chronic idiopathic urticaria (CIU) who remain symptomatic despite H1-antihistamine treatment.[1] Based on the EXCELS study, the FDA informed the applicant that it would reconsider the risk-benefit assessment for the use of omalizumab in patients 6 to 11 years of age with asthma.[2] On July 6, 2016, omalizumab was approved for moderate to severe persistent asthma in pediatric patients 6 to 11 years of age. The safety and efficacy of omalizumab for asthma in this patient population was evaluated in two trials with a total of 926 pediatric patients. The safety and efficacy in pediatric patients with asthma below 6 years of age was not established.[2] On September 28, 2018, FDA approved omalizumab 75 mg and 150 mg liquid prefilled syringes for the treatment of patients 6 years and older with moderate to severe asthma and to treat patients 12 years and older with CIU.[3] Lastly on November 30, 2020, omalizumab was approved for nasal polyps in adult patients 18 years of age and older with inadequate response to nasal corticosteroids, as add-on maintenance treatment.[4]

FDA previously presented OSE's pediatric postmarketing pharmacovigilance and drug utilization reviews for omalizumab to the Pediatric Advisory Committee (PAC) in 2012 and 2016. OSE's first evaluation (DPV's review dated October 31, 2011[5], and the Division of Epidemiology II's drug utilization review dated December 5, 2011)[6] was prompted by the January 4, 2010, pediatric labeling change.[5] The second evaluation, dated August 11, 2016, was prompted by the March 21, 2014, pediatric labeling change for omalizumab.[1] OSE's evaluations did not identify any new safety concerns and both evaluations resulted in recommendations to return to routine monitoring for adverse events with omalizumab.[1, 5]

1.2 RELEVANT LABELED SAFETY INFORMATION

The Boxed Warning, Warnings and Precautions (from the Highlights of Prescribing Information and Full Prescribing Information), Adverse Reactions, and Pediatric Use sections of the omalizumab product labeling are reproduced below.[4]

WARNING: ANAPHYLAXIS

See full prescribing information for complete boxed warning.

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 after the first dose of XOLAIR but also has occurred beyond 1 year after beginning treatment. Initiate XOLAIR therapy in a healthcare setting, closely observe patients for an appropriate period of time after XOLAIR administration and be prepared to manage anaphylaxis which can be life-threatening. Inform patients of the signs and symptoms of anaphylaxis and have them seek immediate medical care should symptoms occur. Selection of patients for self-administration of XOLAIR should be based on criteria to mitigate risk from anaphylaxis. (2.5, 5.1, 6.1, 6.3)

----------**WARNINGS AND PRECAUTIONS**----------

- Anaphylaxis: Initiate XOLAIR therapy in a healthcare setting prepared to manage anaphylaxis which can be life-threatening and observe patients for an appropriate period of time after administration. (5.1)
- Malignancy: Malignancies have been observed in clinical studies. (5.2)
- Acute Asthma Symptoms: Do not use for the treatment of acute bronchospasm or status asthmaticus. (5.3)
- Corticosteroid Reduction: Do not abruptly discontinue corticosteroids upon initiation of XOLAIR therapy. (5.4)
- Eosinophilic Conditions: Be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy, especially upon reduction of oral corticosteroids. (5.5)
- Fever, Arthralgia, and Rash: Stop XOLAIR if patients develop signs and symptoms similar to serum sickness. (5.6)

5.7 Parasitic (Helminth) Infection

Monitor patients at high risk of geohelminth infection while on XOLAIR therapy. Insufficient data are available to determine the length of monitoring required for geohelminth infections after stopping XOLAIR treatment.

In a one-year clinical trial conducted in Brazil in adult and adolescent patients at high risk for geohelminthic infections (roundworm, hookworm, whipworm, threadworm), 53% (36/68) of XOLAIR-treated patients experienced an infection, as diagnosed by standard stool examination, compared to 42% (29/69) of placebo controls. The point estimate of the odds ratio for infection was 1.96, with a 95% confidence interval (0.88, 4.36) indicating that in this study a patient who had an infection was anywhere from 0.88 to 4.36 times as likely to have received XOLAIR than a patient who did not have an infection. Response to appropriate anti-geohelminth treatment of infection as measured by stool egg counts was not different between treatment groups.

5.8 Laboratory Tests

Serum total IgE levels increase following administration of XOLAIR due to formation of XOLAIR:IgE complexes *[see Clinical Pharmacology (12.2)]*. Elevated serum total IgE levels may persist for up to 1 year following discontinuation of XOLAIR. Do not use serum total IgE levels obtained less than 1 year following discontinuation to reassess the dosing regimen for asthma or nasal polyps patients, because these levels may not reflect steady state free IgE levels *[see Dosage and Administration (2.2, 2.3)]*.

