

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

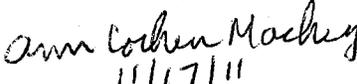
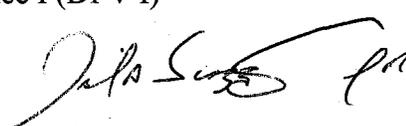
Pediatric Postmarketing Adverse Event Review

Date: October 31, 2011

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Drug Name(s): Omalizumab (Xolair)

Pediatric Exclusivity

Approval Date: June 20, 2003

Application Type/Number: BLA 103976

Applicant/sponsor: Genetech, Inc.

OSE RCM #: 2011-3179

CONTENTS

| | |
|--|----|
| EXECUTIVE SUMMARY | 2 |
| 1 INTRODUCTION | 3 |
| 1.1 Product Formulations and Indications | 3 |
| 1.2 Pediatric Filing history | 4 |
| 1.3 Pediatric labeling | 5 |
| 2 METHODS AND MATERIALS..... | 5 |
| 2.1 AERS Search Strategy | 5 |
| 3 RESULTS | 6 |
| 3.1 Counts of AERS Reports | 6 |
| 3.2 Figure 2: Selection of Serious Pediatric AERS cases..... | 9 |
| 3.3 Case Characteristics From Pediatric Case Series..... | 10 |
| 4 DISCUSSION OF SERIOUS PEDIATRIC CASE SERIES..... | 10 |
| 4.1 Summary of pediatric deaths (n=5)..... | 11 |
| 4.2 Summary of selected pediatric adverse events (n=76) | 12 |
| 4.2.1 Respiratory adverse event-Asthma exacerbation (n=10)..... | 12 |
| 4.2.2 Metabolic adverse event-weight gain (n=2) | 13 |
| 4.2.3 Gastrointestinal adverse events (n=2)..... | 13 |
| 4.2.4 Hypersensitivity reactions (n=33)..... | 14 |
| 4.2.5 Hematologic reaction (n=1)..... | 17 |
| 4.2.6 Renal/urinary reaction (n= 2)..... | 17 |
| 4.2.7 Infections (n= 8)..... | 18 |
| 4.2.8 Musculoskeletal (n=1) | 19 |
| 4.2.9 Neuro-psychiatric events (n=7)..... | 19 |
| 4.2.10 Syncope (n=3)..... | 21 |
| 4.2.11 Blurred vision (n= 2)..... | 21 |
| 4.2.12 In-utero exposure (n= 5) | 21 |
| 5 CONCLUSION..... | 22 |
| 6 RECOMMENDATION | 23 |
| 7 APPENDICES | 24 |
| 7.1 Appendix A: Drug Product Information | 24 |
| 7.2 Appendix B: Standard Searches..... | 33 |
| 7.3 Appendix C: AERS Database Description | 33 |
| 7.4 Appendix D: Control Numbers for Pediatric Case Series: AERS Case Numbers/ISR Numbers and Manufacturer control number..... | 34 |

EXECUTIVE SUMMARY

In accordance with Pediatric Research Equity Act (PREA), the Division of Pharmacovigilance (DPV) was asked to summarize post-marketing reports of adverse events associated with the use of omalizumab injection solution (Xolair) in pediatric patients (0-16 years of age). The main focus of this review is pediatric reports of death and other serious unlabeled adverse events with omalizumab.

Omalizumab is a recombinant DNA-derived humanized IgG1 κ monoclonal antibody that selectively binds to human immunoglobulin E (IgE). It is indicated for 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.¹

The Adverse Event Reporting System (AERS) database was searched for all reports of adverse events (serious and non-serious) from January 4, 2010 (pediatric labeling change date) up to the data-lock date of July 31, 2011. AERS contained 1,799 reports for omalizumab (Xolair). Pediatric reports represent approximately 5.7% of the total (101/1779).

After removing duplicate reports and reconciling null age death values, we identified 81 serious pediatric reports associated with omalizumab. Of these, 5 were death reports and the remaining 76 were serious non-fatal reports. Three of the 5 deaths occurred in premature neonates with transplacental exposure only. The remaining two deaths reported a septic shock (1) and a fatal adrenal insufficiency (1). There is insufficient clinical information to assess causality in the 5 reported deaths.

The most common non-fatal SAEs were hypersensitivity reactions (33) and asthma related conditions such as exacerbation (10), which are adequately described in current labeling. Specifically, the omalizumab label carries a boxed warning for anaphylaxis. The Warnings and Precautions and Adverse Reactions sections of the label also discusses anaphylaxis and acute asthma symptoms, as well most of the other SAEs reported in this review, including infections (8), serum sickness (2), arthralgia (2), headache (2), and thrombocytopenia (1).

Though not a main focus of the review, at the request of the medical officer in the Division of Pulmonary, Allergy and Rheumatology Products (DPARP), the null age reports (age not reported) were assessed for cardiovascular, anaphylaxis, malignancy, eosinophilic, and platelet count abnormalities. While most of these AEs are labeled, the cardiovascular AE is a potential safety signal currently under evaluation by both the sponsor and the FDA. No reports in children met these criteria.

In summary, DPV identified no new safety concerns in children 0-16 years old treated with omalizumab, and has no new labeling recommendations at this time.

DPV will continue to monitor adverse events associated with the use of omalizumab.

¹ Omalizumab injection, solution (Xolair) Prescribing Information. Genetech Inc. San Francisco, California. Revised July 2010.

1 INTRODUCTION

1.1 PRODUCT FORMULATIONS AND INDICATIONS

Omalizumab injection solution is marketed as Xolair and is a monoclonal antibody indicated for the relief of severe persistent asthma in adults and adolescents (12 years of age and above) who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. Omalizumab is administered 150 to 375 mg by subcutaneous injection every 2 or 4 weeks. Doses (in mg) and dosing frequency are determined by serum IgE levels (IU/ml), measured before the start of treatment and body weight (kg). Table 1 and 2 below provides the recommended dose assignment.¹

| Table 1: Administration Every 4 Weeks: Xolair Doses (milligrams) Administered by Subcutaneous Injection Every 4 Weeks for Adults and Adolescents 12 Years of Age and Older | | | | |
|---|------------------|--------------------|---------|----------|
| Pre-treatment Serum IgE (IU/mL) | Body Weight (kg) | | | |
| | 30-60 | > 60-70 | > 70-90 | > 90-150 |
| ≥ 30-100 | 150 | 150 | 150 | 300 |
| > 100-200 | 300 | 300 | 300 | |
| > 200-300 | 300 | | | |
| > 300-400 | | SEE TABLE 2 | | |
| > 400-500 | | | | |
| > 500-600 | | | | |

| Table 2: Administration Every 2 Weeks: Xolair Doses (milligrams) Administered by Subcutaneous Injection Every 2 Weeks for Adults and Adolescents 12 Years of Age and Older | | | | |
|---|------------------|--------------------|--------------------|----------|
| Pre-treatment Serum IgE (IU/mL) | Body Weight (kg) | | | |
| | 30-60 | > 60-70 | > 70-90 | > 90-150 |
| ≥ 30-100 | | SEE TABLE 1 | | |
| > 100-200 | | | | 225 |
| > 200-300 | | 225 | 225 | 300 |
| > 300-400 | 225 | 225 | 300 | |
| > 400-500 | 300 | 300 | 375 | |
| > 500-600 | 300 | 375 | DO NOT DOSE | |
| > 600-700 | 375 | | | |

1.2 PEDIATRIC FILING HISTORY^{2,3}

The original BLA marketing application for Xolair was submitted on June 2, 2000. The original application sought indications for the treatment of asthma and seasonal allergic rhinitis, and included safety and efficacy data for patients 5 through 76 years with a variety of disorders including seasonal allergic rhinitis and perennial allergic rhinitis (SAR/PAR; ages 6 through 75 years), allergic asthma (AA; ages 6 through 75 years), allergic/atopic dermatitis (AD; ages 6 through 16). On July 5, 2001 FDA provided a Complete Response Letter (CRL) letter citing limitations in the original application including limited size of the original safety database which limited the ability to meaningfully assess safety. The CRL requested greater safety information to assess benefit and risk for the proposed AA and SAR indications.

On December 18, 2002 the Sponsor re-submitted the application for the proposed indication for treatment of AA in patients 6 years and older; however, during the course of review of the application, the applicant removed the request indication in patients 6-11 years of age. The re-submission included data from an additional safety study (Q2143g or ALTO) in 1,899 patients 6-75 years of age. The safety database from the re-submission included safety information for all 3,507 study subjects for all studied indications (SAR/PAR, AA, and AD). Age distribution was 6 through 11 years (n=443), 12 through 17 years (n=318), 18 through 64 years (n=2,595), and at least 65 years (n=151).

At the time of approval of the application in June 2003, the Pediatric Rule was in effect but was being challenged in court. A pediatric plan was encouraged to be submitted, pending potential passage of specific legislation. Although not addressed in either the original approval letter or the subsequent letters, with approval of the application for patients 12 years of age and older, PREA was considered completed for pediatric studies in children 12 to <17 years of age.

Thereafter, the responsibility for review of biologic products was transferred from CBER to ODE VI within CDER. An End-of-Phase 2 (EOP2) meeting was held between members of CBER within ODE VI and Novartis (BB-IND 7202) to discuss the pediatric development plan on September 16, 2003. FDA requested additional studies to enlarge the safety and efficacy database. In response, Genentech/Novartis performed a second efficacy and safety study (AI05), and added a 3-year open-label treatment follow-up to study 010, study 010E1. These two studies, along with their follow-up studies, represent the two pivotal studies for this pediatric program.

