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RESEARCH**

APPLICATION NUMBER:

125509Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ANTHIM safely and effectively. See full prescribing information for ANTHIM.

ANTHIM® (obiltoximab) injection, for intravenous use
Initial U.S. Approval: 2016

WARNING: HYPERSENSITIVITY and ANAPHYLAXIS *See full prescribing information for complete boxed warning.*

- Hypersensitivity reactions, including anaphylaxis, have been reported during ANTHIM infusion (5.1)
- ANTHIM should be administered in monitored settings by personnel trained and equipped to manage anaphylaxis (1.2, 2.4, 5.1)
- Stop ANTHIM infusion immediately and treat appropriately if hypersensitivity or anaphylaxis occurs (2.4, 5.1)

INDICATIONS AND USAGE

ANTHIM® is a monoclonal antibody directed against the protective antigen of *Bacillus anthracis*. It is indicated in adult and pediatric patients for 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. (1.1)

Limitations of Use

- ANTHIM should only be used for prophylaxis when its benefit for prevention of inhalational anthrax outweighs the risk of hypersensitivity and anaphylaxis. (1.2, 5.1)
- The effectiveness of ANTHIM is based solely on efficacy studies in animal models of inhalational anthrax. (1.2, 14)
- There have been no studies of the safety or pharmacokinetics (PK) of ANTHIM in the pediatric population. Dosing in pediatric patients was derived using a population PK approach. (1.2, 8.4)
- ANTHIM does not have direct antibacterial activity. ANTHIM should be used in combination with appropriate antibacterial drugs. (1.2)
- ANTHIM is not expected to cross the blood-brain barrier and does not prevent or treat meningitis. (1.2)

DOSAGE AND ADMINISTRATION

- Pre-medicate with diphenhydramine. (2.1, 5.1)
- Recommended Dosage of ANTHIM:
 - o Adult Patients: 16 mg/kg. (2.1)
 - o Pediatric Patients: (2.2)
 - 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
- Dilute the injection in 0.9% Sodium Chloride Injection, USP, before administering as an intravenous (IV) infusion over 1 hour and 30 minutes. (2.3)
- Administer ANTHIM in a monitored setting equipped to manage anaphylaxis. (2.4, 5.1)
- See Full Prescribing Information for instructions on preparation, dilution and administration of ANTHIM injection. (2.3, 2.4)

DOSAGE FORMS AND STRENGTHS

Injection: 600 mg/6 mL (100 mg/mL) solution in single-dose vial. (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

Hypersensitivity reactions, including anaphylaxis (Boxed Warning, 1.2, 2.1, 2.4, 5.1)

ADVERSE REACTIONS

Most frequently reported adverse reactions in healthy adult subjects ($\geq 1.5\%$) 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. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Elusys Therapeutics, Inc. at 1-844-808-0222 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Pediatric Use: There have been no studies of the safety or PK of ANTHIM in the pediatric population. (1.2, 8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 3/2016

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FULL PRESCRIBING INFORMATION

WARNING: HYPERSENSITIVITY and ANAPHYLAXIS

Hypersensitivity and anaphylaxis have been reported during the intravenous infusion of ANTHIM. Due to the risk of hypersensitivity and anaphylaxis, ANTHIM should be administered in monitored settings by personnel trained and equipped to manage anaphylaxis. Monitor individuals who receive ANTHIM closely for signs and symptoms of hypersensitivity reactions throughout the infusion and for a period of time after administration. Stop ANTHIM infusion immediately and treat appropriately if hypersensitivity or anaphylaxis occurs [see *Indications and Usage (1.2)*, *Dosage and Administration (2.4)* and *Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE

1.1 Inhalational Anthrax

ANTHIM is indicated in adult and pediatric patients for the treatment of inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial drugs.

ANTHIM is indicated for prophylaxis of inhalational anthrax due to *B. anthracis* when alternative therapies are not available or not appropriate [see *Indications and Usage (1.2)*].

1.2 Limitations of Use

ANTHIM should only be used for prophylaxis when its benefit for prevention of inhalational anthrax outweighs the risk of hypersensitivity and anaphylaxis [see *Warnings and Precautions (5.1)*].

The effectiveness of ANTHIM is based solely on efficacy studies in animal models of inhalational anthrax. It is not ethical or feasible to conduct controlled clinical trials with intentional exposure of humans to anthrax [see *Clinical Studies (14)*].

