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

Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

Date:	August 11, 2016
Reviewers:	Dipti Kalra, RPh, Safety Evaluator Division of Pharmacovigilance I
	Allen Brinker, MD, Medical Officer Team Leader, Division of Pharmacovigilance I
Drug Use Analyst:	Tracy Pham, PharmD, Drug Utilization Analyst Division of Epidemiology II
Team Leaders:	Eileen Wu, PharmD, Safety Evaluator Team Leader, Division of Pharmacovigilance I
	Travis Ready, PharmD, Drug Utilization Team Leader Division of Epidemiology II
Deputy Director For Drug Utilization:	Grace Chai, PharmD Division of Epidemiology II
Division Director:	Robert Levin, MD Division of Pharmacovigilance I
Product Name:	Xolair (omalizumab)
Pediatric Labeling Approval Date:	March 21, 2014
Application Type/Number:	BLA 103976
Applicant/Sponsor:	Genentech, Novartis
OSE RCM #:	2016-476

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

TABLE OF CONTENTS

EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome and drug utilization data for Xolair (omalizumab) in pediatric patients. This review was triggered by the pediatric study of omalizumab for the indication of chronic idiopathic urticaria.

Omalizumab, an anti-IgE monoclonal antibody, was first approved in June 20, 2003 and is 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, and 2) Chronic idiopathic urticaria in adults and adolescents (12 years of age and above) who remain symptomatic despite H1 antihistamine treatment.

Based on the sample obtained from hospitals, clinics and pharmacies, the utilization data showed that approximately 55,000 patients had a prescription or medical claim for Xolair over the cumulative time period from March 2014 through February 2016. Of these, pediatric patients younger than 17 years of age accounted for approximately 7% (3,834 patients) of total patients. Although the data also show some use in patients under 12 years of age, this use cannot be validated due to the lack of access to patient medical records.

The Food and Drug Administration Adverse Event Reporting System database (FAERS) was searched for all reports of adverse events received from August 1, 2011 through January 31, 2016. The Division of Pharmacovigilance (DPV) focused on the serious pediatric reports of unlabeled events.

The review of the FAERS pediatric cases resulted in the identification of 123 pediatric cases of serious, unlabeled events, including 7 death cases. There were no new pediatric safety signals identified, no apparent increased severity or frequency of any labeled adverse events, and there were no deaths directly associated with omalizumab.

There were 24 cases of unlabeled adverse events for which we could not exclude the role of omalizumab. Nineteen of the 24 cases were foreign reports. There were 19 cases of infections that were not specifically listed in the Adverse Reactions – Clinical Trials Experience section under *Infections and infestations* in patients with chronic idiopathic urticaria. The remaining five cases reported four unlabeled events. Given the small number of reports and the number of pediatric patients who received prescriptions for these products, these reports do not suggest new safety signals at this time. Limitations to case interpretation include underlying medical disorders, confounders such as concomitant medications, and incomplete case descriptions or the paucity of clinical data the cases contain. DPV will continue postmarketing surveillance of all adverse events with the use of omalizumab in the pediatric patients.

1 INTRODUCTION

This review evaluates postmarketing adverse event reports with a serious outcome and drug utilization data for Xolair (omalizumab). This review was triggered by the pediatric study of omalizumab for the indication of chronic idiopathic urticaria.

1.1 PEDIATRIC REGULATORY HISTORY

The following regulatory history was reproduced from Dr. Peter Starke's (associate director for labeling, Division of Pulmonary, Allergy, and Rheumatology Products) clinical review of pediatric supplement to extend the asthma indication to children 6 to 11 years of age for omalizumab.[1]

> Xolair 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 March 21, 2014, Xolair was also approved for use in adults and adolescents 12 years of age and older with chronic idiopathic urticaria (CIU) who remains symptomatic despite H1 antihistamine treatment. The applicants previously submitted a pediatric supplement on December 5, 2008 (s- 5149), to support approval of Xolair for the same indication and population as requested in this supplement ("original supplement").
>
> During the review of the original supplement, an Advisory Committee (AC) meeting was held on November 18, 2009, to discuss the risk-benefit for use of Xolair this population. The AC recommended to not approve Xolair for this population because, while efficacy was shown in the clinical trials, the lingering safety issue of malignancies noted in the original BLA safety database did not provide a favorable risk-benefit balance to support the use of Xolair in patients 6 to 11years of age with asthma. (b) (4) adding information from the clinical trials and a risk benefit statement to the Pediatric Use section (8.4) of the labeling (s-5166, Approved January 4, 2010). With this latter action, the PREA pediatric study requirements (PMC letter dated September 30, 2005) for Xolair for the asthma indication were considered fulfilled for children 6 through 11 years of age, and were waived for children zero through 5 years of age (due to safety concerns[a]). The applicants subsequently (b) (4) (b) (4) Hence, the current supplement
>
> Since the time frame in which the original pediatric supplement was being considered, the results of a large, long-term observational cohort safety study (known by the acronym of "EXCELS") were submitted, reviewed, and incorporated into the Xolair labeling in 2014 (s-5161, Approved September 26, 2014).