Once PREA was enacted on December 3, 2003, Xolair became subject to the Act, and CDER sent a letter to Genentech on June 18, 2004, requesting submission of the pediatric assessments by December 3, 2004. Genentech responded in August 2004, with a request for a deferral of studies in children 6 to <12 years of age until approximately the 4th quarter of 2006, and a deferral of deadlines for children 0 to <6 years of age until after

² Rieves, Dwaine, MD, Clinical Review, BLA STN 103976/0; June 20, 2003.

³ Starke, Peter MD, Omalizumab Clinical Review, Pediatric supplement (ages 6 through 11 years); December 4, 2009.

the safety assessment in children 6 to <12 years of age. In the FDA response dated September 30, 2005, a deferral was granted for pediatric studies in children 6 to <12 years of age until December 31, 2006, and submission of a pediatric plan was requested in children from birth to <6 years of age. This submission completes the pediatric assessment for patients 6 through 11 years of age.

Additionally, in a submission dated October 20, 2008, Genentech requested a waiver for pediatric studies in children from birth to less than 3 years of age, and a deferral for children 3 to less than 6 years of age, and the current supplement makes reference to that request. The Division believes that studies in the age group of 0 through 5 years would be difficult or impossible to conduct because the disease is impossible to diagnose or very infrequent in this age group. Persistent asthma with a positive aeroallergen cannot be diagnosed prior to age 2 years, and most children 2 through 5 years of age with persistent asthma respond to inhaled corticosteroids. As a result, it is highly uncommon to find children 2 through 5 years of age with severe persistent asthma, allergic disease, and an elevated IgE level, who have not responded to other controller therapy. We therefore recommend a waiver for children in the entire age range of zero through 5 years of age.

In 2009, the sponsor submitted a supplement seeking to expand the indication from age 6 through 11 years. The supplement was discussed in a pediatric advisory committee forum, where the proposed indication was denied based on overall risk/benefit assessment.

1.3 PEDIATRIC LABELING

See Appendix for sections of the omalizumab label relating to pediatric patients.

2 METHODS AND MATERIALS

2.1 AERS SEARCH STRATEGY

The main focus of this review employed the Adverse Event Reporting System (AERS) database search strategy described in Table 3 (see Appendix B).

| Table 3: AERS Search Strategy* | |
|---------------------------------------|--|
| Date of search | August 23, 2011 |
| Time period | January 4, 2010 to July 31, 2011 |
| Drug Names | Omalizumab and all associated trade, active ingredient, and verbatim names |
| Additional criteria | Refer to Appendix B |

* See Appendix C for description of the AERS database.

3 RESULTS

3.1 COUNTS OF AERS REPORTS

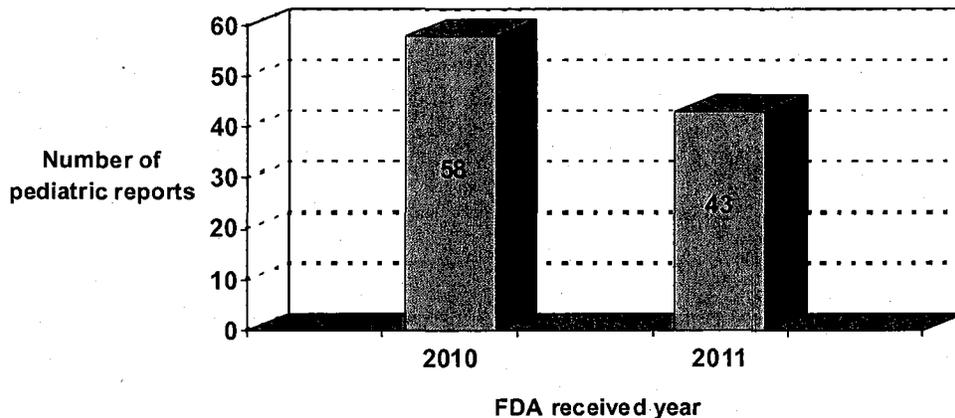
Table 4 depicts AERS data from the date of the pediatric labeling change date, January 4, 2010, through the data-lock date of July 31, 2011.

| Table 4: Counts¹ of AERS Reports (January 4, 2010 to July 31, 2011) | | | |
|---|----------------------------------|---------------------------|----------------|
| | All reports (US) ² | Serious ³ (US) | Death (US) |
| Adults (≥ 17 yrs.) | 1150 (443) | 1137 (434) | 79 (32) |
| Pediatrics (0-16 yrs.) | 101 (37) | 96 (33) | 3 (2) |
| Age unknown (Null values) | 528 (175) | 516 (165) | 54 (20) |
| Total | 1779 (655) | 1749 (632) | 136 (54) |

¹ May include duplicates
² US counts in parentheses
³ 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.
⁴ See Figure 2

Figure 1: Counts of AERS Pediatric Reports for omalizumab by year of FDA receipt from January 4, 2010 to July 31, 2011 (n=101)

These counts include data where age (0-16 years) is known and may contain duplicate reports.



In addition age unknown (i.e., null age) reporting an outcome of death and non-fatal serious outcome using the criteria suggested by the DPARP MO (i.e., cardiovascular, anaphylaxis, malignancy, eosinophilic, and platelet count) to determine if the report concerned a pediatric patient, were included.

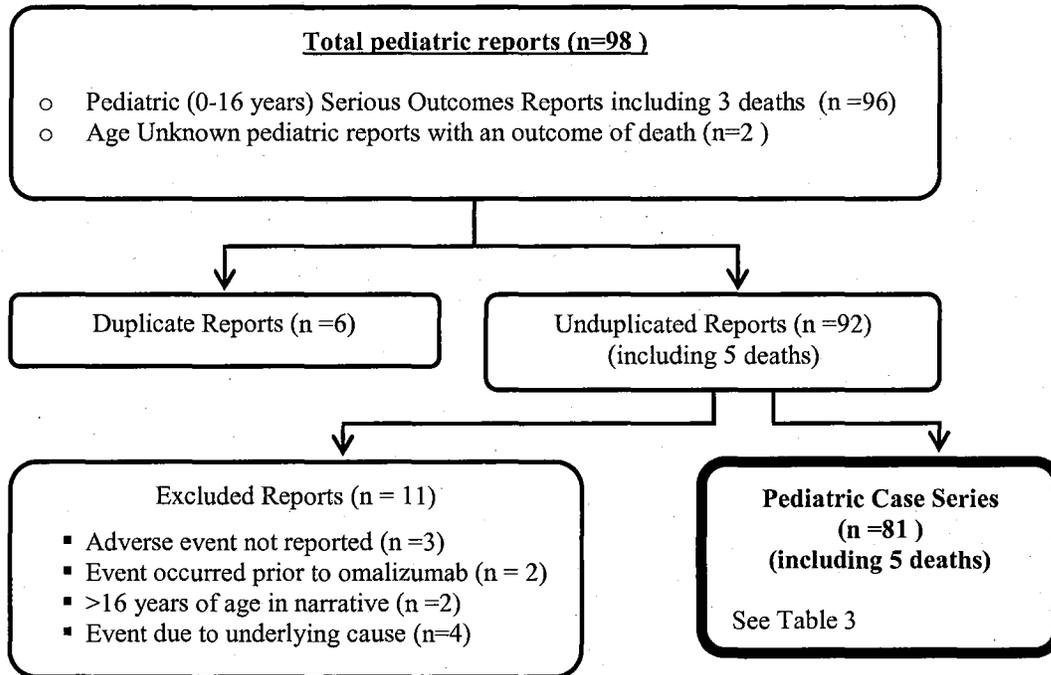
[Note: these particular events, or closely related terms, are described in current labeling.]
Figure 2 below summarizes the specific selection of cases to be reviewed in **Section 4**.

Per agreement with the Office of Pediatric Therapeutics (OPT) and the Pediatric and Maternal Health Staff (PMHS) AERS was also search for events (crude counts only) received from June 20, 2003 (initial marketing of omalizumab for first approved indication) through January 3, 2010 (pediatric labeling update). These results are a summarized in Tables 5 and 6 below.

| Table 5: Counts¹ of AERS Reports (June 20, 2003 to January 3, 2010) | | | |
|--|----------------------------------|---------------------------|------------------|
| | All reports (US) ² | Serious ³ (US) | Death (US) |
| Adults (≥ 17 yrs.) | 2254 (1674) | 1667 (1093) | 89 (65) |
| Pediatrics (0-16 yrs.) | 261 (190) | 183 (112) | 6 (5) |
| Age unknown (Null values) | 1106 (744) | 772 (415) | 55 (33) |
| Total | 3621 (2608) | 2622 (1620) | 150 (103) |
| ¹ May include duplicates ² US counts in parentheses ³ 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. ⁴ See Figure 2 | | | |

| Table 6: Crude Counts of AERS Reports for Omalizumab for Outcome of Death and Selected Adverse Events* (June 20, 2003 to January 3, 2010) | | | | |
|--|--------------------|-----------------|--------------------|------------------|
| | Death (US) | Infections (US) | Neoplasms (US) | Anaphylaxis (US) |
| Pediatrics (0-11 yrs.) | 1 [@] (1) | 9 (6) | 0 (0) | 8 (6) |
| Pediatrics (12-16 yrs.) | 5 (4) | 17 (11) | 0 (0) | 18 (16) |
| Adults (≥ 17 yrs.) | 89 (65) | 241 (156) | 1 [#] (1) | 172 (151) |
| <p>* As specified in the Xolair issues meeting on November 1, 2011, the anaphylaxis and infection cases will not be adjudicated.</p> <p>[@] An 11-year-old male patient had been taking omalizumab 375mg subcutaneously every 2 weeks since October 2006, presented with a fatal asthma attack in the evening after returning from an amusement park and experiencing shortness of breath. Last dose of omalizumab was administered that morning.</p> <p>[#] Report of presumed Churg-Strauss vasculitis reported in a 50-year-old male patient with a “questionable nodule” on x-ray. This case was discussed in a prior review of Churg-Strauss by Renan A. Bonnell, PharmD, MPH</p> | | | | |

3.2 FIGURE 2: SELECTION OF SERIOUS PEDIATRIC AERS CASES



3.3 CASE CHARACTERISTICS FROM PEDIATRIC CASE SERIES

Table 7 summarizes the 81 AERS cases from the Pediatric Case Series with omalizumab.