Safety and PK of ANTHIM have been studied in adult healthy volunteers. There have been no studies of safety or PK of ANTHIM in the pediatric population. A population PK approach was used to derive intravenous infusion dosing regimens that are predicted to provide pediatric patients with exposure comparable to the observed exposure in adults [see *Use in Specific Populations (8.4)*].

ANTHIM binds to the protective antigen (PA) component of *B. anthracis* toxin; it does not have direct antibacterial activity. ANTHIM is not expected to cross the blood-brain barrier and does not prevent or treat meningitis. ANTHIM should be used in combination with appropriate antibacterial drugs.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage for Adult Patients

- Pre-medicate with diphenhydramine prior to administering ANTHIM [see *Warnings and Precautions (5.1)*].
- Dilute the injection in 0.9% Sodium Chloride Injection, USP, before administering as an intravenous infusion [see *Dosage and Administration (2.3)*].
- The recommended dosage of ANTHIM in adult patients is a single dose of 16 mg/kg administered intravenously over 90 minutes (1 hour and 30 minutes) [see *Dosage and Administration (2.4)*].
- For adult patients weighing less than 40 kg, see [Table 1](#) below.

2.2 Dosage for Pediatric Patients

- Pre-medicate with diphenhydramine prior to administering ANTHIM [see *Warnings and Precautions (5.1)*].
- Dilute the injection in 0.9% Sodium Chloride Injection, USP, before administering as an intravenous infusion [see *Dosage and Administration (2.3)*].
- The recommended dose for pediatric patients is based on weight as shown in [Table 1](#) below.

Table 1. Recommended Pediatric Dose of ANTHIM (weight-based dosing)

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

- Administer the recommended dose of ANTHIM intravenously over 90 minutes (1 hour and 30 minutes) [see *Dosage and Administration (2.4)*].

There have been no studies of the safety or PK of ANTHIM conducted in the pediatric population. The dosing recommendations in [Table 1](#) are derived from simulations using a population PK approach designed to match the observed adult exposure to ANTHIM at a 16 mg/kg dose [see *Use in Specific Populations (8.4)*].

2.3 Preparation and Dilution for Administration

Important Preparation Instructions

- Keep vials in their cartons prior to preparation of an infusion solution to protect ANTHIM from light. ANTHIM vials contain no preservative.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
- Discard the vial if the solution is discolored or contains extraneous particles other than a few translucent-to-white, proteinaceous particles [see *Description (11)*].
- Do not shake the vial.

Table 2. ANTHIM Dose, Total Infusion Volume and Infusion Rate by Body Weight

Body Weight (weight-based dosing)	Total Infusion Volume	Infusion Rate
Greater than 40 kg or adult (16 mg/kg)		
Greater than 40 kg	250 mL	167 mL/hr
Greater than 15 kg to 40 kg (24 mg/kg)		
31 kg to 40 kg	250 mL	167 mL/hr
16 kg to 30 kg	100 mL	67 mL/hr
15 kg or less (32 mg/kg)		
11 kg to 15 kg	100 mL	67 mL/hr
5 kg to 10 kg	50 mL	33.3 mL/hr
3.1 kg to 4.9 kg	25 mL	17 mL/hr
2.1 kg to 3 kg	20 mL	13.3 mL/hr
1.1 kg to 2 kg	15 mL	10 mL/hr
1 kg or less	7 mL	4.7 mL/hr

Preparation and Dilution in Bag for Infusion

1. Calculate the milligrams of ANTHIM injection needed by multiplying the recommended mg/kg dose in [Table 2](#) by the patient weight in kilograms.
2. Calculate the required volume in milliliters of ANTHIM injection and number of vials needed for the dose by dividing the calculated dose in milligrams (step 1) by the concentration, 100 mg/mL. Each single vial allows delivery of 6 mL of ANTHIM.
3. Select an appropriate size bag of 0.9% Sodium Chloride Injection, USP. Withdraw a volume of solution from the bag equal to the calculated volume in milliliters of ANTHIM in step 2 above. Discard the solution that was withdrawn from the bag.
4. Withdraw the required volume of ANTHIM injection (calculated from step 2) from the ANTHIM vial(s). Discard any unused portion remaining in the ANTHIM vial(s).
5. Transfer the required volume of ANTHIM injection to the selected infusion bag.
6. Gently invert the bag to mix the solution. Do not shake.
7. The prepared solution is stable for 4 hours stored at room temperature or 4 hours stored in the refrigerator at 2°C to 8°C (36°F to 46°F).

