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 Review

Date:	March 1, 2018
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Product Name:	Anthim® (obiltoxaximab)
Pediatric Labeling Approval Date:	March 18, 2016
Application Type/Number:	BLA 125509
Applicant/Sponsor:	Elusys Therapeutics, Inc.
OSE RCM #:	2018-224

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports for Anthim® (obiltoxaximab) in pediatric patients.

Obiltoxaximab is a monoclonal antibody directed against the protective antigen component of *Bacillus anthracis* toxin. Obiltoxaximab was initially approved in 2016 and is indicated in adult and pediatric patients for the treatment of inhalational anthrax due to *B. anthracis* in combination with appropriate antibacterial drugs and, for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate. The approved pediatric labeling for obiltoxaximab is based on weight.

DPV searched the FDA Adverse Event Reporting System (FAERS) database for all reports of adverse events (serious and non-serious) from March 18, 2016 through December 31, 2017 with obiltoxaximab. The FAERS database contained no pediatric reports for obiltoxaximab.

There is no evidence from these data that there are new pediatric safety concerns with obiltoxaximab at this time. DPV recommends continued pharmacovigilance monitoring.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY[1-2]

Obiltoxaximab is a chimeric IgG1 monoclonal antibody directed against the protective antigen component of *B. anthracis* toxin; it does not have direct antibacterial activity. Obiltoxaximab was initially approved in 2016 and is indicated in adult and pediatric patients for the treatment of inhalational anthrax due to *B. anthracis* in combination with appropriate antibacterial drugs and, for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate. Because it is not ethical or feasible to conduct controlled clinical trials in patients with inhalational anthrax, obiltoxaximab has not been studied in patients with inhalational anthrax. Obiltoxaximab was approved under the FDA's Animal Rule, which allows efficacy findings from adequate and well-controlled animal studies to support FDA approval when it is not feasible or ethical to conduct efficacy trials in humans.

The pharmacokinetics of obiltoxaximab have only been studied in healthy adult volunteers; no pharmacokinetic studies have been conducted in the pediatric population. A population pharmacokinetic approach was used to derive intravenous dosing regimens that are predicted to provide pediatric patients with exposure comparable to the observed exposure in adults receiving a dose of 16 mg/kg. The recommended dose for pediatric patients is based on weight as shown in Table 1.

Table 1. Recommended Pediatric Dose of Obiltoxaximab

Body Weight	Dose
Greater than 40 kg	16 mg/kg
Greater than 15 kg to 40 kg	24 mg/kg
Less than or equal to 15 kg	32 mg/kg

Obiltoxaximab is supplied as 600 mg/6 mL in single-dose vials and administered as a single intravenous infusion over 90 minutes. Premedication with diphenhydramine is recommended prior to the administration of obiltoxaximab; subjects who received pre-medication with diphenhydramine were less likely to experience adverse reactions with the administration of obiltoxaximab compared to those who did not.

The safety of obiltoxaximab has only been studied in healthy adult volunteers; no safety studies have been conducted with obiltoxaximab in the pediatric population. The most frequently reported adverse reactions associated with obiltoxaximab were headache, pruritus, infections of the upper respiratory tract, cough, vessel puncture site bruise, infusion site swelling, urticaria, nasal congestion, infusion site pain, and pain in extremity. Obiltoxaximab was discontinued in 8 of 320 healthy subjects (2.5%) in clinical trials due to hypersensitivity reactions or anaphylaxis.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

The ANTHIM® (obiltoxaximab) labeling provides the following information excerpted from the pertinent sections:[1]

BOXED WARNING

WARNING: HYPERSENSITIVITY AND ANAPHYLAXIS

- Hypersensitivity reactions, including anaphylaxis, have been reported during ANTHIM infusion
- ANTHIM should be administered in monitored settings by personnel trained and equipped to manage anaphylaxis
- Stop ANTHIM infusion immediately and treat appropriately if hypersensitivity or anaphylaxis occurs

WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions, including anaphylaxis

ADVERSE REACTIONS

- Most frequently reported adverse reactions in healthy adult subjects (≥1.5%) were headache, pruritus, infections of the upper respiratory tract, cough, vessel puncture site bruise, infusion site swelling, nasal congestion, infusion site pain, urticaria and pain in extremity

2 POSTMARKET ADVERSE EVENT REPORTS

2.1 METHODS AND MATERIALS

2.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategy described in Table 2. See Appendix A for a description of the FAERS database.

Table 2. FAERS Search Strategy

Date of Search	January 26, 2018
Time Period of Search	March 18, 2016* through December 31, 2017
Search Type	FAERS Business Intelligence Solution (FBIS) Profile Query Product-Manufacturer Reporting Summary
Product Names	Product Name: Anthim Product Active Ingredient: Obiltoxaximab
Search Parameters	All ages, all outcomes, worldwide

** U.S. Approval date*

2.2 RESULTS

FAERS contained no adult or pediatric reports for obiltoxaximab.

The lack of FAERS reports is not surprising because of the low occurrence of inhalational anthrax in the United States and the lack of an outbreak situation since 2001.

3 DISCUSSION

There were no new safety signals or deaths identified in this review.

4 CONCLUSION

There is no evidence from these data that there are pediatric safety concerns with obiltoxaximab at this time.

5 RECOMMENDATIONS

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

6 REFERENCES

1. Development Resources for Medical, Statistical, and Clinical Pharmacology Reviews of Pediatric Studies Conducted under Section 505A and 505B of the Federal Food, Drug, and Cosmetic Act, as amended by the FDA Safety and Innovation Act of 2012 (FDASIA). Available at: http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/ucm316937.htm. Accessed: January 26, 2018.

2. ANTHIM® [package insert]. Pine Brook, NJ: Elusys Therapeutics, Inc; October 2016. (https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125509s001lbl.pdf. Accessed January 26, 2018).

7 APPENDICES

7.1 APPENDIX A FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support 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.

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