Appendix D contains AERS Case numbers / ISR numbers and Manufacturer Control Numbers for the Pediatric Case Series.

| Table 7: Case Characteristics of Serious Pediatric Case Series. [January 4, 2010 to July 31, 2011] (N=81) | | | | |
|--|--|---|---|--|
| Age (n=81) | 0- <1 month (7) 6-11 years (34) | | 1 month- <2 years (1) 12-16 years (39) | |
| Gender | Male (44) | Female (34) | | Unknown (3) |
| Country of occurrence | United States (27) | | Foreign (54) | |
| Event date | 2005 (3) 2010 (29) | 2007 (4) 2011 (20) | 2008 (9) Not stated (5) | 2009 (11) |
| Daily dose | 150mg Q2W (1) 150mg Q4W (3) 150mg UNK (3) 375mg Q2W (14) 375mg UNK (3) 450mg alt with 600mg Q2W (1) | 225mg Q2W (4) 225mg Q4W (1) 225mg UNK (1) 400mg Q2W (1) 600mg UNK (1) | 300mg Q2W (7) 300mg Q4W (8) 300mg UNK (10) 450mg Q4W (1) Unknown (22) | |
| Duration of therapy (n=17) | Mean: 275 days | Median: 90 days | Range: 1 day to 4.5 years | |
| Indications | Asthma (64) | 'Hypersensitivity' (1) | Not stated (16) | |
| Outcome ¹ | Death (5) Life-threatening (6) | Hospitalized (22) Congenital anomaly (3) | Disability (4) Other serious (41) | |
| Time to Onset (n=42) | "Immediate" (4) 1-2 days (2) 30-60 days (5) | 10-40 minutes (4) 3-4 days (3) 90 days (1) | 1-4 hours (8) 5-10 days (4) 120 days (1) | 'That Evening' (5) 14-21 days (3) 365-480 days (2) |
| Rechallenge | Positive rechallenge (4) | | Negative rechallenge (1) | |
| Dechallenge (n=7) | Positive dechallenge (1) | | Negative dechallenge (1) | |

¹Serious 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. A report may have one or more (>1) outcome.

4 DISCUSSION OF SERIOUS PEDIATRIC CASE SERIES

The focus of this review is pediatric deaths, serious adverse events (such as anaphylaxis, malignancy, and platelet count abnormality), and reports of serious unlabeled adverse events with omalizumab.

4.1 SUMMARY OF PEDIATRIC DEATHS (N=5)

From January 4, 2010 to July 31, 2011, the AERS database contained 2 reports of pediatric death in patients receiving at least 1 postnatal dose, and 3 reports of death in infants/fetuses with transplacental exposure only. Gender composition of decedents was 1 male, 2 females, and 2 unknown gender patients. Age range was 1 day to 16 years. Three cases were reported from the US and two cases were reported from foreign sources.

Both postnatal exposure deaths are confounded by other pre-existing or co-existing morbidities and causal relation with omalizumab could not be determined. In addition, there is insufficient clinical information to assess causality in the three transplacental deaths, which occurred at gestational week 15 (1), 37 (1), and undetermined gestational age (1). Summary narratives of the deaths are found below.

Deaths After At Least 1 Postnatal Dose (N=2)

One death was attributed to fatal adrenal insufficiency possibly due to steroid use and the other death was attributed septic shock one week after receiving intravenous piperacillin for presumed upper respiratory tract infection and sinusitis. Case narrative follows below.

- ***ISR 6614300, Foreign, 2008:*** A 10-year-old male, receiving monthly omalizumab for asthma, experienced gastroenteritis followed by necrotising colitis after treatment with oral steroids was interrupted. Treatment with omalizumab began three months prior to the onset of the event. The patient had a medical history of Wolff-Parkinson-White Syndrome and adrenal insufficiency (reported as “morbus cushing” and presumed to be secondary to chronic steroid use). The autopsy report listed the cause of as adrenal cortical insufficiency and necrotising enterocolitis. The physician’s reportedly stated that the patient “needed increased steroid dosages during the infection, instead of interruption of steroid treatment.”
- ***ISR 7458972, US, 2010:*** A 16-year-old male, with unknown past medical history and receiving omalizumab for an unknown indication, presented with high temperature and upper respiratory tract infection and presumed sinusitis, for which he was already receiving intravenous (IV) antibiotics through a central line. Within 24 hour of presentation to the hospital, he developed possible septic shock and died. Concomitant medications included piperacillin and tazobactam for chronic sinus infection, budesonide, formoterol fumarate, pirbuterol acetate and an unspecified nasal spray. The last dose of omalizumab was administered one week prior to the event.

Deaths through Transplacental Exposure Only (N=3)

Three of the fatal cases were in premature neonates who received omalizumab via transplacental exposure only during the entire gestational period (1) or an unspecified

time period (2). Two cases were confounded due to concomitant formoterol fumarate use (labeled Pregnancy Category C)⁴ and fenoterol use (1), and a history of miscarriage in the mother (1). There is insufficient clinical information to assess causality for any of these cases.

- **ISR 6578115, US, 2009:** A female neonate was born at 37 weeks gestation with trisomy 18 or 19 after transplacental exposure of omalizumab for an unspecified period. The infant died on an unreported date. The infant's mother received treatment with omalizumab since 2004. The mother's medical history included a miscarriage at 12 weeks in 2007. No concurrent illnesses, allergies, or concomitant medications were reported for the infant's mother.
- **ISR 6605037, Foreign, 2009:** A female neonate died in utero at 15 weeks gestation after transplacental exposure of omalizumab during the first trimester of pregnancy. The autopsy report did not reveal any internal organ damage. The case is confounded by the mother's concomitant use of medications such as beclomethasone dipropionate (Pregnancy Category C)³, formoterol fumarate (Pregnancy Category C), fenoterol and ipratropium bromide.
- **ISR 7443099, US, 2011:** A stillborn fetus was delivered after receiving transplacental exposure of omalizumab for an unspecified period. This report was submitted by a consumer and provided very little information such as past medical history, concurrent illnesses, allergies, or concomitant medications.

4.2 SUMMARY OF SELECTED PEDIATRIC ADVERSE EVENTS (N=76)

The majority of serious adverse event (SAE) preferred terms (PTs) reported represent labeled events (e.g., asthma related terms) or terms closely related to labeled events (e.g., hypersensitivity reaction related terms), and terms subject to confounding by indication (asthma). The most commonly reported SAEs are hypersensitivity reactions, including anaphylaxis (33), asthma (10), and infections including upper respiratory infections and sinusitis (8) which may be more aggressive in patients with severe asthma. Additionally, there is no consistent pattern for unlabeled PTs.

Brief summaries of the adverse event reports are found in sections 4.1.2 through 4.1.12 below.

Note: the total number of cases discussed in sections 4.2.1-4.2.12 is 76, and no case is reported under more than 1 adverse event category.

4.2.1 RESPIRATORY ADVERSE EVENT-ASTHMA EXACERBATION (N=10)

We identified 10 cases of respiratory events, all from foreign sources. There were 7 males and 3 females, ages 8 to 16 years (median age: 11 years). Range of time to onset

⁴ FDA Pregnancy Category C-Animal reproduction studies have shown an adverse effect on the fetus, there are no adequate and well-controlled studies in humans, and the benefits from the use of the drug in pregnant woman may be acceptable despite its potential risks. There are no animal reproduction studies and no adequate and well-controlled studies in humans.

of event from most recent injection when reported (6) was from immediately after injection to 2 to 3 months later. Dose when reported (7) ranged from 225 mg to 375 mg every 2 weeks (6) to 300 mg every 4 weeks (1). Four cases reported an outcome of hospitalization due to asthma exacerbation and the remaining (6) cases reported other serious outcomes.

One case reported discontinuation of omalizumab after the first injection due to worsening of asthma and "intolerance" (to new formulation of Xolair) medication. Four cases reported continuation with omalizumab. One case reported a negative rechallenge in which the patient did not experience any adverse events after second treatment with omalizumab. Six patients reported that asthma exacerbation improved or resolved after they received steroid treatment (which is the standard of care). In the negative rechallenge case, an 11-year-old male initiated treatment with omalizumab for severe asthma and experienced an asthma attack 30 minutes later. He received treatment with salbutamol and prednisone and recovered. He received a second treatment with omalizumab at an unknown date and did not experience any adverse events. Two cases report use of concomitant asthma medications including fluticasone, salmeterol, albuterol, montelukast, prednisone, and albuterol.

Reviewer Comment: The Warnings and Precautions section of the label states "Xolair has not been shown to alleviate asthma exacerbations acutely." Therefore the cases described may represent lack of efficacy or concomitant serious and severe comorbidities.

DPV concludes no labeling modification regarding asthma exacerbation is warranted at this time.

4.2.2 METABOLIC ADVERSE EVENT-WEIGHT GAIN (N=2)

We identified two cases of weight gain in pediatric patients. Both cases are physician reports from foreign sources. In one case, a 15-year-old male taking omalizumab 300mg every 2 weeks gained 66 pounds in two years. He had a medical history of being overweight. In the other case, a 7-year-old male, experienced a weight gain of 15 to 22 pounds, which lasted one week and then disappeared after the third injection. In both cases, omalizumab was discontinued after the reported event.