Preparation and Dilution in Syringe for Infusion

1. Calculate the milligrams of ANTHIM injection needed by multiplying the recommended mg/kg dose in [Table 2](#) by the patient weight in kilograms.
2. Calculate the required volume in milliliters of ANTHIM injection and number of vials needed for the dose by dividing the calculated dose in milligrams (step 1) by the concentration, 100 mg/mL. Each single vial allows delivery of 6 mL of ANTHIM.
3. Select an appropriate size syringe for the total volume of infusion to be administered.
4. Using the selected syringe, withdraw the required volume of ANTHIM injection (calculated from step 2). Discard any unused portion remaining in the ANTHIM vial(s).
5. Withdraw an appropriate amount of 0.9% Sodium Chloride Injection, USP to prepare the total infusion volume specified in [Table 2](#).
6. Gently mix the solution. Do not shake.
7. Once a diluted solution of ANTHIM has been prepared, administer immediately. Do not store solution in syringe. Discard unused product.

2.4 Administration

- Administer ANTHIM in appropriately monitored settings which are equipped to manage anaphylaxis [*see Warnings and Precautions (5.1)*].
- Dilute ANTHIM injection [*see Dosage and Administration (2.3)*] before administering ANTHIM intravenously using the bag or syringe for infusion.
- After preparation of the bag or syringe for infusion administer the infusion solution using a 0.22 micron inline filter with the infusion rate described in [Table 2](#) [*see Dosage and Administration (2.3)*].
- Administer diluted ANTHIM intravenous infusion over 1 hour and 30 minutes. Monitor patients closely for signs and symptoms of hypersensitivity throughout the infusion and for a period of time after administration [*see Warnings and Precautions (5.1)*].
- Stop the infusion immediately and treat appropriately, if hypersensitivity or anaphylaxis occurs [*see Warnings and Precautions (5.1)*].
- Flush the line with 0.9% Sodium Chloride Injection, USP at the end of the intravenous infusion.

3 DOSAGE FORMS AND STRENGTHS

Injection: 600 mg/6 mL (100 mg/mL) in a single-dose vial.

ANTHIM is a clear to opalescent, colorless to pale yellow to pale brownish-yellow solution and may contain few translucent-to-white proteinaceous particulates.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity and Anaphylaxis

Hypersensitivity reactions were the most common adverse reactions in the safety trials of ANTHIM, occurring in 34/320 healthy subjects (10.6%). Three (0.9%) cases of anaphylaxis occurred during or immediately after the infusion. In clinical trials, manifestations of anaphylaxis were rash/urticaria, cough, dyspnea, cyanosis, postural dizziness and chest discomfort. ANTHIM infusion was discontinued in 8 (2.5%) subjects due to hypersensitivity or anaphylaxis. The adverse reactions reported in these 8 subjects included urticaria, rash, cough, pruritus, dizziness, throat irritation, dysphonia, dyspnea and chest discomfort. The remaining subjects with hypersensitivity had predominantly skin-related symptoms such as pruritus and rash, and 6 subjects reported cough [see *Adverse Reactions* 6.1].

Due to the risk of anaphylaxis, ANTHIM should be administered in monitored settings by personnel trained and equipped to manage anaphylaxis. Patients should be monitored closely throughout the infusion period and for a period of time after administration [see *Patient Counseling Information* (17)]. If anaphylaxis or hypersensitivity reactions occur, stop the infusion immediately and treat appropriately.

Premedication with diphenhydramine is recommended prior to administration of ANTHIM [see *Dosage and Administration* (2.1) and *Adverse Reactions* (6.1)]. Diphenhydramine premedication does not prevent anaphylaxis, and may mask or delay onset of symptoms of hypersensitivity.

6 ADVERSE REACTIONS

The following clinically important adverse reactions are described elsewhere in the labeling:

- Hypersensitivity and Anaphylaxis [see *Warnings and Precautions* (5.1)].

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of ANTHIM has been studied only in healthy volunteers. It has not been studied in patients with inhalational anthrax.

The safety of ANTHIM was evaluated in 320 healthy subjects treated with one or more 16 mg/kg IV doses in three clinical studies. Study 1 was a placebo-controlled study evaluating a single dose of ANTHIM vs. placebo (210 subjects received ANTHIM, 70 received placebo). Study 2 was a repeat-dose study in which 70 subjects received the first dose, but 34 and 31 subjects received a second dose of ANTHIM in sequences A (2 weeks apart) and B (≥ 4 months apart), respectively. Study 3 was a drug interaction study of a single dose of ANTHIM with ciprofloxacin in 40 subjects (20 subjects received ANTHIM alone and 20 subjects received ANTHIM plus ciprofloxacin for 9 days).

