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APPLICATION NUMBER:

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**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management Review

Application Type BLA

Application Number 125509

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Established Name Obiltoxaximab

(Proposed) Trade Name Anthim

Applicant Elusys

Therapeutic Class Pending

Formulation(s) Injection

Dosing Regimen Adults, 16mg/kg intravenously; pediatric patients, 16 to (b) (4) mg/kg, depending on body weight

Proposed Indication(s) Treatment of inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial drugs and for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate

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EXECUTIVE SUMMARY

Obiltoxaximab (Anthim) is a new therapeutic biological product subject to Agency review as new molecular entity.. The proposed indication is treatment of inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial drugs and for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate.

Obiltoxaximab is a monoclonal antibody that binds to free protective antigen of *Bacillus anthracis*. The applicant did not submit a proposed risk evaluation and mitigation strategy (REMS) with the application. Division of Risk Management and Division of Anti-infectious Products agree that a risk evaluation and mitigation strategy (REMS) is not needed to ensure the benefits of Anthim outweigh its risks.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) obiltoxaximab is necessary to ensure the benefits of this product outweigh its risks. Elusys submitted a Biologic Licensing Application (BLA) # 125509 for obiltoxaximab with the proposed indication for treatment of inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial drugs and for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate. The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Obiltoxaximab is a new therapeutic biological product subject to Agency review as an NME. Obiltoxaximab was developed under the Animal Rule.¹ The proposed indication is treatment of inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial

¹ The "Animal Rule" describes provisions for the development of drug and biological products when human efficacy studies are not ethical or feasible. The regulations that set forth the pathway for approval of these products under 21 CFR 314.600 through 314.650 (drugs) or 21 CFR 601.90 through 601.95 (biological products) are commonly referred to as the Animal Rule. The criteria for demonstration of efficacy under the Animal Rule are:

- a. Product has a well-understood mechanism of action against a target with known pathophysiology
- b. Benefit demonstrated in > 1 animal species, unless a single species represents a sufficiently well-characterized model to predict response in humans
- c. Efficacy endpoint relevant to the desired outcome in humans
- d. Pharmacokinetic (PK) data that allow translation of effective animal exposures to recommended human doses.

drugs and for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate.

The Animal Rule provided the regulatory structure for effectiveness to be demonstrated in animals when it is unethical or not feasible to conduct controlled clinical trials in humans.

Obiltoxaximab is a monoclonal antibody that binds to free protective antigen of *Bacillus anthracis*. Obiltoxaximab inhibits the binding of protective antigen to cellular receptors, preventing the intracellular entry of toxin components that cause pathogenesis. The proposed dosage regimen is 16 mg/kg body weight administered as a single intravenous infusion. There are no limitations in the proposed labeling regarding healthcare sites appropriate to administer obiltoxaximab.

The only other monoclonal antibody for the treatment of inhalational anthrax, raxibacumab, does not have a boxed warning or a REMS.

Obiltoxaximab is not currently licensed in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 125509 relevant to this review:

- 05/06/2001: Fast Track Status granted
- 06/09/2006: Orphan status granted
- 08/07/2007: Development plan revised based on National Institute of Allergy and Infectious Disease (NIAID) funding/request
- 03/15/2013: End-of-Phase 2 meeting
- 05/07/2013: Pre-BLA meeting
- 03/20/2015: The Agency received BLA 125509 submission for treatment of inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial drugs and for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate

3 Medical Condition(s) and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Anthrax is a serious infectious disease caused by the gram-positive bacteria, *Bacillus anthracis*. Anthrax is present naturally in soil and can infect animals that come in contact. Although it is

rare in the United States, people can get sick with anthrax if they come in contact with infected animals or contaminated animal products.²

Three forms of anthrax disease occur in humans, cutaneous, gastrointestinal, and inhalational. The cutaneous form accounts for most naturally acquired anthrax infections. Gastrointestinal infection is uncommon, as are natural cases of inhalational anthrax. Inhalation anthrax is the most dangerous form of anthrax. Signs of infection usually develop within a week to 2 months after exposure. Without treatment, about 10 - 15% of patients with inhalation anthrax survive. With aggressive treatment, about 55% of patients survive.³ Anthrax meningitis can be a complication of infection with anthrax. Typical signs of meningoencephalitis develop, and patients quickly lose consciousness and die.

Aerosolized biological weapons would be expected to produce a high percentage of inhalational anthrax. In 2001, 11 cases of inhalational anthrax and 11 cases of cutaneous anthrax were associated with a bioterrorist attack via anthrax-contaminated mail. Five of the 22 infected people died. The Center for Disease Control stated, that if a bioterrorist attack were to happen again, anthrax would be one of the biological agents most likely to be used.⁴ Should an attack occur on a larger scale, treatment for anthrax could be needed for hundreds to thousands of affected people.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Antibiotics are used to treat anthrax infection. Antibiotics are effective only against the vegetative stage of *B. anthracis*, and not against spores. Supportive therapy is often necessary, especially for the inhalational and gastrointestinal forms.⁵

Raxibacumab was approved by the FDA December 2012 for the treatment of inhalational anthrax, in combination with antibiotics, and for the prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate. Like obiltoximab, raxibacumab is a monoclonal antibody that binds to the protective antigen of *B. anthracis*. Raxibacumab contains an entry in *Warnings and Precautions* for infusion reactions.⁶

4 Benefit Assessment

² <http://www.cdc.gov/anthrax/basics/index.html>. Accessed November 5, 2015.

³ <http://www.cdc.gov/anthrax/basics/types/inhalation.html>. Accessed November 5, 2015.

⁴ <http://www.cdc.gov/anthrax/bioterrorism/threat.html>. Accessed November 5, 2015.