Reviewer Comment: Weight gain is an unlabeled event but there are too few reports to indicate a positive temporal relationship and insufficient clinical information to assess causality.

DPV concludes no labeling modification regarding metabolic events is warranted at this time.

4.2.3 GASTROINTESTINAL ADVERSE EVENTS (N=2)

We identified two cases of gastrointestinal adverse events in pediatric patients, including 1 report each of jaundice and abdominal pain. Both of the cases were reported from foreign report sources. In one case, an 8-year-old patient received omalizumab 300mg subcutaneously (frequency not stated), was admitted to the hospital for abdominal pain and received a polyethylene glycol preparation (Movicol) for constipation secondary to codeine treatment for pain. The patient was also treated for a worm infection. The action

taken with omalizumab was not reported. In the other case, a 14-year-old experienced icterus and mild hepatomegaly after treatment with omalizumab, 150mg subcutaneously every 4 weeks for 3 years. The physician reported the event as possibly due to adenovirus, or post-infectious origin, or Meulengracht's disease (also called Gilbert's disease, a common benign disorder of hereditary unconjugated hyperbilirubinemia reported in the patient's family). The outcome was reported as recovered with continued treatment with omalizumab.

Reviewer Comment: Jaundice and abdominal pain are not labeled events. It is important to note that both cases are confounded by concomitant medications and contributing comorbidities.

DPV concludes no labeling modification regarding jaundice or abdominal pain is warranted at this time.

4.2.4 HYPERSENSITIVITY REACTIONS (N=33)

We identified 33 cases of hypersensitivity reactions in pediatric patients associated with the use of omalizumab. Eight cases reported an outcome of hospitalization and 25 cases reported the serious outcome, Other. Among the 33 cases, 18 cases were reported from the US and 15 were from foreign report sources. There were 16 males and 17 females ranging in age from 8 to 16 years (median age: 13 years). Time to onset of adverse events when reported (25), ranged from 10 minutes to 2 months. Fourteen cases reported a dose, which ranged from 300 mg every 2 weeks to 600mg every 2 weeks. Three cases reported a positive rechallenge and one case a positive dechallenge.

Anaphylaxis (7)

Three of the seven cases reported resolution of symptoms upon administration of epinephrine or systemic corticosteroids, and five patients reportedly discontinued omalizumab due to the adverse event. Case vignettes are located immediately below.

- A 16-year-old female, presented with an anaphylactic reaction after receiving her first dose of omalizumab. She was hospitalized and treated with epinephrine and event resolved. Treatment with omalizumab was discontinued. Her medical history included gastroesophageal disorder and concomitant medications included montelukast, fluticasone, salmeterol, ranitidine, lansoprazole, cetirizine, and albuterol.
- A 15-year-old female patient with reported allergy to shellfish presented with an anaphylactic reaction after eating at a restaurant (the physician suspected cross contamination at the restaurant; however, this reviewer notes that a reaction to omalizumab can not be excluded). The omalizumab dose was reduced and the event resolved. Four months later, the patient presented with another anaphylactic reaction and treatment with omalizumab was discontinued (positive rechallenge). The patient was receiving concomitant allergy medications for environmental allergies and was allergic to penicillin.
- A 15-year-old female experienced two anaphylactic reactions on the same day of her dose and another anaphylactic reaction the following day. The patient was

receiving treatment with omalizumab for 1.5 years. The outcome of the event was not reported. Omalizumab treatment was discontinued.

- A 10-year-old male reported an anaphylaxis-like reaction (rash and difficulty breathing) shortly after the first administration with omalizumab. Concomitant medications included fluticasone propionate, prednisone, cetirizine hydrochloride, and montelukast sodium (hypersensitivity reactions including anaphylaxis are listed in the Adverse Reactions section of the montelukast label). No medical history, concurrent illnesses, allergies, or outcome was reported.
- A 14-year-old male received the first dose of omalizumab injection, kept for observation for 3 to 4 hours and in the evening, he experienced labial oedema and urticaria. The patient went to the emergency room and was treated with corticosteroids. A final diagnosis of anaphylactic reaction was made by the physician. The patient recovered but discontinued treatment with omalizumab.
- The remaining two cases involved a 16-year-old female who experienced anaphylaxis after her second dose and a 12-year-old male who experienced anaphylaxis after the first dose of omalizumab. Both patients “responded well” to treatment with epinephrine. Past medical history, concurrent illnesses, allergies or dose of omalizumab were not reported.

Type III (2)

Two patients developed serious type III hypersensitivity reactions reported as serum sickness (1), and drug-induced lupus erythematosus (1).

- An 8-year-old male reportedly developed serum sickness during omalizumab treatment and was hospitalized. He had been treated with omalizumab 300 mg every 2 weeks for asthma for 6 months. Within one week after the last injection he experienced lower limb edema, inguinal adenopathy, fever, and fatigue. He recovered and was diagnosed with serum sickness. Three or four weeks later, his asthma worsened and a half dose of omalizumab was administered. He was hospitalized again with similar symptoms in addition to arthritis (type not specified). He recovered, though type of treatment was not specified. His medical history includes severe allergic asthma, several food-related allergies, and severe eczema.
- A 13-year-old female who presented with drug-induced lupus erythematosus confirmed by a positive SSA antibody test. Concomitant medications included methimazole, which lists a lupus-like syndrome in the adverse reactions section of the label. The dose, date, duration, route, and action taken with omalizumab were not reported.

Shortness of breath (5)

Three cases reported discontinuation of omalizumab in response to the event. Two of these same three cases reported a history of anaphylaxis related to allergy shots. One case was a 13-year-old female who experienced shortness of breath, 30 minutes after receiving her fifth course of omalizumab. The patient discontinued the medication and the adverse event resolved (positive dechallenge). This patient had a history of

anaphylaxis and urticaria with allergy shots. The other four cases provided little information as to the event outcome or action taken with omalizumab

Cardiovascular (where case characteristics suggest possible allergic/hypersensitivity)

Chest pain (4)

- An 11-year-old female reported chest pain after the second through fifth injections of omalizumab (positive re-challenges). The events resolved after 1 to 2 days on each occasion, though on one occasion, the patient was hospitalized. The patient discontinued treatment with omalizumab.
- A 12-year-old male experienced chest tightness within 5 minutes of his first and only dose of omalizumab. The event resolved and the reporter stated that the mother did not want to continue treatment with omalizumab.
- A 14-year-old female experienced chest pain on an unspecified date after receiving her second dose of omalizumab. At the time of the event report she was recovering, but action taken with omalizumab was not reported.
- A 6-year-old male had 'pain in heart' for half an hour after the first injection of omalizumab. The outcome of the event was not reported and treatment with omalizumab was reported to be ongoing. No further information was available.

Hypotension (1)

A 14-year-old female, who had been treated with omalizumab for five months, experienced low blood pressure 20 minutes after receiving a dose of omalizumab. The event resolved and treatment with omalizumab was not reported. The case is confounded by concomitant medication labeled for hypotension (sertraline).

Tachycardia (1)

An 8-year-old female experienced tachycardia after the fourth injection of omalizumab (exact date and time not reported). The action taken with omalizumab was unknown. The patient was hospitalized and then discharged four days later. Concomitant medications were desloratadine, fluticasone propionate, salmeterol xinafoate, terbutaline, and montelukast.

Other serious allergic reactions (13)

Other serious allergic reactions associated with the use of omalizumab were reported as: swelling of lip (2) swelling of tongue (1), swelling of face (1), rash (6), blue lips (1), and eczema (2). Eight patients reported improvement or resolution of symptoms after treatment with a corticosteroid or antihistamine. Three patients were hospitalized, however action taken with omalizumab in these patients was not reported. Synopses of the hospitalized patients are found immediately below.

- A 7-year-old male patient experienced wheezing and facial swelling 3 hours after his first dose of omalizumab. He was treated with corticosteroids and the event resolved. His medical history was not reported.
- A 13-year-old male who was hospitalized for urticaria on the neck, abdomen, and lower extremities six days after receiving omalizumab. The symptoms resolved after treatment with epinastine hydrochloride tablets.
- A 15-year-old female, was hospitalized after experiencing diffuse significant eczema 24 hours after her omalizumab infusion. She was treated with corticosteroids and antibiotics and was still recovering per the most recent report.

Additionally, a positive rechallenge case involved a 7-year-old male with reported a bilateral rash on his cheeks three days after his initial omalizumab injection. The rash resolved four days after onset. He received a second dose of omalizumab two weeks later and 15 minutes after the injection, he experienced tightness in his chest, and he was evaluated for pulse oximetry, blood pressure, heart rate, and signs of anaphylaxis. All findings were “negative”. Per the patient's mother, the physician believed that chest tightness was due to anxiety.

Reviewer Comment: Anaphylaxis including hypersensitivity events (e.g., bronchospasm, syncope, and urticaria) are listed in the box warning, Adverse Reactions, and Warning and Precautions section of the omalizumab label. The omalizumab label lists rash, urticaria, angioedema, and reports of fever and lymphadenopathy similar to serum sickness in the postmarketing section of the label. Palpitations are a labeled adverse event in the postmarketing section of the montelukast label. Events such as “chest pain” are nonspecific and may represent a hypersensitivity reaction, underlying cardiovascular problems, or some other conditions, and there is insufficient clinical information in the AERS reports to further assess nature of the events discussed in this review or their causality.

DPV concludes no labeling revision regarding hypersensitivity reactions are warranted at this time.