Subjects were 18 to 79 years of age, 54% were male, 70% Caucasian, 26% Black/African American, 2% American Indian/Alaska Native, 1% Asian and 10% Hispanic.

Adverse Reactions Leading to Discontinuation of ANTHIM Infusion

ANTHIM infusion was discontinued in 8/320 healthy subjects (2.5%) in clinical trials due to hypersensitivity reactions or anaphylaxis [see *Warnings and Precautions (5.1)*].

Most Frequently Reported Adverse Reactions

The most frequently reported adverse reactions 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.

Table 3 shows the adverse reactions that occurred in $\geq 1.5\%$ of healthy subjects receiving a single dose of ANTHIM (16 mg/kg IV) and more frequently than those receiving placebo.

Table 3. Adverse Reactions Reported in $\geq 1.5\%$ of Healthy Adult Subjects Exposed to a Single Dose of ANTHIM 16 mg/kg IV

Adverse Reactions	Placebo N = 70 (%)	Single Dose ANTHIM N = 300* (%)
Headache	4 (6%)	24 (8%)
Pruritus	1 (1%)	11 (4%)
Infections of the upper respiratory tract	2 (3%)	14 (5%)
Cough	0	9 (3%)
Vessel puncture site bruise	1 (1%)	8 (3%)
Infusion site swelling	1 (1%)	8 (3%)
Nasal congestion	1 (1%)	5 (2%)
Infusion site pain	0	7 (2%)
Urticaria	0	5 (2%)
Pain in extremity	1 (1%)	5 (2%)

*Single-dose population: 210 subjects in study 1 plus 70 subjects in the first treatment period of study 2 plus 20 subjects in the ANTHIM alone treatment arm of study 3

Effect of Diphenhydramine on the Incidence of Adverse Reactions

Overall in the single-dose population, subjects who received pre-medication with diphenhydramine were less likely to experience adverse reactions with administration of ANTHIM compared to those who did not (42% vs. 58% respectively). Specifically, the incidence of the following adverse reactions was lower in the subjects who received diphenhydramine prior to ANTHIM infusion compared to those who did not: headache (5% vs. 16%), cough (1% vs. 8%), rash (2% vs. 7%), pruritus (3% vs. 4%) throat irritation (0 vs. 3%), rhinorrhea (0 vs. 3%), and infusion site erythema (0% vs. 4%). Somnolence was only reported in subjects who were pretreated with diphenhydramine.

Less Common Adverse Reactions

Clinically important adverse reactions that were reported in $< 1.5\%$ of subjects exposed to ANTHIM and at rates higher than in placebo subjects are listed below:

- *General disorders and administration site conditions:* chest discomfort/pain, fatigue, pyrexia, intravenous site discoloration
- *Musculoskeletal and connective tissue disorders:* myalgia, musculoskeletal pain
- *Respiratory, thoracic and mediastinal disorders:* oropharyngeal pain, sinus congestion, rhinorrhea, dysphonia, dyspnea

- *Investigations:* lymphocyte count decreased, neutrophil count decreased, white blood count decreased, increased creatine phosphokinase
- *Cardiac disorders:* palpitations, cyanosis
- *Neurologic disorders:* dizziness
- *Gastrointestinal disorders:* vomiting, dry mouth

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The development of anti-ANTHIM antibodies was evaluated in all subjects receiving single and double doses of ANTHIM in studies 1, 2 and 3. Eight subjects (2.5%) who received at least one dose of IV ANTHIM were positive for a treatment-emergent anti-therapeutic antibody (ATA) response. Quantitative titers were low ranging from 1:20 – 1:320. There was no evidence of altered PK or toxicity profile in subjects with ATA development.

The incidence of antibody formation is highly dependent on the sensitivity and specificity of the immunogenicity assay. Additionally, the observed incidence of any antibody positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to obiltoximab with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

7.1 Ciprofloxacin

Co-administration of 16 mg/kg ANTHIM intravenously with intravenous or oral ciprofloxacin in human subjects did not alter the PK of either ciprofloxacin or obiltoximab [see *Clinical Pharmacology* (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

No adequate and well-controlled studies in pregnant women were conducted. Because animal reproduction studies are not always predictive of human response, ANTHIM should be used during pregnancy only if clearly needed.