⁵ <http://www.cfsph.iastate.edu/Factsheets/pdfs/anthrax.pdf>. Accessed November 5, 2015.

⁶ Raxibacumab labeling as edited by the FDA as of November 13, 2015.

The efficacy of obiltoxaximab was demonstrated in studies in New Zealand White rabbits and cynomolgus macaques with inhalational anthrax.⁷ Treatment with obiltoxaximab plus antibiotics⁸ was superior to treatment with antibiotics alone in all studies. Animals were exposed to anthrax and, 30-96 hours post-exposure, the animals were treated with antibiotics alone or antibiotics + obiltoxaximab. In the studies, animals treated with obiltoxaximab had higher survival than animals treated with antibiotics alone. The difference in survival rate between the groups ranged from 4% to 60%.⁹

Obiltoxaximab alone was compared to placebo in treatment of inhalational anthrax. Obiltoxaximab was superior to placebo. In 2 studies in New Zealand White rabbits receiving obiltoxaximab 16mg/kg, 93% and 62% of rabbits survived, compared to no surviving rabbits in the placebo groups. In 2 studies in cynomolgus macaques receiving obiltoxaximab 16mg/kg, 47% and 31% of obiltoxaximab-treated cynomolgus macaques survived, compared to 6% and 0% in the placebo groups, respectively.

5 Risk Assessment

The safety of obiltoxaximab was evaluated in 320 healthy adult subjects infused in 3 clinical trials with 16 mg/kg obiltoxaximab. The subjects were mostly male (54%), and white (70%). Eight of the 320 had the infusion stopped because of adverse events, all hypersensitivity events. The events were rash, urticaria, pruritus, and anaphylaxis.

5.1 HYPERSENSITIVITY REACTIONS

The safety of obiltoxaximab was examined in infusions of 16mg/kg administered to 320 healthy subjects. Most (250) subjects received a single infusion of obiltoxaximab. The remaining subjects received 2 infusions administered 2 weeks to more than 4 weeks apart. Eight (2.5%) of the infusions of obiltoxaximab were stopped because of hypersensitivity reactions. Two other subjects withdrew from study for hypersensitivity reactions. Seven patients experienced hypersensitivity reactions consistent with a diagnosis of anaphylaxis.¹⁰ The patients responded to interventions to manage the reactions, and no subjects died.

Some, but not all, of the subjects received pretreatment with diphenhydramine 50 mg orally 30 minutes before receiving the infusion. Pretreatment with diphenhydramine did not prevent all

⁷ Testing in humans with inhalational anthrax is not feasible or ethical.

⁸ Levofloxacin, ciprofloxacin, doxycycline

⁹ In the 6 studies, the difference in survival between the treatment groups, all in favor of the obiltoxaximab-treated animals, was 4%, 10%, 26%, 40%, 46%, and 60%.

¹⁰ Ramya Gopinath, draft Safety Review BLA 125509, Nov 2015.

hypersensitivity reactions. Of the 10 subjects in whom the infusion of obiltoxaximab was interrupted, or who withdrew from the study due to hypersensitivity, 6 had received diphenhydramine premedication, and 4 had not. Overall, 2.4% of subjects who received diphenhydramine and 5.5% of subjects who did not receive diphenhydramine pretreatment experienced significant hypersensitivity reactions.¹¹

6 Expected Postmarket Use

The need for treatment options for inhalational anthrax became apparent in the wake of the 2001 bioterrorism attack with anthrax in the U.S. Obiltoxaximab was developed for the possibility of biowarfare attack with anthrax, and obiltoxaximab is a candidate for future acquisition into the Strategic National Stockpile, the U.S. repository of critical medical supplies for biowarfare preparedness.

Ideally, treatment for inhalational anthrax would be accomplished in hospitals and other healthcare settings experienced in administering medications via intravenous infusions, and infectious disease specialists would be involved in the patients' care. However, in a mass casualty situation, treatment of numerous anthrax-infected patients might be needed. Care settings could possibly extend beyond hospitals, and infectious disease specialists might not be involved in the care of each patient.

The safety database includes administration of obiltoxaximab to healthy subjects, not to anthrax-infected patients. The known safety issues are well-described in the FDA-edited draft labeling; however, given the limited safety data available, it is possible that additional safety issues could surface with wider use in a mass casualty situation.

7 Discussion of Need for a REMS

DRISK and DAIP believe that a REMS is not needed to ensure the benefits of obiltoxaximab outweigh its risks. Results from clinical testing show an acceptable safety profile and clinically important activity against *Bacillus anthracis*. The most important risk of obiltoxaximab is hypersensitivity reactions. A similar product, raxibacumab, also carries a risk of hypersensitivity, although likely to a lesser degree than obiltoxaximab. It was determined that a REMS is not needed for raxibacumab to ensure that benefits outweigh the risks.

The hypersensitivity reactions observed with obiltoxaximab can be partially prevented with antihistamine pre-treatment, and can be managed with medication and supportive therapy. Obiltoxaximab likely will be used only rarely, except in the instance of a bioterrorism attack

¹¹ Ramya Gopinath, draft Safety Review BLA 125509, Nov 2015.

with anthrax. The hypersensitivity safety issue will be communicated through labeling (i.e., inclusion of the event in *Warnings and Precautions*), and additional requirements are not necessary to maintain a favorable risk–benefit balance.

8 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for Anthim beyond routine measures. The applicant stated that a REMS or risk management plan is not required for obiltoxaximab.

9 Conclusion & Recommendations

Based on the available data, the benefit–risk profile is acceptable and DRISK and DAIP agree that a REMS is not necessary for Anthim to ensure the benefits outweigh the risks. If new safety information becomes available that changes the benefit–risk profile, this recommendation can be reevaluated.

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/s/

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