

OBE/DE Review Memo

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To: Michael Kennedy, PhD, Chair, BLA Review Committee
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FDA STN: BLA 125488

Subject: Review of the Pharmacovigilance plan (PVP) for Anavip®, Crotalidae (pit viper) Immune F(ab')₂ (Equine) Injection

Applicant: Instituto Bioclon (Manufacturer), Rare Disease Therapeutics, Inc. (RDT) (US marketing partner)

Product: Anavip®, Crotalidae (pit viper) Immune F(ab')₂ (Equine) Injection

Proposed Indication: Management of patients with North American crotalid envenomation regardless of severity, including the prevention of late or recurrent coagulopathies

Submission Type: Original BLA

BLA Number: STN 125488

Submitted to FDA: 125488/0.0 (Original application) - March 16, 2013
125488/0.4 (PVP version 1.0) - April 11, 2013

First Action due: March 18, 2014

Material reviewed: Sections within BLA 125488/0.0 pertaining to the pharmacovigilance plan (PVP) version 1.0 and 125488/0.4

1. Introduction

a. Pit Viper Envenomation

Pit viper envenomation is an Orphan Disease that affects less than 8,000 patients annually in the United States. Symptoms around the bite site emerge within 30 to 60 minutes after most pit-viper envenomations, and consist of pain, edema, erythema, or ecchymosis. Systemic effects include nausea, vomiting, weakness, coagulopathy, hypofibrinogenemia, thrombocytopenia, myotoxicity resulting in rhabdomyolysis or compartment syndrome, hypotension, tachypnea, respiratory distress, severe tachycardia, and altered sensorium. Prior to the availability of antivenom, fatality rates were as high as 35%. With antivenom and modern medicine, fatality rates are less than 1% (2.6% mortality without antivenom and 0.28% with antivenom therapy (PVP 3)).

Portions of this memo taken directly from the sponsor submission are in italics.

b. Product information

Anavip® [Crotalidae (Pit-Viper) Immune F(ab')₂ (Equine) Injection] is a sterile, nonpyrogenic, lyophilized, polyvalent preparation of equine immune globulin F(ab')₂ fragments, manufactured from plasma of horses immunized with venom of Bothrops asper and Crotalus durissus. The product is obtained by pepsin digestion of horse plasma to remove the Fc portion of immune globulin, followed by fractionation and purification steps. The F(ab')₂ content is not less than 85%, F(ab) content is not more than 7%, and the product contains less than 5% intact immunoglobulin. Each vial of Anavip® contains 25.2-56.8 mg of sodium chloride, 18.2-85.8 mg of sucrose, and 16.2-51.8 mg of glycine as stabilizers. Trace amounts of pepsin, cresol (< 0.99 mg/vial), borates (<1 mg/vial), and sulfates (<1.7 mg/vial) may be present from the manufacturing process. Each vial contains no more than 120 mg of protein and will neutralize no less than 780 times the LD50 of Bothrops asper venom and 790 times the LD50 of Crotalus durissus venom in a mouse neutralization assay (proposed product insert 6).

c. Regulatory history

The original BLA application was submitted on March 16, 2013. There are currently two approved products to treat pit viper envenomation in the US: Wyeth Polyvalent Crotalidae Antivenom and Crofab®. The Wyeth product is no longer being produced and distributed. Since its introduction in 2000, Crofab® has become the standard of care for treatment of snakebites.

Crofab® is manufactured by BTG International Inc., and it is a sterile preparation of ovine Fab (monovalent) immunoglobulin fragments obtained from the blood of healthy sheep flocks immunized with one of the following North American snake venoms: *Crotalus atrox* (Western Diamondback rattlesnake), *Crotalus adamanteus* (Eastern Diamondback rattlesnake), *Crotalus scutulatus* (Mojave rattlesnake), and *Agkistrodon piscivorus* (Cottonmouth or Water Moccasin). Compared to whole IgG antivenom, Crofab contains antibody fragments with 1 antigen binding site (Fab) and the Fc portion of the immunoglobulin removed, which results in a decreased rate of hypersensitivity reactions.