A single embryonic-fetal development study was conducted in pregnant, healthy New Zealand White (NZW) rabbits administered 4 intravenous doses of ANTHIM up to 32 mg/kg (2 times the human dose on a mg/kg basis) on gestation days 6, 10, 13, and 17. No evidence of harm to the pregnant dam or the fetuses due to ANTHIM was observed. Cumulative exposures in NZW rabbits (10,000 mcg•day/mL) at the NOAEL of 32 mg/kg/dose (n=4 doses) based on AUC_{0-15 days} were approximately two-fold the human male and female combined mean AUC at the clinical intravenous dose of 16 mg/kg. C_{max} values following a 32 mg/kg/dose were 1180 mcg•day/mL.

8.3 Nursing Mothers

ANTHIM has not been evaluated in nursing women. Although human immunoglobulins are excreted in human milk, published data suggest that neonatal consumption of human milk does not result in substantial absorption of these maternal immunoglobulins into circulation. Inform a nursing woman that the effects of local gastrointestinal and systemic exposure to ANTHIM on nursing infant are unknown.

8.4 Pediatric Use

As in adults, the effectiveness of ANTHIM in pediatric patients is based solely on efficacy studies in animal models of inhalational anthrax. As exposure of healthy children to ANTHIM is not ethical, a population PK 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 16 mg/kg. The dose for pediatric patients is based on weight [see *Dosage and Administration* (2.2)].

There have been no studies of safety or PK of ANTHIM in the pediatric population.

8.5 Geriatric Use

Clinical studies of ANTHIM did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Of the 320 subjects in clinical studies of ANTHIM, 9.4% (30/320) were 65 years and over, while 2% (6/320) were 75 years and over. No alteration of dosing is needed for patients ≥ 65 years of age [see *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

There is no clinical experience with overdosage of ANTHIM. In case of overdosage, monitor patients for any signs or symptoms of adverse effects.

11 DESCRIPTION

Obiltoxaximab is a chimeric IgG1 kappa monoclonal antibody (mAb) that binds the PA component of *B. anthracis* toxin. It has an approximate molecular weight of 148 kDa.

ANTHIM injection is a sterile, preservative-free, clear to opalescent, colorless to pale yellow to pale brownish-yellow solution that may contain few translucent-to-white proteinaceous particulates. ANTHIM is supplied as 600 mg/6 mL in single-dose vials for intravenous infusion. Each mL contains 100 mg obiltoxaximab in L-histidine (6.2 mg), polysorbate 80 (0.1 mg), sorbitol (36 mg) with a pH of 5.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Obiltoxaximab is a monoclonal antibody that binds the PA of *B. anthracis* [see *Microbiology* (12.4)].

12.3 Pharmacokinetics

The PK of obiltoxaximab are linear over the dose range of 4 mg/kg (0.25 times the lowest recommended dose) to 16 mg/kg following single IV administration in healthy subjects. Following single IV administration of ANTHIM 16 mg/kg in healthy, male and female human subjects, the mean C_{max} and AUC_{inf} were 400 ± 91.2 mcg/mL and 5170 ± 1360 mcg•day/mL, respectively.

Repeat Dosing

Although ANTHIM is intended for single dose administration, the PK of obiltoxaximab following a second dose administration of 16 mg/kg IV given 2 weeks or ≥ 4 months after the first 16 mg/kg IV dose was assessed in 65 healthy subjects (study 2). The obiltoxaximab AUC_{inf} following two 16 mg/kg doses 2 weeks apart was approximately twice that after a single 16 mg/kg dose on Day 1 or Day 120. No significant differences in mean estimates of C_{max} , AUC_{inf} , CL, or half-life of obiltoxaximab between the 2 doses administered ≥ 4 months apart were observed.

Distribution

Mean obiltoxaximab steady-state volume of distribution was greater than plasma volume, suggesting some tissue distribution.

Elimination

Clearance values were much smaller than the glomerular filtration rate, indicating that there is virtually no renal clearance of obiltoxaximab.

Because the effectiveness of ANTHIM cannot be evaluated in humans, a comparison of ANTHIM exposures achieved in healthy human subjects to those observed in animal models of inhalational anthrax in therapeutic efficacy studies is necessary to support the dosage regimen of 16 mg/kg IV as a single dose for the treatment of inhalational anthrax in humans. Based on observed and simulated data, humans achieve similar obiltoxaximab $C_{\max}$ and greater AUC_{inf} following a single 16 mg/kg IV dose compared to exposures achieved in NZW rabbits and cynomolgus macaques.