[a] Studies in patients 0 to 5 years were not required because of the safety concerns of anaphylaxis and malignancy associated with use of Xolair in adults and adolescents.

The EXCELS study was conducted in response to a post-marketing commitment (PMC #3)[b] instituted at the time of approval of the original BLA in 2003. The study was intended to evaluate the incidence of serious adverse events with Xolair treatment, including malignancy. The EXCELS study included adolescent and adult patients 12 years of age and older with moderate to severe persistent asthma and a positive skin test reaction or in vitro reactivity to a perennial aeroallergen, 5007 of whom were treated with Xolair and 2829 of whom were not treated with Xolair, and followed for up to 5 years. Importantly, while the EXCELS study had significant limitations that precluded definitively ruling out a malignancy risk[c], similar incidence rates of primary malignancies (per 1000 patient years) were noted in the Xolair-treated (12.3) and the non-Xolair-treated patients (13.0). While the EXCELS study did not include children below 12 years of age, it was felt that the results contribute to the overall risk-benefit evaluation of Xolair. Therefore, following approval of the labeling for the EXCELS supplement, the Division informed the applicants that the Agency would reconsider the risk-benefit assessment for the use of Xolair in patients 6-11 years of age with asthma, should the applicants still wish consideration of an extension of the age range for this indication.

On July 6, 2016, Xolair was approved for use in patients 6 to 11 years of age with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to airborne allergens and whose symptoms are controlled adequately by corticosteroids.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES[2]

After initial marketing, in February 2007, the label warning for omalizumab was strengthened to include a boxed warning for anaphylaxis. The label also notes that treatment with omalizumab is known to increase risk for infections with certain parasitic agents (helminths).

Given the concerns over the long term safety of omalizumab, including the risk of malignancy, the sponsor was required to conduct a post marketing observational cohort study (EXCELS) in patients ≥ 12 years old with moderate to severe persistent asthma and a positive skin test reaction to a perennial aeroallergen. Approved labeling for omalizumab was recently updated to note that interim results of EXCELS suggest a potential increased risk of serious cardiovascular and cerebrovascular events in patients treated with omalizumab. In contrast, omalizumab did not detect a signal for an increased malignancy risk.

BOXED WARNING

[b] PMC #3 was as follows: "To conduct a prospective, observational cohort study of 5,000 Omalizumab treated and 2,500 untreated patients that assess the clinical safety of Omalizumab by determining the incidence of malignancy and other serious adverse events (SAEs) in Omalizumab-treated patients with moderate to severe persistent asthma and skin test or in vitro reactivity to an aeroallergen compared with patients not treated with Omalizumab. Study subjects will be followed for at least 5 years, and Omalizumab-treated patients will be matched at enrollment to untreated patients by age, gender, and race/ethnicity. Interim reports will be filed yearly. The final protocol of the study will be submitted to FDA by December 31, 2003, patient accrual will be completed by March 31, 2006, the study will be completed by March 31, 2011, and a final study report will be submitted to the FDA by September 30, 2011."

[c] As noted in the Prescribing Information (Package Insert), the EXCELS study limitations included: the observational study design, the bias introduced by allowing enrollment of patients previously exposed to Xolair (88%), enrollment of patients (56%) while a history of cancer or a premalignant condition were study exclusion criteria, and the high study discontinuation rate (44%).

WARNING: ANAPHYLAXIS
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 1 year after beginning regularly administered treatment. Because of the risk of anaphylaxis, observe patients closely for an appropriate period of time after Xolair administration. Health care providers administering Xolair should be prepared to manage anaphylaxis that can be life-threatening. Inform patients of the signs and symptoms of anaphylaxis and instruct them to seek immediate medical care should symptoms occur.

WARNINGS AND PRECAUTIONS

Anaphylaxis

Anaphylaxis has been reported to occur after administration of Xolair in premarketing clinical trials and in postmarketing spontaneous reports. Signs and symptoms in these reported cases have included bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue.

Malignancy

Malignant neoplasms were observed in 20 of 4127 (0.5%) Xolair-treated patients compared with 5 of 2236 (0.2%) control patients in clinical studies of adults and adolescents (≥ 12 years of age) with asthma and other allergic disorders.