4.2.5 HEMATOLOGIC REACTION (N=1)

A 14-year-old female with uncontrolled asthma was hospitalized due to the appearance of skin bruising which appeared four days after receiving her first dose of omalizumab (450mg subcutaneously) for treatment of her asthma. A diagnosis of immunothrombocytopenia was made and she was treated with intravenous corticosteroids and discharged. Therapy with omalizumab was withdrawn due to the event. This patient had a medical history of perennial allergy to dust mites and mold.

Reviewer Comment: The omalizumab label lists thrombocytopenia in the post marketing section of the label. DPV concludes no labeling revision regarding thrombocytopenia is warranted at this time.

4.2.6 RENAL/URINARY REACTION (N= 2)

An 11-year-old male with severe persistent asthma was treated with omalizumab 150 mg alternating with 300 mg every 2 weeks subcutaneously since July 2007. He developed

nephrotic syndrome on (b) (6) and was hospitalized for 8 days. The symptoms improved with diuretics and prednisolone but the patient experienced two relapses of his nephrotic syndrome (November 2010 and January 2011). He was treated with prednisolone and cyclosporine and the outcome of the event was not provided. He had a history of allergic rhinitis, morbus cushing, Meulengracht disease (i.e., Gilbert disease) and various environmental and food allergies.

A 14-year-old male received omalizumab for 3 years, presented with nephrotic syndrome, and was hospitalized. The action taken with omalizumab was not reported. The report had insufficient clinical information to assess causality.

Reviewer Comment: Nephrotic syndrome is not listed in the omalizumab label. One case was confounded by the patient's underlying complication and the other case provided few clinical details to draw any conclusions. In both cases, the patients were receiving omalizumab for three years before experiencing the adverse event. DPV concludes no labeling revision regarding renal or urinary events is warranted at this time.

4.2.7 INFECTIONS (N= 8)

We identified eight cases of infections in pediatric patients: respiratory tract (4), sepsis (1), meningitis (1) swine flu (1), and osteomyelitis (1). All four cases of respiratory infection reported an outcome of hospitalization. Two cases indicated treatment with antibiotics. Three patients reported having cold symptoms or viral infection. There were no reported cases of discontinuation of omalizumab.

- An 11-year-old female was admitted to the hospital due to cough and chest infection. The patient had been treated with omalizumab for 1.5 years and the action taken was not reported. The medical history and concurrent conditions of the patient were not reported.
- A 10-year-old male was diagnosed with upper respiratory inflammation eight days after the 4th dose of omalizumab. The patient had a medical history of atopic dermatitis, allergic conjunctivitis, allergic rhinitis and chronic sinuses. The patient continued treatment with omalizumab.
- A 9-year-old female experienced upper respiratory tract infection and presented with pulmonary super infection. The patient reported allergy to cats and dust mites. The patient had been taking omalizumab for 1&1/2 years. There was no change in treatment with omalizuamb.
- a 14-year-old-male experienced pulmonary infection and was treated with antibiotics, four weeks after his last dose of omalizumab. The outcome or action taken with omalizumab was not reported.
- A 6-year-old male presented with sepsis and mild encephalitis five days after starting omalizumab therapy. The patient was hospitalized and recovered after antibiotic therapy. Omalizumab was discontinued due to the events. He was concomitantly treated for gastroesophageal reflux disease with multiple medications.

- A 12-year-old female was diagnosed with suspected bacterial meningitis. This case provided little information as to dose of omalizumab, outcome, or concomitant medications.
- An 11-year-old male developed osteomyelitis. The patient had been receiving omalizumab therapy for six months at a dose of 375mg. The patient was immunocompromised due to long term steroid use for severe asthma. The patient continued omalizumab therapy; he was treated with antibiotics and was recovering at the time of the report.
- A 14-year-old male was diagnosed with the swine flu. The patient was treated with an antiviral medication and the outcome of the event or action taken with omalizumab was not reported. Concomitant medication included doxepin and allergies reported included seasonal and food allergy

Reviewer Comment: Upper respiratory tract infection and viral infections are described in the Adverse Reactions section of the omalizumab label. Patients with underlying asthma may be more prone to respiratory infections. The patient who developed osteomyelitis was immunocompromised which likely contributed to the event. DPV concludes no labeling revision regarding infections is warranted at this time.

4.2.8 MUSCULOSKELETAL (N=1)

An 11-year-old female received her first dose of omalizumab (300 mg in both arms) for severe allergy and was hospitalized 5 days later for arthralgia and myalgia. The outcome of the event or action taken with omalizumab was not reported and there is insufficient clinical information in the report to further characterize causality.

Arthralgia is listed in the warnings and precautions section of the label. DPV concludes no labeling revision regarding this issue is warranted at this time; however DPV will continue routine pharmacovigilance for this issue.

4.2.9 NEURO-PSYCHIATRIC EVENTS (N=7)

We identified seven cases of neuro-psychiatric events in pediatric patients, including 1 domestic report and 6 foreign reports. The cases include: headache (2), numbness (1), seizure (1), amnesia (1), and depression/emotional disorder (2). Outcomes included hospitalization (2), disability (2), and Other serious outcomes (3). There were two males and five females ranging in age from 6 to 16 years, with a median age of 14 years. Four cases reported a time to onset of events from the most recent dose, which ranged from immediately to sixteen months. Three cases reported a dose, which ranged from 375mg to 400 mg every two weeks to 300mg every 4 weeks subcutaneously. Case vignettes follow immediately below and are separated by headache (2) and other events (5).

Headache (2)

- An 11-year-old female experienced moderate headache after her first injection of omalizumab. After her second injection, she experienced a substantial headache lasting a week. Magnetic resonance imaging on the brain showed sinusitis. The

headaches did not improve after omalizumab was discontinued (negative dechallenge case).

- A 14-year-old female, started treatment with omalizumab and presented with severe headaches, which were disabling. The dose was reduced from 300 mg to 250 mg every 4 weeks subcutaneously then increased back to 300 mg every 4 weeks for better asthma control. Concomitant medications included sumatriptan succinate. The event remained ongoing and the event or action taken with omalizumab was not reported.

Neuro-Psychiatric Events (5)

- A 12-year-old female experienced a possible seizure (reported by physician as shivering-like movements that lasted 5 minutes) ten days after receiving omalizumab. The patient had no prior history of seizures. Concomitant medications included fluticasone propionate, salmeterol, salbutamol, omeprazole, montelukast, aminophylline, domperidone, and loratadine (note that seizures are listed in the Adverse Reactions section of the aminophylline label). The patient recovered and action taken with omalizumab was not reported.
- A 14 -year-old male on an unspecified date after his omalizumab injection experienced emotional episodes and in the evening of the injection developed mood swings. It was reported that the symptoms were “still ongoing” as per the most recent report and action taken with omalizumab was not reported. Concomitant medication included triamcinolone. Neuro-psychiatric events such as depression and mood swings are listed in the Precautions section of the triamcinolone label.
- A 16-year-old female experienced numbness and tingling in right hand for ten minutes after receiving first two injections of omalizumab. The patient had been on therapy for sixteen months at the time of the first event. The patient was treated with Tylenol and the outcome of the event was reported as being recovered. The patient had a medical history of allergy to latex, penicillin, peanuts fish, eggs and balloon. Omalizumab therapy was ongoing.
- A 6-year-old male suffered from memory loss nine months after starting omalizumab. The school staff mentioned that this child had poor memory/retention of information. The condition was still present as per the most recent report and action taken with omalizumab was not stated.
- A 15-year-old female was treated with omalizumab for two years for asthma; following the last injection, she experienced depression and sadness. The events resolved within 48 hours and treatment with omalizumab was stopped.

Headache is a labeled adverse event in the Adverse Reactions section of the omalizumab label. The other neuro-psychiatric events either have insufficient clinical information to assess causality, or are confounded by concomitant medications some of which are labeled for the reported events. DPV concludes no labeling revision regarding these issues is warranted at this time; however, DPV will continue routine pharmacovigilance for these issues.

4.2.10 SYNCOPE (N=3)

- A 12-year-old female with a 14-month history of omalizumab use, presented with syncope three weeks after the last dose of omalizumab. The event resolved and there was no action taken with omalizumab.
- A 10-year-old male experienced fainting and dizziness after his second treatment with omalizumab. These events resolved and action taken with omalizumab was not reported. No further details were provided.
- An 8-year-old male complained of headache and dizziness and the fifth dose of omalizumab was not administered. It was reported that the dizziness was so severe that the patient would fall down steps occasionally. The CT scan and MRI brain scan were normal. Omalizumab was discontinued and when restarted the symptoms reappeared (positive rechallenge case).

Syncope is listed as a component of anaphylaxis in the Box warning and Warnings and Precautions section of the current omalizumab label. Additionally, any injection or infusion of any drug may be followed by vaso-vagal reactions such as syncope. There is insufficient clinical information to further characterize these cases. DPV concludes no labeling revision regarding syncope is warranted at this time; however, DPV will continue routine pharmacovigilance for this issue.

4.2.11 BLURRED VISION (N= 2)

- A 10-year-old female developed headache and blurred vision two hours after the first injection of omalizumab. The outcome and action taken with omalizumab was not provided.
- An 11-year-old male experienced blurred vision four days later after his first omalizumab dose. He patient recovered and action taken with omalizumab was not reported.

Blurred vision is not a labeled event however the cases provide insufficient clinical information to assess causality. Additionally blurred vision is a nonspecific adverse event potentially caused by a number of factors. DPV concludes no labeling revision regarding these issues is warranted at this time; however, DPV will continue routine pharmacovigilance for this issue.

4.2.12 IN-UTERO EXPOSURE (N= 5)

We identified five non-fatal cases of in-utero exposure to omalizumab (see section 4.1 above for the description of 3 fatal cases reported with in-utero exposure). Three of the non-fatal reports were from US sources and two were from foreign sources. Duration of exposure was specified as throughout the pregnancy (2), during the pregnancy (2), and omalizumab was stopped when the mother was informed of her pregnancy (1).