Specific Populations

Gender, Age, and Race

ANTHIM PK were evaluated via a population PK analysis using serum samples from 303 healthy adult subjects who received a single IV dose across 3 clinical trials. Based on this analysis, gender (female versus male), race (non-Caucasian versus Caucasian), or age (elderly versus young) had no meaningful effects on the PK parameters for ANTHIM.

Pediatric Population

ANTHIM PK have not been evaluated in children [see *Dosage and Administration (2.2)* and *Use in Specific Populations (8.4)*].

Drug Interaction Studies

Ciprofloxacin

In an open-label study evaluating the effect of ciprofloxacin on obiltoxaximab PK in healthy adult male and female subjects (study 3), the administration of 16 mg/kg ANTHIM IV infusion prior to ciprofloxacin IV infusion or ciprofloxacin oral tablets twice daily did not alter the PK of obiltoxaximab. Likewise, obiltoxaximab did not alter the PK of ciprofloxacin administered orally and/or intravenously [see *Drug Interactions (7.1)*].

12.4 Microbiology

Mechanism of Action

Obiltoxaximab is a monoclonal antibody that binds free PA with an affinity equilibrium dissociation constant (K_d) of 0.33 nM. Obiltoxaximab inhibits the binding of PA to its cellular receptors, preventing the intracellular entry of the anthrax lethal factor and edema factor, the enzymatic toxin components responsible for the pathogenic effects of anthrax toxin.

Activity *In Vitro* and *In Vivo*

Obiltoxaximab binds *in vitro* to PA from the Ames, Vollum, and Sterne strains of *B. anthracis*. Obiltoxaximab binds to an epitope on PA that is conserved across reported strains of *B. anthracis*.

In vitro studies in a cell-based assay, using murine macrophages, suggest that obiltoxaximab neutralizes the toxic effects of lethal toxin, a combination of PA + lethal factor.

In vivo efficacy studies in NZW rabbits and cynomolgus macaques challenged with the spores of the Ames strain of *B. anthracis* by the inhalational route, showed a dose-dependent increase in survival following treatment with ANTHIM. Exposure to *B. anthracis* spores resulted in increasing concentrations of PA in the serum of NZW rabbits and cynomolgus macaques. After treatment with ANTHIM there was a decrease in PA concentrations in a majority of surviving animals. PA concentrations in placebo animals increased until they died [see *Clinical Studies (14)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, genotoxicity, and fertility studies have not been conducted with obiltoxaximab.

13.2 Animal Toxicology and/or Pharmacology

Central nervous system (CNS) lesions (bacteria, inflammation, hemorrhage and occasionally necrosis) were seen in anthrax-infected non-surviving NZW rabbits and cynomolgus macaques administered IV obiltoxaximab (≥ 4 mg/kg) or control at the time of disease confirmation. Microscopic changes in the non-surviving animals that received obiltoxaximab were due to the presence of extravascular bacteria and not the effect of obiltoxaximab. No dose response relationship for brain histopathology was identified. No treatment-related brain lesions were shown in anthrax-infected surviving NZW rabbits (at day 28) or cynomolgus macaques (up to day 56) after a single administration of obiltoxaximab at doses up to 16 mg/kg and up to 32 mg/kg/dose, respectively. No obiltoxaximab-related neurobehavioral effects were observed in surviving anthrax-infected cynomolgus macaques following treatment with obiltoxaximab.

14 CLINICAL STUDIES

Overview

Because it is not feasible or ethical to conduct controlled clinical trials in humans with inhalational anthrax, the efficacy of ANTHIM for the treatment of inhalational anthrax is based on efficacy studies in NZW rabbits and cynomolgus macaques. The animal efficacy studies are conducted under widely varying conditions, such that the survival rates observed in the animal studies cannot be directly compared between studies and may not reflect the rates observed in clinical practice.

Types of Studies

The efficacy of ANTHIM for treatment and prophylaxis of inhalational anthrax was studied in multiple studies in the cynomolgus macaque and NZW rabbit models of inhalational anthrax. These studies tested the efficacy of ANTHIM compared to placebo and the efficacy of ANTHIM in combination with antibacterial drugs relative to the antibacterial drugs alone.