Acute Asthma Symptoms

Xolair has not been shown to alleviate asthma exacerbations acutely. Do not use Xolair to treat acute bronchospasm or status asthmaticus.

Corticosteroid Reduction

Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of Xolair therapy for asthma. Decrease corticosteroids gradually under the direct supervision of a physician. In CIU patients, the use of Xolair in combination with corticosteroids has not been evaluated.

Fever, Arthralgia, and Rash

In post-approval use, some patients have experienced a constellation of signs and symptoms including arthritis/arthralgia, rash, fever and lymphadenopathy with an onset 1 to 5 days after the first or subsequent injections of Xolair. These signs and symptoms have recurred after additional doses in some patients.

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.

ADVERSE REACTIONS

Clinical Trials Experience

Adverse Reactions from Clinical Studies in Patients with Asthma

The adverse events most frequently resulting in clinical intervention (e.g., discontinuation of Xolair, or the need for concomitant medication to treat an adverse event) were injection site reaction (45%), viral infections (23%), upper respiratory tract infection (20%), sinusitis (16%), headache (15%), and pharyngitis (11%).

Adverse Reactions from Clinical Studies in Patients with Chronic Idiopathic Urticaria (CIU)

Additional reactions reported during the 24 week treatment period in Trials 1 and 3 [≥2% of patients receiving Xolair (150 or 300 mg) and more frequently than those receiving placebo] included: toothache, fungal infection, urinary tract infection, myalgia, pain in extremity, musculoskeletal pain, peripheral edema, pyrexia, migraine, sinus headache, anxiety, oropharyngeal pain, asthma, urticaria, and alopecia.

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

Proprietary databases available to the Agency were used to conduct the drug utilization analyses in this review (see Appendix A for full database descriptions and limitations).

2.1.1 Determining Settings of Care

Based on the IMS Health, IMS National Sales Perspectives™ database, approximately 54%, 45%, and <1% of Xolair vials were distributed to mail-order/specialty settings, non-retail settings[d], and outpatient retail pharmacies, respectively, in 2015. Among the non-retail settings, approximately 59% and 27% of Xolair vials were distributed to clinics and non-federal hospitals, respectively.[e] As a result, we examined Xolair utilization patterns from a sample of patients who had a prescription or medical claim for Xolair from various retail and non-retail settings of care. This analysis was conducted using a sample of patients; nationally projected data are not available for products used in mail-order/specialty pharmacies and clinics.

2.1.2 Data Sources Used

The Symphony Health Solutions' Integrated Dataverse (IDV) database was used to provide estimates of patients who had a prescription or medical claim for Xolair, stratified by patient age (0-5, 6-11, 12-16, and 17+ years), for the cumulative time period from March 1, 2014 through February 29, 2016. Patient age was based on age at the time of the first prescription or medical claim. These data are not nationally projected, but only provide raw counts of unique patients obtained from a sample of 453 pharmacies and 2,156 non-retail settings during the study time period.

Patients who had a submitted claim for Xolair were identified using the National Drug Codes (NDCs 50242-0040-62 and 50242-0042-01) and the Health Care Common Procedure Coding System (J-code 2357). Patients' claims histories were searched based on the occurrence of one or more Xolair prescription or medical claim(s) during the study period. In addition, a 90 day look-back period was used to determine the number of patients with a prior prescription or medical claim that allowed for at least one day of Xolair therapy during the study period. For example, patients who did not have a prescription filled or a medical claim during the study time period would also be counted as using Xolair if they filled a prescription or had a medical claim during the 90 days prior to the study time period and the fill date of their prescription plus its day supply extended into the study time period by one day or more.

---

[d] Non-retail settings include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

[e] IMS Health, IMS National Sales Perspectives™. Year 2015. Data extracted March 2016. File: NSP 2016-476 xolair BPCA channel 3-24-2016.xlsx

2.2 RESULTS

2.2.1 Number of Patients

Table 2.2.1. 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.

3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategy described in Table 3.1.1. See Appendix B for a description of the FAERS database.

Table 3.1.1 FAERS Search Strategy	
Date of Search	April 28, 2016
Time Period of Search	August 1, 2011* - January 31, 2016
Search Type	Quick Query
Product Name	Active Ingredient: Omalizumab
Search Parameters	All ages, all outcomes, worldwide

* Cut-off date of latest OSE pediatric safety review for omalizumab.