----------**ADVERSE REACTIONS**----------

- Asthma: The most common adverse reactions (≥ 1% of patients) in clinical studies with adult and adolescent patients ≥12 years of age were arthralgia, pain (general), leg pain, fatigue, dizziness, fracture, arm pain, pruritus, dermatitis, and earache. In clinical studies with pediatric patients 6 to <12 years of age, the most common adverse reactions were nasopharyngitis, headache, pyrexia, upper abdominal pain, pharyngitis streptococcal, otitis media, viral gastroenteritis, arthropod bites, and epistaxis. (6.1)
- Nasal Polyps: The most common adverse reactions (≥ 3% of patients) in clinical studies with adult patients included the following: headache, injection site reaction, arthralgia, upper abdominal pain, and dizziness. (6.1)
- Chronic Idiopathic Urticaria: The most common adverse reactions (≥2% of patients) included the following: nausea, nasopharyngitis, sinusitis, upper respiratory tract infection, viral upper respiratory tract infection, arthralgia, headache, and cough. (6.1)

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

Asthma

Safety and effectiveness of XOLAIR for moderate to severe persistent asthma who had a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids, have been established in pediatric patients aged 6 years and older. Use of XOLAIR for this indication is supported by evidence from adequate and well-controlled studies. XOLAIR was evaluated in 2 trials in 926 (XOLAIR 624; placebo 302) pediatric patients 6 to <12 years of age with moderate to severe persistent asthma who had a positive skin test or in vitro reactivity to a perennial aeroallergen. One trial was a pivotal trial of similar design and conduct to that of adult and adolescent Asthma Trials 1 and 2. The other trial was primarily a safety study and included evaluation of efficacy as a secondary outcome. In the pivotal trial, XOLAIR-treated patients had a statistically significant reduction in the rate of exacerbations (exacerbation was defined as worsening of asthma that required treatment with systemic corticosteroids or a doubling of the baseline ICS dose) *[see Clinical Studies (14.1)]*.

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

Nasal Polyps

Safety and effectiveness in pediatric patients with nasal polyps below 18 years of age have not been established.

Chronic Idiopathic Urticaria

The safety and effectiveness of XOLAIR for chronic idiopathic urticaria have been established in pediatric patients aged 12 years and older. Use of XOLAIR in this population is supported by evidence from adequate and well-controlled studies. Adolescent patients with CIU were evaluated in 39 patients 12 to 17 years of age (XOLAIR 29, placebo 10) included in three randomized, placebo-controlled CIU trials. A numerical decrease in weekly itch score was observed, and adverse reactions were similar to those reported in patients 18 years and older.

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

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 1.

Table 1. FAERS Search Strategy*	
Date of search	October 29, 2021
Time period of search	February 1, 2016† to September 30, 2021

Table 1. FAERS Search Strategy*	
Search type	FBIS Quick Query
Product terms	Product Active Ingredient: Omalizumab
MedDRA search terms (Version 24.0)	All PTs

* See Appendix A for a description of the FAERS database.
†Data-lock date from last OSE pediatric postmarketing pharmacovigilance review
Abbreviations: FBIS = FDA Business Intelligence System; MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports from February 1, 2016 to September 30, 2021 with omalizumab.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From February 1, 2016 to September 30, 2021 With Omalizumab			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	13,735 (5,641)	10,195 (2,155)	499 (252)
Pediatrics (0 - <18 years)	1,129‡ (542)	770‡ (191)	16‡ (11)

* May include duplicates and transplacental exposures and have not been assessed for causality.
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.
‡ See Figure 1. Seven reports of pediatric deaths were identified among reports not reporting an age. These reports are reflected in the counts of pediatric reports.

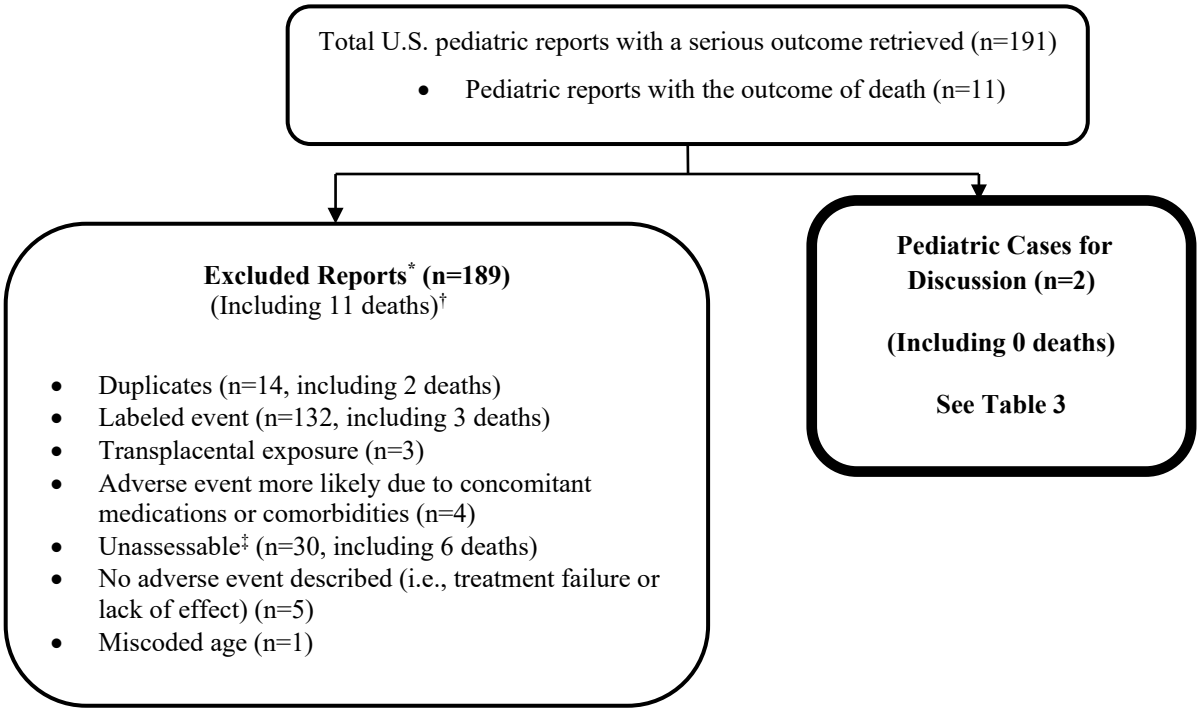
3.1.2 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved 191 U.S. serious pediatric reports from February 1, 2016 to September 30, 2021.