Study Design

The animals were challenged with aerosolized *B. anthracis* spores (Ames strain) at approximately 200xLD₅₀ to achieve 100% mortality if untreated. In prophylaxis studies of inhalational anthrax, animals were treated prior to the development of symptoms. In treatment studies, animals were administered treatment after exhibiting clinical signs or symptoms of systemic anthrax. Cynomolgus macaques were treated at the time of a positive serum electrochemiluminescence (ECL) assay for *B. anthracis* PA at a mean time of approximately 40 hours post-challenge with *B. anthracis*. In NZW rabbit treatment studies, animals were treated after a positive ECL assay for PA or sustained elevation of body temperature above baseline, at a mean time of approximately 30 hours post-challenge; the majority of animals triggered by temperature. In some of the treatment studies assessing the effect of ANTHIM in combination with antibacterial drugs, treatment was delayed to 72 to 96 hours post-challenge. Most study animals were bacteremic and had a positive ECL assay for PA prior to treatment. Survival was assessed at 28 days post-challenge with *B. anthracis* in most studies.

Results

NZW rabbit studies 1 and 2 and cynomolgus macaque studies 3 and 4 evaluated treatment with ANTHIM 16 mg/kg IV single dose compared to placebo in animals with systemic anthrax. Treatment with ANTHIM alone resulted in statistically significant improvement in survival relative to placebo ([Table 4](#)).

Table 4. Survival Proportions in Monotherapy Treatment Studies of 16 mg/kg IV, All Randomized Animals Positive for Bacteremia Prior to Treatment

	Proportion of Survival at Day 28 ¹ (# survived/n)		p-value ²	95% CI ³
	Placebo	ANTHIM 16 mg/kg IV		
NZW Rabbits				
Study 1	0 (0/9)	93% (13/14)	0.0010	(0.59, 1.00)
Study 2	0 (0/13)	62% (8/13)	0.0013	(0.29, 0.86)
Cynomolgus Macaques				
Study 3	6% (1/16)	47% (7/15)	0.0068	(0.09, 0.68)
Study 4 ⁴	0 (0/17)	31% (5/16)	0.0085	(0.08, 0.59)
		35% (6/17)	0.0055	(0.11, 0.62)

IV: intravenous, CI: Confidence Interval

¹Survival assessed 28 days after spore challenge

²p-value is from 1-sided Boschloo Test (with Berger-Boos modification of gamma=0.001) compared to placebo

³Exact 95% confidence interval of difference in survival rates

⁴ANTHIM products manufactured at two different facilities were tested in two separate treatment arms

ANTHIM administered in combination with antibacterial drugs (levofloxacin, ciprofloxacin and doxycycline) for the treatment of systemic inhalational anthrax disease resulted in higher survival outcomes than antibacterial therapy alone in multiple studies where ANTHIM and antibacterial therapy was given at various doses and treatment times.

ANTHIM administered as prophylaxis resulted in higher survival outcomes compared to placebo in multiple studies where treatment was given at various doses and treatment times. In one study, cynomolgus macaques were administered ANTHIM 16 mg/kg at 18 hours, 24 hours or 36 hours after exposure. Survival was 6/6 (100%) at 18 hours, 5/6 (83%) at 24 hours, and 3/6 (50%) at 36 hours. Another cynomolgus macaque study evaluated ANTHIM 16 mg/kg administered 72, 48 or 24 hours prior to exposure. Survival was 100% at all three time points (14/14, 14/14, 15/15, respectively) at day 56 (end of study).

16 HOW SUPPLIED/STORAGE AND HANDLING

ANTHIM injection is a sterile, preservative-free, clear to opalescent, colorless to pale yellow to pale brownish-yellow solution that may contain few translucent-to-white proteinaceous particulates in single-dose vials containing 600 mg/6 mL (100 mg/mL) and is available in the following packaging configuration:

Carton: Contains one (1) single-dose vial of ANTHIM 600 mg/6 mL (NDC 69604-204-02).

Store in refrigerator at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. *Do Not Freeze. Do Not Shake.*

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling ([Patient Information](#)).

Efficacy Based on Animal Models Alone

Inform patients that:

- The effectiveness of ANTHIM has been studied only in animals with inhalational anthrax. ANTHIM has not been tested in people who have inhalational anthrax.
- The safety of ANTHIM has been studied in healthy adults, but no safety data are available in pediatric patients or pregnant women. Limited data are available in geriatric subjects [see *Use in Specific Populations* (8.5)].

Hypersensitivity Reactions and Anaphylaxis

Inform patients that hypersensitivity reactions, including anaphylaxis, have occurred with administration of ANTHIM. Inform patients of the signs and symptoms of hypersensitivity reactions and anaphylaxis and instruct patients to seek immediate medical care if they experience such symptoms during or following administration of ANTHIM [see *Warnings and Precautions* (5.1)].