3.2 RESULTS

3.2.1 Total number of FAERS reports by Age

Table 3.2.1 Total adult and pediatric FAERS reports* August 1, 2011 - January 31, 2016 with omalizumab

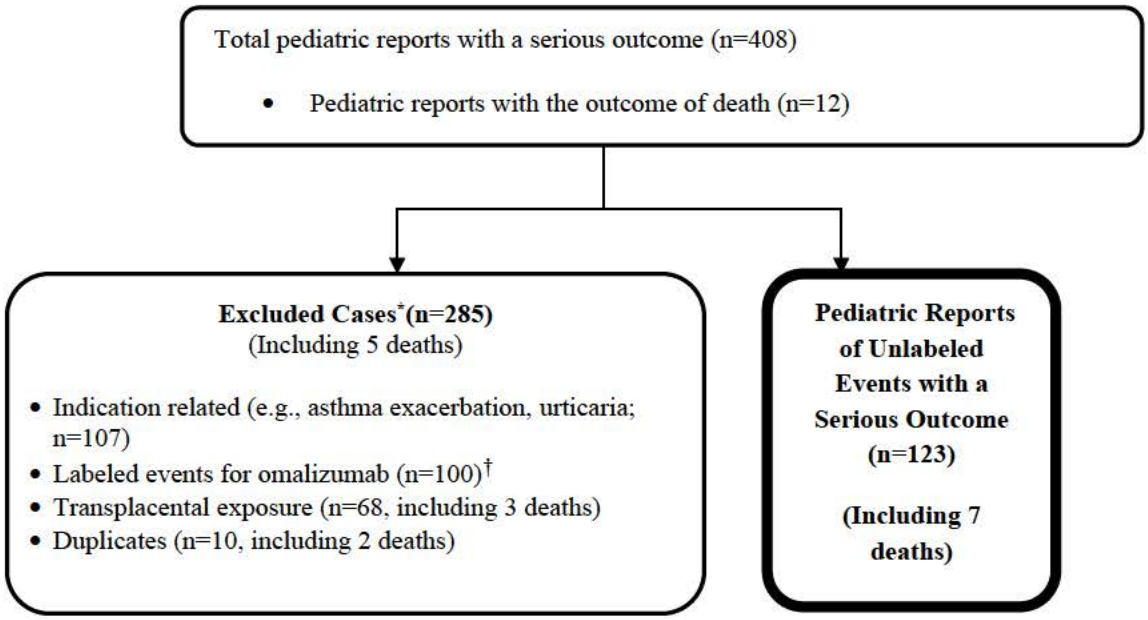
	All reports (US)	Serious† (US)	Death (US)
Adults (≥ 17 years)	4344 (1462)	4249 (1405)	275 (118)
Pediatrics (0 - <17 years)	420 (149)	**405‡ (143)**	9§ (2)

* 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, and other serious important medical events.
‡ See Figure 3.2.2
§ Three additional reports of pediatric deaths were identified among reports not reporting an age.

3.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 408 pediatric reports with a serious outcome. See Figure 3.2.2 below for the specific selection of serious pediatric cases with omalizumab in Sections 3.3 and 3.4.

Figure 3.2.2 Selection of Serious Pediatric Cases with Omalizumab



* DPV reviewed these cases, but they were excluded from the case series for the reasons listed above.
†The labeled events/PTs were: anaphylaxis (n=42), hypersensitivity (n=9), angioedema (n=8), arthralgia (n=6), fracture (n=6), syncope (n=6), headache (n=5), erythema (4), thrombocytopenia (n=3), bronchospasm (n=2), myalgia (n=2), dyspnea (n=2), serum sickness (n=2), wheezing (n=2), altered vision (n=1). They did not appear to occur at an increased frequency or severity.

3.2.3 Characteristics of Pediatric Reports of Unlabeled Events that had a Serious Outcome

Appendix C lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the Pediatric Case Series.

Table 3.2.3 Characteristics of Pediatric Reports of Unlabeled Events that had a Serious Outcome with Omalizumab (N=123)

Age	0 - < 1 month	0
	1 month - <2 years	1
	2- < 6 years	3
	6- <12 years	40
	12- < 17 years	79
Sex	Male	67
	Female	53
	Unknown	3
Country	United States	28
	Foreign	95
Reported Reason for Use	Asthma	86
	Unknown	20
	Dermatitis atopic	4
	Urticaria	3
	Bronchopulmonary aspergillosis allergic	2
	Anaphylactic reaction	1
	Cystic fibrosis	1
	Food allergy	1
	Immune system disorder	1
	Lung disorder	1
	Off label use	1
	Otomastoiditis	1
	Vaccination complication	1
Serious Outcome*	Death	7
	Hospitalized	47
	Disability	6
	Other serious	82

* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events. Reports may have more than one outcome.

3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=7)

Of the seven pediatric death cases, the reported age ranged from 21 months to 16 years (mean 10 years; median 13 years). The 7 cases described the following adverse events: septic shock caused by gastrointestinal infection with *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), and death (not otherwise specified; n=1).