Four cases reported a primary or secondary outcome of congenital anomaly. Congenital anomalies included transposition of great vessels (TGV) (1), inguinal hernia (1), cardiac septal defect, jaundice, respiratory distress syndrome (1), and melanocytic naevus (1).

The remaining case reported prematurity (1). Three patients required surgery (repair of hernia, TGV, and excision of umbilical mole) and one patient required phototherapy.

One case (ISR 6929110) was confounded by the mother's medical history which included previous premature pregnancy at the age of 18 years old and maternal use of concomitant medications which carry the FDA pregnancy category C rating³ (fluticasone propionate and salmeterol xinafoate, albuterol and ipratropium inhalation, albuterol, hydrocodone and acetaminophen, epinephrine). In another case (ISR 6966325), the mother's pregnancy history included preeclampsia, positive group B streptococcus test, and use of concomitant medications which carry the FDA pregnancy category C rating (fluticasone propionate, salmeterol, desloratadine, tiotropium). No other possible etiological causes were reported for the other cases.

Reviewer Comment: Omalizumab classified as Pregnancy Category B: There are no adequate and well-controlled studies of Xolair in pregnant women. Reproduction studies have been performed in Cynomolgus monkeys at subcutaneous doses up to 10 times the maximum recommended human dose on a mg/kg basis and have revealed no evidence of impaired fertility or harm to the fetus due to Xolair. Because animal reproduction studies are not always predictive of human response, administer Xolair during pregnancy only if clearly needed.¹ In general, it is difficult to associate congenital anomalies with drug therapy. Additionally there is a pregnancy exposure registry. DPV concludes there is no identifiable pattern of congenital malformation and recommends no labeling revision for these issues at this time. DPV will continue routine pharmacovigilance for congenital anomalies.

5 CONCLUSION

This review of 81 serious Pediatric AERS reports with omalizumab exposure, including 5 deaths (2 postnatal exposures and 3 in utero exposures), identified predominantly known and labeled events.

The postnatal are confounded by pre-existing or co-existing morbidities, and the 3 in utero exposure deaths lack sufficient clinical information to attribute and causal relation to omalizumab.

The majority of non-fatal SAEs, such as hypersensitivity reactions (33) and asthma related conditions such as exacerbation (10) are adequately described in current labeling. Specifically, anaphylaxis is discussed in the box warning. The Warnings and Precautions section of the label discusses anaphylaxis and related terms, acute asthma symptoms, and serum sickness and arthralgia, all of which are reported in cases presented in this review. Additionally, respiratory tract infection, viral infection, and headache are listed in the Adverse Reactions section of the omalizumab label, and thrombocytopenia is listed in the Postmarketing Experience section of the label.

The reports of serious unlabeled events in children discussed in this review include blurred vision, seizures and other neuro-psychiatric events, weight gain, jaundice, abdominal pain, and nephrotic syndrome all have too few case reports and insufficient clinical data to assess causality. These events will be followed with routine pharmacovigilance activities.

DPV concludes that current labeling adequately reflects the safety findings described in this of this review.

Reviewer Comment: The main limitation of this review is the inherent limitations of AERS; that is, incomplete clinical data. Additionally, in many instances where substantial clinical information is available, confounding medical issues including exposure to a variety of concomitant medications impairs assessment of causality. Lastly, for most of the unlabeled events discussed in this review, the events are common in the general population which further impairs assessment.

6 RECOMMENDATION

DPV has no labeling recommendations regarding the pediatric population at this time. Additionally, DPV recommends no additional safety reviews at this time.

DPV will continue routine monitoring of adverse events reported with omalizumab use.

7 APPENDICES

7.1 APPENDIX A: DRUG PRODUCT INFORMATION

5 WARNINGS AND PRECAUTIONS

5.1 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. Some of these events have been life-threatening. In premarketing clinical trials the frequency of anaphylaxis attributed to Xolair use was estimated to be 0.1%. In postmarketing spontaneous reports, the frequency of anaphylaxis attributed to Xolair use was estimated to be at least 0.2% of patients based on an estimated exposure of about 57,300 patients from June 2003 through December 2006. Anaphylaxis has occurred as early as after the first dose of Xolair, but also has occurred beyond one year after beginning regularly scheduled treatment.

Administer Xolair only in a healthcare setting by healthcare providers prepared to manage anaphylaxis that can be life-threatening. Observe patients closely for an appropriate period of time after administration of Xolair, taking into account the time to onset of anaphylaxis seen in premarketing clinical trials and postmarketing spontaneous reports [*see Adverse Reactions (6)*]. Inform patients of the signs and symptoms of anaphylaxis, and instruct them to seek immediate medical care should signs or symptoms occur.

Discontinue Xolair in patients who experience a severe hypersensitivity reaction [*see Contraindications (4)*].

5.2 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. The observed malignancies in Xolair-treated patients were a variety of types, with breast, non-melanoma skin, prostate, melanoma, and parotid occurring more than once, and five other types occurring once each. The majority of patients were observed for less than 1 year. The impact of longer exposure to Xolair or use in patients at higher risk for malignancy (e.g., elderly, current smokers) is not known [*see Adverse Reactions (6)*].

5.3 Acute Asthma Symptoms

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

5.4 Corticosteroid Reduction

Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of Xolair therapy. Decrease corticosteroids gradually under the direct supervision of a physician.

5.5 Eosinophilic Conditions

In rare cases, patients with asthma on therapy with Xolair may present with serious systemic eosinophilia sometimes presenting with clinical features of vasculitis consistent with Churg-

Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between Xolair and these underlying conditions has not been established.

5.6 Fever, Arthralgia, and Rash

In post-approval use, some patients have experienced a constellation of signs and symptoms including arthritis/arthralgia, rash (urticaria or other forms), 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. Although circulating immune complexes or a skin biopsy consistent with a Type III reaction were not seen with these cases, these signs and symptoms are similar to those seen in patients with serum sickness. Physicians should stop Xolair if a patient develops this constellation of signs and symptoms. [*see Adverse Reactions, Postmarketing Experience (6.2)*]

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 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.

6 ADVERSE REACTIONS

Use of Xolair has been associated with:

- Anaphylaxis [*see Boxed Warning and Warning and Precautions (5.1)*]
- Malignancies [*see Warnings and Precautions (5.2)*]

Anaphylaxis was reported in 3 of 3507 (0.1%) patients in clinical trials. Anaphylaxis occurred with the first dose of Xolair in two patients and with the fourth dose in one patient. The time to onset of anaphylaxis was 90 minutes after administration in two patients and 2 hours after administration in one patient. In clinical trials the observed incidence of malignancy among Xolair-treated patients (0.5%) was numerically higher than among patients in control groups (0.2%).

6.1 Clinical Trials Experience

Adult and Adolescent Patients 12 years of Age and Older

The data described below reflect Xolair exposure for 2076 adult and adolescent patients ages 12 and older, including 1687 patients exposed for six months and 555 exposed for one year or more, in either placebo-controlled or other controlled asthma studies. The mean age of patients receiving Xolair was 42 years, with 134 patients 65 years of age or older; 60% were women, and 85% Caucasian. Patients received Xolair 150 to 375 mg every 2 or 4 weeks or, for patients assigned to control groups, standard therapy with or without a placebo. Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical

studies of one drug cannot be directly compared with rates in the clinical studies of another drug and may not reflect the rates observed in medical practice.

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%). These events were observed at similar rates in Xolair-treated patients and control patients.

Table 4 shows adverse reactions from four placebo-controlled asthma studies that occurred $\geq 1\%$ and more frequently in patients receiving Xolair than in those receiving placebo. Adverse events were classified using preferred terms from the International Medical Nomenclature (IMN) dictionary. Injection site reactions were recorded separately from the reporting of other adverse events and are described following Table 4.

| Table 4: Adverse Reactions $\geq 1\%$ More Frequent in Xolair-Treated Adult or Adolescent Patients 12 years of age and older: Four placebo-controlled asthma studies | | |
|--|--------------------|---------------------|
| Adverse reaction | Xolair n = 738 (%) | Placebo n = 717 (%) |
| Body as a whole | | |
| Pain | 7 | 5 |
| Fatigue | 3 | 2 |
| Musculoskeletal system | | |
| Arthralgia | 8 | 6 |
| Fracture | 2 | 1 |
| Leg pain | 4 | 2 |
| Arm pain | 2 | 1 |
| Nervous system | | |
| Dizziness | 3 | 2 |
| Skin and appendages | | |
| Pruritus | 2 | 1 |
| Dermatitis | 2 | 1 |
| Special senses | | |
| Earache | 2 | 1 |

There were no differences in the incidence of adverse reactions based on age (among patients under 65), gender or race.

Injection Site Reactions

Injection site reactions of any severity occurred at a rate of 45% in Xolair-treated patients compared with 43% in placebo-treated patients. The types of injection site reactions included:

bruising, redness, warmth, burning, stinging, itching, hive formation, pain, indurations, mass, and inflammation.

Severe injection site reactions occurred more frequently in Xolair-treated patients compared with patients in the placebo group (12% versus 9%).

The majority of injection site reactions occurred within 1 hour-post injection, lasted less than 8 days, and generally decreased in frequency at subsequent dosing visits.