We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded reports from the case series for various reasons, such as duplicate reports, labeled adverse events, reports of transplacental exposure, adverse event was more likely due to concomitant medications or comorbidities, unassessable reports, reports describing no adverse events, or miscoded reports. We summarize the remaining cases in the sections below.

Figure 1 presents the selection of cases for the pediatric case series. Appendix B contains a line listing of the two pediatric cases for discussion.

Figure 1. Selection of Serious U.S. Pediatric Cases with Omalizumab



* DPV reviewed these reports, but they were excluded from further discussion for the reasons listed above.

† Eleven excluded reports described fatal outcomes. Most reports were coded with outcome of death but provided no clinical details in the narrative (n=6). The remaining reports described death secondary to asthma complications (n=2) and pulmonary embolism (n=1). Two reports were duplicates.

‡ Unassessable: Report cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome), the information is contradictory, or information provided in the report cannot be supplemented or verified.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

We did not identify any fatal pediatric adverse event cases for further discussion.

3.1.4 Summary of Non-Fatal Pediatric U.S. Serious Cases (N=2)

We identified two serious FAERS cases with omalizumab in the U.S. pediatric population reporting a non-fatal outcome. There were no clear patterns or trends suggestive of a new safety signal associated with the reported serious unlabeled adverse events in our pediatric cases. The cases are summarized below by System Organ Class.

Cardiac Disorders (n=1)

FAERS #17377196 involves a 16-year-old female on omalizumab 150 mg subcutaneously once every four weeks. Three days after first omalizumab injection, patient had a fever then experienced infections of her ear, sinus, eye, and urinary tract over the next two months. Patient also developed left ventricular failure.

Reviewer's comment: The case provides no clinical details to analyze reported infections or left ventricular failure for causality with omalizumab. A search of the FAERS database performed on January 19, 2022, for reports with the MedDRA Preferred Term Left ventricular failure with omalizumab in patients of all ages identified three cases involving adults; causality for omalizumab and left ventricular failure was unlikely in all three cases. We do not have sufficient evidence to support a signal of left ventricular failure with omalizumab at this time. Note that in a 5-year observational cohort study for omalizumab conducted in patients ≥12 years of age, a higher incidence rate of overall cardiovascular serious adverse reactions was observed in omalizumab-treated patients compared to non-omalizumab-treated patients.[4]

Reproductive System and Breast Disorders (n=1)
FAERS #13931569 involves an 11-year-old male on omalizumab. Two to three hours after receiving the first omalizumab injection, the patient developed scrotal edema. No further information was provided.

Reviewer's comment: The differential for scrotal edema in a child is broad and the most common causes for scrotal swelling include inguinal hernias or hydroceles.[7-12] *There is limited clinical information in the narrative to assess the causality of scrotal edema with omalizumab. A search of the FAERS database performed on January 13, 2022, for additional cases of scrotal edema in patients of all ages identified 1 additional case of scrotal edema reported with omalizumab; the causality for scrotal edema and omalizumab was unassessable in this case. We did not identify a safety signal based on an evaluation of the scrotal edema cases.*

4 DISCUSSION

We reviewed all U.S. serious FAERS reports with omalizumab in the pediatric population (ages 0 – 17 years) for the period from February 1, 2016 to September 30, 2021. We identified singular cases reporting unlabeled events of left ventricular failure and scrotal edema. The cases lacked clinical information and additional FAERS searches did not identify sufficient evidence to support a signal for either adverse event. We identified no new safety signals, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with omalizumab.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for omalizumab during this review.

6 RECOMMENDATION

DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of omalizumab.

7 REFERENCES

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8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=2)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	9/4/2017	13931569	1	US-ROCHE-1988524	Expedited (15-Day)	11	MALE	USA	OT
2	2/6/2020	17377196	1	US-ROCHE-2537836	Expedited (15-Day)	16.52019	FEMALE	USA	OT

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter and are coded as non-serious. A case may have more than one serious outcome.
Abbreviations: USA= United States of America, OT=other medically significant

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/s/

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