Reviewer's Comment: Overall, clinical details surrounding the deaths were not well-described; therefore it was difficult to perform definitive causality assessments. Cases reported underlying diseases, had concurrent medications, or lacked a temporal relationship between the adverse event and omalizumab. In summary, these cases with an outcome of death did not appear attributable to treatment with omalizumab.

3.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENTS (N=116)

We reviewed 116 reports that described serious unlabeled events. 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), or on concomitant medications that contributed to the adverse event (n=13). The remaining 24 cases that described serious and unlabeled events are briefly described in **sections 3.4.1 to 3.4.5**.

Cases in these sections are categorized by preferred terms (PTs) that best represent the reported adverse event(s). The PTs are then grouped by like terms and organized by System Organ Class: Pneumonia (n=12), Varicella (n=3), Body height increased (n=2), Osteomyelitis (n=2), Pain in extremity (n=1), Abscess (n=1), Secondary adrenocortical insufficiency (n=1), Stevens-Johnson Syndrome (n=1), Wound infection (n=1). Nineteen of the 24 cases were foreign reports. Narratives of the 24 cases are found below:

3.4.1 *Infections and infestations (N=19)*

Upper respiratory tract infection is listed in the Medication Guide section of the omalizumab label for the chronic idiopathic urticaria indication. The infections listed in the Adverse Reactions – Clinical Trials Experience Section include sinusitis, nasopharyngitis, fungal infection, and urinary tract infection. Treatment with omalizumab is known to increase risk for infections with certain parasitic agents (helminths). See Section 1.2 for the warning on parasitic (helminth) infection in the current label.

Pneumonia (n=12)

Twelve cases reported pneumonia in males (n=6) and females (n=6). The median age was 12 years, with a range of 7 years to 16 years. In four cases the reason for use was an off-label use. Nine cases documented a time to onset of event after omalizumab administration that ranged from "immediate" to 1&1/2 years. Eight of 12 cases reported hospitalization. The patients recovered in six of the 12 cases.

Reviewer's Comment: Pneumonia is a relatively common event in the population especially one with refractory asthma. None of these cases indicated infection with a rare organism or rare pathologic process which would suggest a new safety concern.

Varicella (n=3)
The varicella cases included 2 males and 1 female aged 7, 9, and 10 years old, respectively. The time to onset of event after omalizumab administration was 1&1/2 months, 4 months, and 8 months. Omalizumab was discontinued in all of the cases but restarted in one. The patient was hospitalized in one case and the outcome was reported as recovered.

Reviewer's Comment: Varicella is a relatively common event in the population. None of these cases indicated infection with a rare organism or rare pathologic process which would suggest a new safety concern.

Osteomyelitis (n=2)
The first case was of a 6-year-old male who experienced leg pain two months after starting omalizumab. The patient was diagnosed with osteomyelitis. Omalizumab was discontinued and the outcome was reported as recovering. The other case was of a 9-year-old male who experienced osteomyelitis and leg pain when omalizumab was restarted. Therapy status of omalizumab and the outcome was not reported.

Reviewer's Comment: Neither of these cases described apparent risk factors for osteomyelitis such as a traumatic wound with penetration to the bone.

Abscess (n=1)
A 15-year-old male started omalizumab (450 mg every 15 days) and experienced "the abscess throughout the body" after the first dose. Treatment included antibiotics. Omalizumab was discontinued and the patient recovered. A few months later, the patient restarted omalizumab (900 mg every two months). After each injection he had similar process that immobilized him and he could not walk. Treatment included antibiotics and omalizumab was ongoing and the events recovered.

Reviewer's Comment: This case represents the development of a unique symptom complex in association with treatment with omalizumab. There is not enough information provided to fully assess this case or similar cases to signal a safety concern at this time. We will continue postmarketing surveillance of these events for increase in frequency and severity of reports.

Wound Infection (n=1)
A 6-year-old male had perioral hives and felt tired 5-6 days after the first dose of omalizumab. Five days after the fourth dose, the patient had "even more hives, infected wound outside and inside the mouth, genital affected, and wound around wrist." The patient was hospitalized and was treated with intravenous cefotaxime, clemastine fumarate, and intravenous rehydration. The physician said it appeared to be a bacterial infection. The action taken with omalizumab was unknown, and the outcome of the events was not reported.

Reviewer's comment: This case illustrates the potential effect of immunosuppression or exaggerated viral exanthem with secondary infection in a patient treated with omalizumab. A constellation of symptoms – including rash – is associated with omalizumab and described in approved labeling as a Warning. It is not known if this case represents background disease potentiated by omalizumab, a true effect of omalizumab, or an interaction between host and drug effects. We will continue postmarketing surveillance of these events for increase in frequency and severity of reports.