Anavip® is the proposed Tradename for the US. The active ingredient in Anavip is predominantly F(ab)₂ molecules, which are antibody fragments with 2 antigen binding sites and the Fc portion of the immunoglobulin molecule removed. The larger size of a F(ab)₂ molecule, when compared to a Fab molecule, results in an increased circulation time due to decreased renal clearance. This results in lower rates of recurrent coagulopathy from hypofibrinogenemia and thrombocytopenia caused by the presence of circulating crotaline venom. Additionally, like Crofab, Anavip® produces fewer adverse reactions than seen with whole immunoglobulin due to the elimination of the Fc portion of the immunoglobulin molecule. This product has been registered in Mexico under the name Antivipmyn® since 1984, and has been available in US and European zoos. Approximately (b) (4) vials were sold in Mexico between 2004 and 2012, with an estimate of 25,000 snakebite patients treated with Antivipmyn® in the past nine years (based on manufacturers' distribution data). The company did not receive any report of possible adverse events until 2012.

Review of an English translation of the Antivipmyn® product insert confirmed its similarity to Anavip®.

d. Proposed Indications, Contraindications, Warnings and Precautions

Anavip® is an antivenom indicated for the management of patients with North American crotalid envenomation regardless of severity, including the prevention of late or recurrent coagulopathies. Early use of Anavip® is advised to prevent clinical deterioration and the occurrence of systemic coagulation abnormalities. Antivipmyn®, the equivalent product in Mexico, is indicated for the treatment of snake bites from: *Crotalus durissus*, *Crotalus atrox*, *Crotalus scutulatus*, *Bothrops asper*.

e. Blood Product Advisory Committee (BPAC) meetings

This product has not been presented to a BPAC, and it is not scheduled to be presented.

f. Objectives of the review

The purpose of this review is to identify potential safety issues that may need to be addressed through postmarketing safety surveillance or studies if the product is licensed. This entails determining whether the sponsor's proposed PVP is adequate to monitor the safety of the product after licensure, and is in accordance with FDA regulations.

2. Materials reviewed

- a. PVP version 1.0 (125488/0.4)
- b. Pertinent sections of the original application (125488/0.0 sections 1.16 and 2.74 (Integrated Summary of Safety (ISS)) , 125488/0.15 sections on the natural history of snake bites and "Experience in the management of patients with snakebites in the Tampico General Hospital," 125488/0.22 information request response for English Antivipmyn® product insert and further information on allergic reactions)
- c. CBER's clinical review (when available, date) and statistical review (when available, date)
- d. Medical literature

3. PVP review

- a. Safety database

U.S. Clinical Studies					
Clinical Study Number	Type	Number of Patients	IND #	Phase	CSR
AN 03/02	Randomized, Prospective, Open-Label, Controlled, Comparative, Multicenter Study, U.S.	6 Anavip/Anavip 6 CroFab/CroFab	11,275	2	YA-C-01
YA 07/02	Randomized, Prospective, Blinded, Controlled, Comparative, Multicenter Study, U.S.	43 Anavip/Anavip 41 CroFab/CroFab 37 Anavip/Placebo	11,275	3	YA-C-02
Foreign Clinical Studies					
YA 06/07	Healthy Volunteer, Safety, Pharmacokinetic Study, Mexico	14 Anavip	11,275	1	YA-C-08

A total of 147 patients received an antivenom in clinical trials (100 Anavip® or Antivipmyn®, and 47 Crofab®). The sponsor conducted two clinical trials in the U.S.: one was a randomized, open-label comparison with Crofab® (AN-03/02); the other was a three way, randomized, blinded comparison of: initial dosing of Anavip® with

maintenance dosing of Anavip®; initial dosing of Anavip® with maintenance dosing of a saline placebo; and initial dosing of Crofab® with maintenance dosing of Crofab®. Patients were enrolled in the studies if they presented for emergency treatment with clinically important signs of pit viper (crotaline) snakebite envenomation (YA-07/2). In both trials, subjects received an initial dose of 10 vials of Anavip® or 5 Crofab® vials. Maintenance dosing was 4 vials every 6 hours of Anavip, 2 vials every 6 hours of Crofab®, or 4 vials of saline in the Anavip/placebo arm of YA-07/2. This dosing regimen was repeated every 6 hours, for a total of 3 maintenance doses. Additional dosing, consisting of 4 vials of Anavip® or 2 vials of Crofab®, could be administered at the investigator's discretion. Dosing for Crofab® adheres to suggested dosing according to the package insert. The 2:1 vial ratio is necessary because two vials of Anavip® have less protein than one vial of Crofab®.

The amount of antivenom that is administered to an individual patient is directly related to the severity of envenomation, and may be related to weight. The Antivipmyn® product insert recommends higher doses in children than adults due to a greater concentration of venom per kilogram, but the proposed Anavip® product insert and the Crofab® insert recommend the same initial dosing for adults and children, and additional dosing based on the level of envenomation.