Manufactured by:



Elusys Therapeutics, Inc.
25 Riverside Drive
Unit 1
Pine Brook, NJ 07058
U.S. License Number 1907

PATIENT INFORMATION

ANTHIM[®] (an(t)-thim)

obiltoxaximab

injection, for intravenous use

What is the most important information I should know about ANTHIM?

ANTHIM can cause serious side effects, including:

- **Serious allergic reactions.** Tell your healthcare provider right away if you have itching, hives, rash, throat irritation, cough, dizziness, shortness of breath or chest discomfort while receiving ANTHIM.

What is ANTHIM?

- ANTHIM is a prescription medicine used along with antibiotic medicines to treat people with inhalational anthrax. ANTHIM can also be used to prevent anthrax disease when there are no other treatment options.
- The effectiveness of ANTHIM has been studied only in animals with inhalational anthrax. There have been no studies in people who have inhalational anthrax.
- The safety of ANTHIM was studied in healthy adults. There have been no studies of ANTHIM in children younger than 18 years.
- ANTHIM is not used in prevention or treatment of anthrax meningitis.

Before you receive ANTHIM, tell your healthcare provider about all of your medical conditions, including if you are:

- allergic to obiltoxaximab or any of the ingredients in ANTHIM. See the end of this leaflet for a list of ingredients in ANTHIM.
- allergic to diphenhydramine (Benadryl[®])
- pregnant or planning to become pregnant. It is not known if ANTHIM will harm your unborn baby.
- breastfeeding or plan to breastfeed. It is not known if ANTHIM passes into your breast milk. You and your healthcare provider should decide if you will receive ANTHIM or breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive ANTHIM?

- You will be given 1 dose of ANTHIM by a healthcare provider through a vein (IV or intravenous infusion). It takes about 1 hour and 30 minutes to give you the full dose of medicine.
- Your healthcare provider should give you a medicine called diphenhydramine (Benadryl[®]) before you receive ANTHIM to help reduce your chances of developing a skin reaction from ANTHIM. Benadryl may be given to you to take by mouth or through a vein.
- Benadryl may make you sleepy, and you should use caution if you will be driving or operating equipment.

What are the possible side effects of ANTHIM?

The most common side effects of ANTHIM include headache, itching, upper respiratory tract infections, cough, IV site bruising, swelling and/or pain, stuffy nose (nasal congestion), hives, and pain in the hands or feet.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of ANTHIM. For more information, ask your healthcare provider.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. For more information go to **dailymed.nlm.nih.gov**.

General information about the safe and effective use of ANTHIM.

- This patient information leaflet summarizes the most important information about ANTHIM. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about ANTHIM that is written for health professionals.

What are the ingredients in ANTHIM?

Active ingredient: Obiltoxaximab

Inactive ingredients: L-histidine, sorbitol and polysorbate 80

Manufactured by: Elusys Therapeutics, Inc., Pine Brook, NJ 07058, U.S. License Number 1907

For more information call 1-844-808-0222

The Patient Information has been approved by the U.S. Food and Drug Administration

03/2016

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NDC 69604-204-02 Rx only

Rx only

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**For Intravenous Infusion
Must Be Diluted Prior To Use**

Single-Dose Vial. Discard unused portion

No Preservative.
No U.S. Standard of Potency.

REFRIGERATE: Store at 2° to 8°C (36° to 46°F).

DO NOT FREEZE
DO NOT SHAKE

PROTECT FROM LIGHT
by storing in original package until use.

Rx only

600 mg/6 mL
(100 mg/mL)

**For Intravenous Infusion
Must Be Diluted Prior To Use**

Single-Dose Vial. Discard unused portion

DOSAGE AND ADMINISTRATION:
See prescribing information for
dilution and dosage information.

For additional information about
Anthem, call 1-844-808-0222.



Manufactured by:
Elusys Therapeutics, Inc.
Pine Brook, NJ 07058
U.S. License Number 1907

RM-3450 Rev. 000

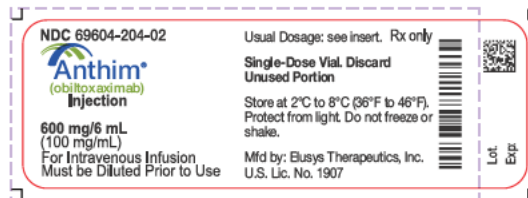
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/s/

EDWARD M COX
03/18/2016