ADDENDUM FOR THE CLINICAL PHARMACOLOGY REVIEW

BLA:	125509
Submission Date(s):	03/20/2015
Brand Name:	Anthim®
Generic Name:	Obiltoxaximab
Primary Reviewer:	Zhixia (Grace) Yan, Ph.D.
Team Leader:	Kimberly L. Bergman, Pharm.D.
PM Reviewer:	Fang Li, Ph.D.
PM Team Leader:	Jeff Florian, Ph.D.
OCP Division:	DCP4
OND Division:	DAIP
Applicant:	Elusys Therapeutics, Inc.
Submission Type; Code:	Original BLA submitted under 21 CFR 601.90
Formulation; Strength(s):	Injection for intravenous use; 600 mg/6 mL (100 mg/mL) solution in single-dose vial
Indication	Anthim is indicated in adult and pediatric patients for: • Treatment of inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial drugs. • Prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate.

BACKGROUND

Elusys Therapeutics, Inc. submitted a biologic license application (BLA) for Anthim® (obiltoxaximab) for the 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 current BLA for obiltoxaximab seeks approval under the "Animal Efficacy Rule" (21 CFR 601.90 "Approval of Biological Products when Human Efficacy Studies are not Ethical or Feasible"). The effectiveness of Anthim is based solely on efficacy studies in animal models of inhalational anthrax. The recommended dose of Anthim in adult patients is a single dose of 16 mg/kg administered intravenously over 90 minutes and pre-medicated with diphenhydramine prior to dosing. 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. 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)

Pediatric Body Weight	Pediatric Dose
Greater than 40 kg	16 mg/kg
Greater than 15 kg to 40 kg	24 mg/kg
Less than or equal to15 kg	32 mg/kg

The following analytical inspection summary and labeling recommendations are provided as an addendum to the Clinical Pharmacology Review (DARRTS dated 12/07/2015).

ANALYTICAL INSPECTION SUMMARY

At the request of the review team, analytical inspections of 12 nonclinical and clinical studies were conducted by the Division of New Drug Bioequivalence Evaluation (DNDBE) in the Office of Study Integrity and Surveillance (OSIS). A Form FDA 483 was not issued at the close-out of the inspections for the clinical studies (see the Review of establishment inspection reports (EIRs), covering BLA 125509 dated 2/14/16 in DARRTS). However, a five-item Form FDA 483 was issued at the close-out for the nonclinical studies. The final classification for this inspection is voluntary action indicated (VAI). Following the evaluation of the inspectional findings and the firm's response to the Form FDA 483, the analytical data from the audited studies were found to be reliable. Therefore, it was recommended that the analytical data from the nonclinical and clinical studies be accepted for review by the Agency with certain limitations, as follows (see the Analytical Inspection Report for details in DARRTS dated 1/15/2016):

Nonclinical Studies (AP116, AP202, AP203, AP204, and AP301):
1. Reassessing validation and study data without background subtraction in the confirmatory assay may provide a more specific assay.
2. Reassessing validation and study data with a statistically calculated confirmatory cut point may provide a more specific method.
3. Pre-dose samples that test positive for anti-drug antibodies should be evaluated for the presence of interfering anthrax molecules that may skew assay results.

The Clinical Pharmacology Review Team reviewed the Analytical Inspection Report and concluded that the limitations described in this report are not expected to affect obiltoxaximab pharmacokinetics observed in nonclinical and clinical studies.

LABELING RECOMMENDATIONS

Sponsor's draft label version: 03/20/2015

The following proposed package insert has been marked by revisions made by the Reviewer, indicated with ~~red strikethrough font~~ for deleted text and underlined blue font for inserted text. Affected sections include **Highlights, Indications and Usage (1**), **Dosage and administration (2), Drug Interactions (7), Use in Specific Populations (8), and Clinical Pharmacology (12).**

17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

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03/02/2016

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03/02/2016