US Clinical Studies

1. **AN-03/02** (n=12) was designed to assess the safety and efficacy of Anavip® compared to Crofab®. Patients ranged in age from 22 to 63. Half of the subjects (n=6) received 22 to 52 vials of Anavip® compared to the other half (n=6) who received 11 to 28 vials of Crofab®.
2. **YA-07/02** (n=121) was designed to assess the safety and efficacy of Anavip® compared to Crofab® and placebo. Subjects receiving initial doses of Anavip® were randomized to maintenance with either Anavip® (ANA/ANA) or Placebo (ANA/PBO), while other patients received Crofab® initially and for maintenance (CRO/CRO). Patients ranged in age from 2 to 80. Forty-three ANA/ANA subjects received 22 to 46 vials, while 37 ANA/PBO subjects received 10-38 vials, 41 CRO/CRO subjects received 5 to 38 vials of Crofab®. The ANA/PBO arm was created to assess the longer half-life of Anavip and demonstrate its sustained efficacy and lack of persistent venom antigenemia previously reported in Crofab recipients.

Foreign Study

1. YA-06/07 (N=14) examined safety of Antivipmyn® in 14 healthy subjects. One vial of Antivipmyn® (Anavip® equivalent marketed in Mexico) was administered intravenously over 30 minutes on Day 1 and Day 21 to 14 healthy, normal volunteers in a pharmacokinetic study. Five subjects experienced Adverse Events (AEs), none of which were serious or considered related to the study drug (e.g. 2 subjects reported influenza illness). Only one of these subjects had symptoms that could have been due to an allergic reaction (pruritus).

Table 5.3.1 from page 19 of ISS

Table 5.3.1. Summary of Adverse Events (AEs)

Protocol Number(s)	YA-06/07	YA-07/02 & AN-03/02		YA-07/01
	Antivipmyn Normal Volunteers N=14	Anavip Patients N=86	CroFab Patients N=47	Antivipmyn Patients N=26
Subjects with ≥ 1 AE	5 (36%)	65 (76%)	39 (83%)	13 (50%)
Subjects who withdrew due to an AE	0	0	0	1 (7.7%)
Subjects with SAEs	0	7 (8.1%)	4 (8.5%)	4 (31%)
Subject deaths	0	1 (1.2%)	0	1 (7.7%)
Subjects with ≥ 1 AE by intensity ¹				
Mild	1 (7.1%)	43 (50%)	19 (40%)	9 (35%)
Moderate	4 (29%)	15 (17%)	16 (34%)	3 (12%)
Severe	0	7 (8.1%)	4 (8.5%)	1 (3.8%)
Subjects with ≥ 1 AE by relationship to study drug ¹				
Definitely related	0	5 (5.8%)	1 (2.1%)	1 (3.8%)
Possibly related	0	20 (23%)	17 (36%)	5 (19%)
Not related	5 (36%)	39 (45%)	21 (45%)	7 (27%)
Not assessable	0	1 (1.2%)	0	0
Reports (i.e., AEs)				
Number of AE reports	10	234	181	23
Number of SAE reports	0	7	6	4
Number of AEs considered definitely related to study drug	0	7	2	5

¹ Note: Only the adverse event with the highest intensity or the closest relationship is considered when a patient reported more than 1 adverse event.

SAE = Serious adverse event

Source: ISS Tables 4.1, 4.2; Sponsor (data on file)

AE review

Data on specific Adverse Events (AEs) are presented cumulatively for the two US clinical trials. The safety profiles of Anavip® (ANA/ANA and ANA/PBO) and Crofab® (CRO/CRO) were similar; pruritus was the most frequently reported AE (55% vs. 60% respectively), followed by nausea (23% vs. 21%).

Overall, 76% (65/86) of Anavip® patients reported at least one adverse event (AE) compared to 83% (39/47) of CroFab® patients; 36% (5/14) of normal volunteers and 50% (13/26) of Phase 4 patients receiving Antivipmyn reported an AE (ISS 15).

Relatedness

Per the sponsor's assessment, AEs occurring in greater than 5% of any study population are considered related to the treatment (See table 5.3.2.1) *.

For Anavip, 5 patients had AEs that were considered "definitely" related to treatment; 4 of these 5 subjects had hypersensitivity reactions ranging from pruritus to anaphylactoid reaction. The fifth case experienced nausea. One Crofab® subject had a "definitely" related anaphylactoid reaction.

Two patients required dose interruptions due to AEs that were potentially treatment related: one in the ANA/PBO arm due to hypersensitivity/anaphylaxis, and one Crofab® patient due to hypotension and nausea.