3.4.2 *Investigations (N=2)*

Body height increased (n=2)

Two literature articles of a 14- and 15-year-old male who experienced rapid increase in linear growth within 4 months following initiation of omalizumab treatment. The event outcome and therapy status was not reported. The author concluded that omalizumab was "thought to decrease the release of mast cell mediators, which may decrease the amount of platelet activating factor (PAF) released, increasing prostaglandin E2 production to allow linear skeletal growth to occur."[3]

Reviewer's comment: We are unable to draw any conclusions based on one publication. DPV will continue postmarketing surveillance of these events for increase in frequency and severity of reports.

3.4.3 *Skin and subcutaneous tissue disorders (N=1)*

Stevens-Johnson Syndrome (n=1)

A 6-year-old male developed "Stevens-Johnson type reaction." Ten days after the first injection the patient had a rash around the mouth. Seven days after the second injection the same reaction happened again and healed within a few days. A week after the third injection, the rash occurred again and healed within a few days. Four days after the fourth injection, the patient had a rash, wound formation on the wrists, mouth sores, and passed out at one point. The wounds were not typical of impetigo. His condition worsened further with fever. The patient could not eat for a few days because of pain in the mouth and throat. The patient was hospitalized and treated with cefotaxime, "painkillers," lidocaine hydrochloride, cortisone, and antihistamine. Treatment with omalizumab was stopped and the patient fully recovered. The response to IV antibiotics was "quite slower than expected." Concomitant medications included fluticasone propionate/formoterol fumarate, salbutamol, montelukast sodium, loratadine, and IV nutrition.

Reviewer's comment: We are unable to draw any conclusions from this singular case for this event. DPV will continue postmarketing surveillance of these events for increase in frequency and severity of reports.

3.4.4 *Endocrine Disorders (N=1)*

Secondary adrenocortical insufficiency (n=1)

A 6-year-old male experienced secondary adrenal insufficiency and growth retardation while being treated with omalizumab for atopic dermatitis. The patient's growth and thyroid axis were without findings. The patient's magnet resonance imaging (MRI) of pituitary gland showed no anatomic abnormalities and the cortisol level was very low. Two years after starting omalizumab, the patient was diagnosed with secondary adrenal insufficiency and growth

retardation. On an unknown date, the endocrinological examination revealed a secondary adrenocortical insufficiency. Treatment with omalizumab was discontinued and the events of secondary adrenal insufficiency and growth retardation were completely recovered.

Reviewer's Comment: We are unable to draw any conclusions from this singular case for this event. DPV will continue postmarketing surveillance of these events for increase in frequency and severity of reports.

3.4.5 *Musculoskeletal and connective tissue disorders (N=1)*

Pain in extremity (n=1)

A 16-year-old female developed allodynia, elevated IgE, severe leg pain, elevated eosinophils, inability to walk, and allergies while being treated with omalizumab and prednisone. The patient's concurrent condition included environmental allergies, wheelchair use, and rhinitis. Concomitant medications included formoterol fumarate/mometasone furoate, montelukast sodium, desloratadine, and mometasone furoate. The patient started therapy with subcutaneous omalizumab injection (dose and frequency not reported) for the treatment of recurrent asthma exacerbations. After the fifth injection of omalizumab, she had severe leg pain/pain/intractable pain in both legs, allodynia, and abasia because of pain. The patient was hospitalized. She was mobilizing with a wheel chair and could not attend school because of the pain. She received treatment with morphine for the pain. Treatment with omalizumab was stopped and the outcome of events was unknown.

Reviewer's Comment: Leg pain is a labeled event in the Adverse Reactions section of the label, and this patient's concurrent condition included wheelchair use. DPV will continue postmarketing surveillance of these events for increase in frequency and severity of report.

4 DISCUSSION

Based on the sample obtained from hospitals, clinics and pharmacies, the utilization data showed that approximately 55,000 patients had a prescription or medical claim for Xolair over the study time period. Of these, pediatric patients less than 17 years of age accounted for approximately 7% of total patients. Although the data show some use in patients under 12 years of age, this use cannot be validated due to the lack of access to patient medical records.

The review of the FAERS pediatric cases resulted in the identification of 123 pediatric cases of serious, unlabeled events, including 7 death cases. There were no new pediatric safety signals identified, no apparent increased severity or frequency of any labeled adverse events, and there were no deaths directly associated with omalizumab.