Immunogenicity

Antibodies to Xolair were detected in approximately 1/1723 (< 0.1%) of patients treated with Xolair. The data reflect the percentage of patients whose test results were considered positive for antibodies to Xolair in an ELISA assay and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in the assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. Therefore, comparison of the incidence of antibodies to Xolair with the incidence of antibodies to other products may be misleading.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Xolair in adult and adolescent patients 12 years of age and older. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Anaphylaxis: Based on spontaneous reports and an estimated exposure of about 57,300 patients from June 2003 through December 2006, the frequency of anaphylaxis attributed to Xolair use was estimated to be at least 0.2% of patients. Diagnostic criteria of anaphylaxis were skin or mucosal tissue involvement, and, either airway compromise, and/or reduced blood pressure with or without associated symptoms, and a temporal relationship to Xolair administration with no other identifiable cause. Signs and symptoms in these reported cases included bronchospasm, hypotension, syncope, urticaria, angioedema of the throat or tongue, dyspnea, cough, chest tightness, and/or cutaneous angioedema. Pulmonary involvement was reported in 89% of the cases. Hypotension or syncope was reported in 14% of cases. Fifteen percent of the reported cases resulted in hospitalization. A previous history of anaphylaxis unrelated to Xolair was reported in 24% of the cases.

Of the reported cases of anaphylaxis attributed to Xolair, 39% occurred with the first dose, 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). The time to onset of anaphylaxis in these cases was up to 30 minutes in 35%, greater than 30 and up to 60 minutes in 16%, greater than 60 and up to 90 minutes in 2%, greater than 90 and up to 120 minutes in 6%, greater than 2 hours and up to 6 hours in 5%, greater than 6 hours and up to 12 hours in 14%, greater than 12 hours and up to 24 hours in 8%, and greater than 24 hours and up to 4 days in 5%. In 9% of cases the times to onset were unknown.

Twenty-three patients who experienced anaphylaxis were rechallenged with Xolair and 18 patients had a recurrence of similar symptoms of anaphylaxis. In addition, anaphylaxis occurred upon rechallenge with Xolair in 4 patients who previously experienced urticaria only.

Eosinophilic Conditions: Eosinophilic conditions have been reported [*see Warnings and Precautions (5.5)*].

Fever, Arthralgia, and Rash: A constellation of signs and symptoms including arthritis/arthralgia, rash (urticaria or other forms), fever and lymphadenopathy similar to serum sickness have been reported in postapproval use of Xolair [see *Warnings and Precautions* (5.6)]

Hematologic: Severe thrombocytopenia has been reported.

Skin: Hair loss has been reported.

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category B

There are no adequate and well-controlled studies of Xolair in pregnant women. Reproduction studies have been performed in Cynomolgus monkeys at subcutaneous doses up to 10 times the maximum recommended human dose on a mg/kg basis and have revealed no evidence of impaired fertility or harm to the fetus due to Xolair. Because animal reproduction studies are not always predictive of human response, administer Xolair during pregnancy only if clearly needed [see *Nonclinical Toxicology* (13.2)].

Pregnancy Exposure Registry

To monitor outcomes of pregnant women exposed to Xolair, including women who are exposed to at least one dose of Xolair within 8 weeks prior to conception or any time during pregnancy, a pregnancy exposure registry has been established. Encourage patients to call 1-866-4XOLAIR (1-866-496-5247) to enroll in the Xolair Pregnancy Exposure Registry. Call this number to obtain further information about this registry.

8.3 Nursing Mothers

There are no data from controlled clinical trials on the use of Xolair by nursing mothers. It is not known whether Xolair is excreted in human breast milk. However, IgG is excreted in human breast milk and therefore it is expected that Xolair will be excreted in human breast milk. The potential for Xolair absorption or harm to the infant is unknown; therefore caution should be exercised when Xolair is administered to a nursing woman.

The excretion of omalizumab in milk was evaluated in female Cynomolgus monkeys at a subcutaneous dose approximately 10 times the maximum recommended human dose on a mg/kg basis. Neonatal plasma levels of omalizumab after in utero exposure and 28 days of nursing were between 11% and 94% of the maternal plasma level. Milk levels of omalizumab were 1.5% of maternal blood concentration [see *Nonclinical Toxicology* (13.2)].

8.4 Pediatric Use

Safety and effectiveness of Xolair were evaluated in 2 studies in 926 (Xolair 624; placebo 302) asthma patients 6 to <12 years of age. One study was a pivotal study of similar design and conduct to that of adult and adolescent studies 1 and 2 [see *Clinical Trials (14)*]. The other study was primarily a safety study and included evaluation of efficacy as a secondary outcome. In the pivotal study, 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), but other efficacy variables such as nocturnal symptom scores, beta-agonist use, and measures of airflow (FEV1) were not significantly different in Xolair-treated patients compared to placebo. Considering the risk of anaphylaxis and malignancy seen in Xolair-treated patients ≥ 12 years old and the modest efficacy of Xolair in the pivotal pediatric study, the risk-benefit assessment does not support the use of Xolair in patients 6 to <12 years of age. Although patients treated with Xolair in these two studies did not develop anaphylaxis or malignancy, the studies are not adequate to address these concerns because patients with a history of anaphylaxis or malignancy were excluded, and the duration of exposure and sample size were not large enough to exclude these risks in patients 6 to <12 years of age. Furthermore, there is no reason to expect that younger pediatric patients would not be at risk of anaphylaxis and malignancy seen in adult and adolescent patients with Xolair. [see *Warnings and Precautions (5.1) (5.2)*; and *Adverse Reactions (6)*].

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

14 CLINICAL STUDIES

Adult and Adolescent Patients 12 Years of Age and Older

The safety and efficacy of Xolair were evaluated in three randomized, double-blind, placebo-controlled, multicenter trials.

The trials enrolled patients 12 to 76 years old, with moderate to severe persistent (NHLBI criteria) asthma for at least one year, and a positive skin test reaction to a perennial aeroallergen. In all trials, Xolair dosing was based on body weight and baseline serum total IgE concentration. All patients were required to have a baseline IgE between 30 and 700 IU/mL and body weight not more than 150 kg. Patients were treated according to a dosing table to administer at least 0.016 mg/kg/IU (IgE/mL) of Xolair or a matching volume of placebo over each 4-week period. The maximum Xolair dose per 4 weeks was 750 mg.

In all three studies an exacerbation was defined as a worsening of asthma that required treatment with systemic corticosteroids or a doubling of the baseline ICS dose. Most exacerbations were managed in the out-patient setting and the majority were treated with systemic steroids. Hospitalization rates were not significantly different between Xolair and placebo-treated patients; however, the overall hospitalization rate was small. Among those patients who experienced an exacerbation, the distribution of exacerbation severity was similar between treatment groups.

Studies 1 and 2

At screening, patients in Studies 1 and 2 had a forced expiratory volume in one second (FEV1) between 40% and 80% predicted. All patients had a FEV1 improvement of at least 12% following beta2-agonist administration. All patients were symptomatic and were being treated with inhaled corticosteroids (ICS) and short acting beta2-agonists. Patients receiving other concomitant controller medications were excluded, and initiation of additional controller medications while on study was prohibited. Patients currently smoking were excluded.

Each study was comprised of a run-in period to achieve a stable conversion to a common ICS (beclomethasone dipropionate), followed by randomization to Xolair or placebo. Patients received Xolair for 16 weeks with an unchanged corticosteroid dose unless an acute exacerbation necessitated an increase. Patients then entered an ICS reduction phase of 12 weeks during which ICS dose reduction was attempted in a step-wise manner.

The distribution of the number of asthma exacerbations per patient in each group during a study was analyzed separately for the stable steroid and steroid-reduction periods.

In both Studies 1 and 2 the number of exacerbations per patient was reduced in patients treated with Xolair compared with placebo (Table 5).

Measures of airflow (FEV1) and asthma symptoms were also evaluated in these studies. The clinical relevance of the treatment-associated differences is unknown. Results from the stable steroid phase Study 1 are shown in Table 6. Results from the stable steroid phase of Study 2 and the steroid reduction phases of both Studies 1 and 2 were similar to those presented in Table 6=

| Table 5: Frequency of Asthma Exacerbations per Patient by Phase in Studies 1 and 2 | | | | |
|--|----------------------------------|---------------------------|--------------------------|---------------------------|
| | Stable Steroid Phase (16 wks) | | | |
| | Study 1 | | Study 2 | |
| | Xolair N = 268 (%) | Placebo N = 257 (%) | Xolair N = 274 (%) | Placebo N = 272 (%) |
| Exacerbations per patient | | | | |
| 0 | 85.8 | 76.7 | 87.6 | 69.9 |
| 1 | 11.9 | 16.7 | 11.3 | 25.0 |
| ≥ 2 | 2.2 | 6.6 | 1.1 | 5.1 |
| p-Value | 0.005 | | < 0.001 | |
| Mean number exacerbations/patient | 0.2 | 0.3 | 0.1 | 0.4 |
| | Steroid Reduction Phase (12 wks) | | | |
| | Xolair N = 268 (%) | Placebo N = 257 (%) | Xolair N = 274 (%) | Placebo N = 272 (%) |
| | Exacerbations per patient | | | |
| 0 | 78.7 | 67.7 | 83.9 | 70.2 |
| 1 | 19.0 | 28.4 | 14.2 | 26.1 |
| ≥ 2 | 2.2 | 3.9 | 1.8 | 3.7 |
| p-Value | 0.004 | | < 0.001 | |
| Mean number exacerbations/patient | 0.2 | 0.4 | 0.2 | 0.3 |

| Table 6: Asthma Symptoms and Pulmonary Function During Stable Steroid Phase of Study 1 | | | | |
|---|--------------------|-----------------------------------|---------------------|-----------------------------------|
| Asthma symptom scale: total score from 0 (least) to 9 (most); nocturnal and daytime scores from 0 (least) to 4 (most symptoms). | | | | |
| * Number of patients available for analysis ranges 255-258 in the Xolair group and 238-239 in the placebo group. | | | | |
| † Comparison of Xolair versus placebo (p < 0.05). | | | | |
| | Xolair N = 268* | | Placebo N = 257* | |
| Endpoint | Mean Baseline | Median Change (Baseline to Wk 16) | Mean Baseline | Median Change (Baseline to Wk 16) |
| Total asthma symptom score | 4.3 | -1.5 † | 4.2 | -1.1 † |
| Nocturnal asthma score | 1.2 | -0.4 † | 1.1 | -0.2 † |
| Daytime asthma score | 2.3 | -0.9 † | 2.3 | -0.6 † |
| FEV1 % predicted | 68 | 3 † | 68 | 0 † |

Study 3

In Study 3, there was no restriction on screening FEV1, and unlike Studies 1 and 2, long-acting beta2-agonists were allowed. Patients were receiving at least 1000 µg/day fluticasone propionate and a subset was also receiving oral corticosteroids. Patients receiving other concomitant controller medications were excluded, and initiation of additional controller medications while on study was prohibited. Patients currently smoking were excluded.