There were 24 cases of unlabeled events that we could not exclude the role of omalizumab. Nineteen of the 24 cases were foreign reports. There were 19 cases of infections that were not specifically listed in the Adverse Reactions – Clinical Trials Experience section under *Infections and infestations* in patients with chronic idiopathic urticaria. The remaining five cases reported four unlabeled events. Given the small number of reports and the number of pediatric patients who received prescriptions for these products, these reports do not suggest new safety signals at this time. Limitations to case interpretation include underlying medical disorders, confounders

such as concomitant medications, and incomplete case descriptions or the paucity of clinical data the cases contain. DPV plans to continue postmarketing surveillance of these events.

5 CONCLUSION

Overall, there were no clear patterns of reported adverse events in the cases to suggest a new safety signal associated with omalizumab in pediatric patients. The pediatric safety profile described in these reports is consistent with the known safety profile and the current omalizumab label. We did not identify any new safety concerns in children 0 to < 17 years old treated with omalizumab.

6 RECOMMENDATIONS

DPV will continue postmarketing surveillance of all adverse events with the use of omalizumab in the pediatric patients.

7 REFERENCES

1. Starke, Peter, MD. Omalizumab Clinical Review. May 26, 2016.
2. Xolair [package insert]. San Francisco, CA: Genentech; December 14, 2015 (https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7f6a2191-adfb-48b9-9bfa-0d9920479f0d. Accessed June 17, 2016).
3. Richards NB, McGeady S, Chang C, and Doyle D. Effects of Omalizumab on Two Patients with Short Stature and Atopic Disease. *J Allergy Clin Immunol*. 2012; 129.

8 APPENDICES

8.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

Symphony Health Solutions' IDV® (Integrated Dataverse)

Symphony Health Solutions' IDV (Integrated Dataverse) contains longitudinal patient data sources that capture adjudicated prescription, medical, and hospital claims across the United States for all payment types, including commercial plans, Medicare Part D, cash, assistance programs, and Medicaid. The IDV contains over 10 billion prescriptions claims linked to over 220 million unique prescription patients of with an average of 4.2 years of prescription drug

history. Claims from hospital and physician practices include over 190 million patients with CPT/HCPCS medical procedure history as well as ICD-9 diagnosis history of which nearly 140 million prescription drug patients are linked to a diagnosis. The overall sample represents over 54,000 pharmacies, 1,500 hospitals, 800 outpatient facilities, and 80,000 physician practices.

Data from Symphony Health Solutions' IDV provides raw counts of unique patients who had a prescription or medical claim for Xolair® from a sample of 453 pharmacies and 2,156 non-retail settings during the study time period. Due to the sample size and the unreported pharmacy information, there are limitations in the ability to identify national trends in the data. In addition, the universe of mail order/specialty pharmacies and clinics contributing to these data are unknown; therefore, nationwide projections are not available at this time. The patient estimates are from a sample of outpatient pharmacy and clinic settings; therefore, they may not be representative of utilization in other settings of care such as inpatient use.

8.2 APPENDIX B. 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 the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference 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.

8.3 APPENDIX C. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH DRUG (N=123)

FAERS Case Number	Version Number	Manufacturer Control Number	FAERS Case Number	Version Number	Manufacturer Control Number
10083208	1	FR-ROCHE-1385079	8351886	2	AR-ROCHE-1032996
10094028	1	US-ROCHE-1387692	8418444	1	MX-ROCHE-1040836
10168423	3	IE-ROCHE-1399395	8428937	2	US-ROCHE-1042840
10168898	3	PL-ROCHE-1400179	8428973	2	US-ROCHE-1042493
10175756	2	VE-ROCHE-1402012	8480938	1	FR-ROCHE-1053519
10191143	1	PL-ROCHE-1405906	8498501	2	FR-ASTRAZENECA-2012SE21799
10256867	3	CA-ROCHE-1423592	8544632	2	FR-ROCHE-1064515
10426895	2	GR-ROCHE-1457735	8555844	1	ES-ROCHE-1066622
10429615	1	FR-ROCHE-1458112	8583974	6	JP-ROCHE-1071380
10444082	8	US-ROCHE-1460319	8591275	1	GB-ROCHE-1071695
10463322	1	US-ROCHE-1463502	8649109	1	SE-ROCHE-1083306
10480026	1	FR-ROCHE-1467485	8680915	2	US-ROCHE-1089803
10506567	2	CH-ROCHE-1471757	8684534	1	CO-ROCHE-1091213
10556162	1	ES-ROCHE-1481941	8697848	1	US-ROCHE-1094115
10586298	2	CO-ROCHE-1489597	8730359	1	BR-ROCHE-1102917
10624810	8	CA-ROCHE-1325548	8743982	7	CA-ROCHE-1103093
10656718	2	RU-ROCHE-1508843	8912745	1	MX-ROCHE-1155354
10669962	1	CO-ROCHE-1511326	8927116	2	GB-ROCHE-1160030
10686877	2	US-ROCHE-1496192	8930101	1	PT-ROCHE-1160666
10764195	1	US-ROCHE-1531107	8930451	2	FR-ROCHE-1160523

FAERS Case Number	Version Number	Manufacturer Control Number	FAERS Case Number	Version Number	Manufacturer Control Number
10890421	2	CH-ROCHE-1548546	8987389	1	US-ROCHE-1173726
10906349	1	GB-ROCHE-1550399	8988891	1	US-ROCHE-1174207
10955185	1	CO-ROCHE-1556217	9012794	1	US-MERCK-1301USA003276
10955317	2	US-ROCHE-1556427	9059239	4	CO-ROCHE-1187721
10985846	1	1350442	9093793	1	
10986158	1	1459665	9122815	1	US-009507513-1301USA002103
11070782	2	CO-ROCHE-1569145	9125132	5	US-ROCHE-1195582
11134308	6	CA-ROCHE-1581598	9160310	1	GB-ROCHE-1199887
11227301	1	AT-ROCHE-1600947	9163186	1	BR-ROCHE-1199931
11281589	1	DE-ROXANE INC.-2015-RO-01134RO	9184545	2	CA-ROCHE-1151088
11385781	2	JP-ROCHE-1621736	9186558	1	DE-ROCHE-1206062
11422549	3	JP-ROCHE-1626959	9188874	2	GB-ROCHE-1205529
11499740	1	JP-ROCHE-1633704	9220296	2	US-ROCHE-1211738
11512145	1	US-ROCHE-1627894	9251451	1	CA-ROCHE-1001568
11516347	2	SE-ROCHE-1635038	9275225	1	
11559361	1		9285546	1	VE-ROCHE-1223685
11604045	4	JP-ROCHE-1643010	9314768	1	GR-ROCHE-1229823
11631745	2	CA-ROCHE-1645938	9321651	3	PT-ROCHE-1229218
11631973	2	AE-ROCHE-1646560	9354795	1	CA-ROCHE-1237023
11647939	1	FR-ROCHE-1649004	9383407	2	CA-ROCHE-1244254
11648538	1	JP-ROCHE-1648959	9401909	2	MX-ROCHE-1242667
11680098	1	JP-ROCHE-1651941	9457860	1	CA-ROCHE-1261174

FAERS Case Number	Version Number	Manufacturer Control Number	FAERS Case Number	Version Number	Manufacturer Control Number
11689076	3	JP-ROCHE-1654106	9485605	3	DE-ROCHE-1265892
11692418	1	SE-ROCHE-1651959	9490740	1	RU-ROCHE-1268645
11719860	2	MX-ROCHE-1646761	9492072	1	RU-ROCHE-1268791
11745186	5	CA-ROCHE-1661132	9511826	1	CA-ROCHE-1271893
11745975	1		9516256	2	US-ROCHE-1273572
11809714	1	DK-ROCHE-1674022	9534106	4	CA-ROCHE-1276475
11820371	3	GB-ROCHE-1675541	9604042	3	CA-ROCHE-1285641
11849287	2	CA-ROCHE-1679159	9644292	9	CA-ROCHE-1293087
11862793	1	US-ROCHE-1682674	9657914	2	VE-ROCHE-1296309
11870117	1	SE-ROCHE-1684706	9664266	1	US-ROCHE-1298259
11909660	1	ES-ROCHE-1692949	9709379	3	GB-ROCHE-1307728
11912959	1	US-ROCHE-1693480	9741576	1	GB-ROCHE-1315601
8127431	1	FR-GENENTECH-323879	9822508	1	CO-ROCHE-1332732
8140827	1	CO-GENENTECH-324247	9847530	1	US-ROCHE-1340339
8144848	1	US-GENENTECH-324373	9857446	2	CO-ROCHE-1341956
8191258	1	CO-ROCHE-1005501	9868939	2	VE-ROCHE-1343394
8247782	6	CA-ROCHE-1012545	9886922	1	US-ROCHE-1345993
8265646	1	VE-ROCHE-1015723	9892771	2	CH-ROCHE-1347826
8286233	1	BR-ROCHE-1020525	9927794	1	MX-ROCHE-1356940
8286334	1				

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DIPTI KALRA
08/11/2016

ALLEN D BRINKER
08/11/2016

TRACY M PHAM
08/11/2016

TRAVIS W READY
08/12/2016

EILEEN WU
08/12/2016

GRACE CHAI
08/12/2016

CINDY M KORTEPETER
08/12/2016