The study was comprised of a run-in period to achieve a stable conversion to a common ICS (fluticasone propionate), followed by randomization to Xolair or placebo. Patients were stratified by use of ICS-only or ICS with concomitant use of oral steroids. Patients received Xolair for 16 weeks with an unchanged corticosteroid dose unless an acute exacerbation necessitated an increase. Patients then entered an ICS reduction phase of 16 weeks during which ICS or oral steroid dose reduction was attempted in a step-wise manner.

The number of exacerbations in patients treated with Xolair was similar to that in placebo-treated patients (Table 7). The absence of an observed treatment effect may be related to differences in the patient population compared with Studies 1 and 2, study sample size, or other factors.

| Table 7: Percentage of Patients with Asthma Exacerbations by Subgroup and Phase in Study 3 | | | | |
|--|----------------------------------|--------------------|-----------------------|-------------------|
| | Stable Steroid Phase (16 wks) | | | |
| | Inhaled Only | | Oral + Inhaled | |
| | Xolair N = 126 | Placebo N = 120 | Xolair N = 50 | Placebo N = 45 |
| % Patients with ≥ 1 exacerbations | 15.9 | 15.0 | 32.0 | 22.2 |
| Difference (95% CI) | 0.9 (-9.7, 13.7) | | 9.8 (-10.5, 31.4) | |
| | Steroid Reduction Phase (16 wks) | | | |
| | Xolair N = 126 | Placebo N = 120 | Xolair N = 50 | Placebo N = 45 |
| % Patients with ≥ 1 exacerbations | 22.2 | 26.7 | 42.0 | 42.2 |
| Difference (95% CI) | -4.4 (-17.6, 7.4) | | -0.2 (-22.4, 20.1) | |

In all three of the studies, a reduction of asthma exacerbations was not observed in the Xolair-treated patients who had FEV1 > 80% at the time of randomization. Reductions in exacerbations were not seen in patients who required oral steroids as maintenance therapy.

Pediatric Patients 6 to < 12 Years of Age

Clinical studies with Xolair in pediatric patients 6 to 11 years of age have been conducted [see *Use in Specific Populations (8.4)*]

Pediatric Patients <6 Years of Age

Clinical studies have with Xolair in pediatric patients less than 6 years of age have not been conducted [see *Use in Specific Populations (8.4)*]

7.2 APPENDIX B: STANDARD SEARCHES

A. Adults (17 yrs and above)

1. All outcomes from January 4, 2010 to July 31, 2011
2. Serious outcomes from January 4, 2010 to July 31, 2011
3. Death as an outcome from January 4, 2010 to July 31, 2011

B. Ages 0-16 yrs ONLY

1. All outcomes from January 4, 2010 to July 31, 2011
2. Serious outcomes from January 4, 2010 to July 31, 2011
3. Death as an outcome from January 4, 2010 to July 31, 2011

7.3 APPENDIX C: AERS DATABASE DESCRIPTION

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonization. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do 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 all adverse event reports that occur 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, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

7.4 APPENDIX D: CONTROL NUMBERS FOR PEDIATRIC CASE SERIES: AERS CASE NUMBERS/ISR NUMBERS AND MANUFACTURER CONTROL NUMBER

| Case Number | ISR number | Manufacturer Control Number | Case Number | ISR number | Manufacturer Control Number |
|-------------|------------|-----------------------------|-------------|------------|-----------------------------|
| 7228236 | 6532438 | GB-GENENTECH-296044 | 7660614 | 7120260 | CA-GENENTECH-308960 |
| 7269777 | 6568783 | DE-GENENTECH-297449 | 7709788 | 7159502 | US-GENENTECH-310969 |
| 6988961 | 6571226 | DE-GENENTECH-282226 | 6801802 | 7159986 | NL-GENENTECH-270110 |
| 7214400 | 6576144 | DE-GENENTECH-295669 | 7261703 | 7163933 | GB-GENENTECH-297354 |
| 7237759 | 6576171 | DE-GENENTECH-296512 | 7217297 | 7218185 | DE-GENENTECH-295678 |
| 7234550 | 6577221 | US-GENENTECH-296253 | 7658629 | 7221645 | GB-GENENTECH-308922 |
| 7241209 | 6578115 | US-GENENTECH-296597 | 7611634 | 7238595 | US-GENENTECH-306988 |
| 7288424 | 6605037 | DE-GENENTECH-298240 | 7687932 | 7266425 | JP-GENENTECH-310148 |
| 6745523 | 6614300 | DE-GENENTECH-266774 | 7798737 | 7274008 | CA-GENENTECH-312988 |
| 7310297 | 6621493 | US-GENENTECH-298824 | 7655608 | 7291777 | GB-GENENTECH-308661 |
| 7314253 | 6626625 | AR-GENENTECH-298989 | 7886060 | 7302824 | US-GENENTECH-314066 |
| 7318442 | 6632405 | CA-GENENTECH-298966 | 7295136 | 7306725 | CA-GENENTECH-298534 |
| 6653095 | 6633634 | US-GENENTECH-261264 | 7854778 | 7350747 | DE-GENENTECH-314954 |
| 7302645 | 6639050 | IL-GENENTECH-298701 | 7870394 | 7373222 | DE-GENENTECH-315483 |
| 7308730 | 6641408 | GB-GENENTECH-298870 | 7892252 | 7404480 | US-GENENTECH-315872 |
| 7302053 | 6666273 | NO-GENENTECH-298669 | 7899647 | 7415932 | CA-GENENTECH-316354 |
| 7359273 | 6687437 | US-GENENTECH-300568 | 7915660 | 7438727 | US-GENENTECH-317368 |
| 7367372 | 6698317 | CA-GENENTECH-300902 | 7907476 | 7441035 | US-GENENTECH-316732 |
| 6680389 | 6700772 | GB-GENENTECH-262487 | 7809974 | 7443099 | US-PFIZER INC-2006105114 |
| 7365210 | 6720465 | US-GENENTECH-300648 | 7863065 | 7448298 | US-GENENTECH-315375 |
| 7384206 | 6736285 | FR-GENENTECH-301417 | 7894258 | 7457948 | GB-GENENTECH-316198 |
| 7414944 | 6763094 | US-GENENTECH-302479 | 7930815 | 7458962 | US-GENENTECH-316719 |
| 7406145 | 6768407 | JP-GENENTECH-302282 | 7844353 | 7458972 | US-GENENTECH-314698 |
| 7420287 | 6770542 | US-GENENTECH-301932 | 6528633 | 7461048 | US-GENENTECH-254070 |
| 7379741 | 6826558 | FR-GENENTECH-301032 | 7944690 | 7479650 | DE-GENENTECH-318030 |
| 6615465 | 6929110 | US-GENENTECH-259247 | 7956321 | 7497737 | FR-GENENTECH-318955 |
| 7549011 | 6934574 | SK-GENENTECH-305212 | 7967959 | 7514163 | CO-GENENTECH-319338 |
| 7535085 | 6966298 | VE-GENENTECH-304954 | 7967991 | 7514206 | US-GENENTECH-319281 |
| 6379422 | 6966325 | US-GENENTECH-245607 | 7970279 | 7517565 | SE-GENENTECH-319600 |
| 7427002 | 7003582 | FR-GENENTECH-303016 | 7974469 | 7523866 | US-GENENTECH-319538 |
| 7587468 | 7005735 | SE-GENENTECH-306303 | 7979313 | 7530813 | FR-GENENTECH-319802 |
| 6929550 | 7013897 | US-GENENTECH-278456 | 7990969 | 7547647 | FR-MERCK-1106FRA00019 |
| 7606422 | 7013932 | CA-GENENTECH-306923 | 8003554 | 7565234 | CA-GENENTECH-216909 |
| 7610597 | 7019196 | CA-GENENTECH-306898 | 8009280 | 7572458 | SE-GENENTECH-320567 |
| 7616739 | 7027653 | US-GENENTECH-307182 | 6773158 | 7575535 | CA-GENENTECH-267947 |
| 7555269 | 7030772 | GB-GENENTECH-305621 | 7990739 | 7579272 | US-GENENTECH-319963 |
| 7622489 | 7035969 | IN-GENENTECH-307287 | 7956323 | 7586586 | GB-GENENTECH-318825 |
| 7442697 | 7080069 | CA-GENENTECH-303318 | 7986313 | 7637336 | GB-GENENTECH-319808 |
| 7655316 | 7081730 | GB-GENENTECH-308511 | 8063305 | 7641527 | CTU 460251 |
| 7611990 | 7082179 | FR-GENENTECH-306901 | 7941267 | 7641717 | JP-GENENTECH-318037 |
| 7676205 | 7113334 | FR-GENENTECH-30986 | 8067744 | 7673012 | US-GENENTECH-322075 |