In addition, one Anavip®/Placebo patient and 2 CroFab® had adverse events that the investigator coded as "Not assessable". An additional 23% of Anavip®-treated patients and 36% of CroFab®-treated patients experienced AEs that were considered "Possibly" related to study drug (ISS 16).

Specific populations

The Anavip® pediatric patients reported similar or lower incidences of most AEs than the adult patients. Pediatric patients did not have any AE reports associated with coagulopathy or immune response. The

* Note: Given the small number of subjects in pre-market clinical trials, the Medical Reviewer agrees this is a reasonable approach for identifying AEs that occur at a greater frequency, but this is not sufficient for identifying rare AEs that may still be associated with the product. In these cases the severity of individual reports and the biological plausibility of association were individually assessed by the DE reviewer.

sample size of patients more than 65 years of age was small, making comparisons difficult. There were no consistent patterns of adverse events with respect to gender, body weight, or race (ISS 17)

Severe AEs

In all treatment groups, over half of AEs were of mild or moderate severity, and severe AEs accounted for 10% or less of events.

Eleven patients in the controlled Anavip® vs. CroFab® studies (5 Anavip®/Anavip®, 2 Anavip®/Placebo, 4 CroFab®) had adverse events that were considered to be of severe intensity. Ten of the 11 events were considered “Not related”. The remaining event, leg swelling, was considered “Possibly” related to Anavip®; however, the investigator later wrote a note to file that the AE was due to the envenomation (ISS 16).

Review of these serious AE reports revealed no unrecognized, new AEs that are potentially related to receipt of Anavip, instead, AEs were most likely related to envenomation.

Table 5.3.2.1 from page 21 of ISS

Table 5.3.2.1. Adverse Events Reported in >5% Patients in any Treatment Group in Anavip vs. CroFab Studies YA-07/02 and AN-03/02 (Safety Population)

	ANA/ANA N=49	ANA/PBO N=37	Overall Anavip N=86	CroFab N=47
Patients Reporting at Least One Adverse Event	41 (84%)	24 (65%)	65 (76%)	39 (83%)
Skin and subcutaneous tissue disorders	30 (61%)	17 (46%)	47 (55%)	28 (60%)
Pruritus	24 (49%)	13 (35%)	37 (43%)	26 (55%)
Rash	6 (12%)	4 (11%)	10 (12%)	8 (17%)
Blister	2 (4.1%)	2 (5.4%)	4 (4.7%)	0
Erythema	3 (6.1%)	0	3 (3.5%)	2 (4.3%)
Gastrointestinal disorders	19 (39%)	9 (24%)	28 (33%)	17 (36%)
Nausea	14 (29%)	6 (16%)	20 (23%)	10 (21%)
Vomiting	2 (4.1%)	3 (8.1%)	5 (5.8%)	3 (6.4%)
Musculoskeletal and connective tissue disorders	12 (24.5%)	7 (19%)	19 (22%)	14 (30%)
Arthralgia	6 (12%)	3 (8.1%)	9 (10.5%)	8 (17%)
Myalgia	4 (8.2%)	2 (5.4%)	6 (7.0%)	8 (17%)
Pain in extremity	2 (4.1%)	3 (8.1%)	5 (5.8%)	2 (4.3%)
General disorders and administration site conditions	13 (26.5%)	8 (22%)	21 (24%)	8 (17%)
Oedema peripheral	3 (6.1%)	4 (11%)	7 (8.1%)	0
Chills	3 (6.1%)	0	3 (3.5%)	3 (6.4%)
Pyrexia	3 (6.1%)	1 (2.7%)	4 (4.7%)	0
Nervous system disorders	8 (17%)	4 (11%)	12 (14%)	9 (19%)
Headache	5 (10%)	0	5 (5.8%)	5 (11%)
Psychiatric disorders	3 (6.1%)	1 (2.7%)	4 (4.7%)	7 (15%)
Anxiety	1 (2.0%)	1 (2.7%)	2 (2.3%)	4 (8.5%)
Insomnia	2 (4.1%)	0	2 (2.3%)	3 (6.4%)
Metabolism and nutrition disorders	4 (8.2%)	0	4 (4.7%)	5 (11%)
Dehydration	2 (4.1%)	0	2 (2.3%)	3 (6.4%)
Respiratory, thoracic and mediastinal disorders	4 (8.2%)	1 (2.7%)	5 (5.8%)	3 (6.4%)
Dyspnoea	1 (2.0%)	0	1 (1.2%)	3 (6.4%)
Blood and lymphatic system disorders	2 (4.1%)	0	2 (2.3%)	6 (13%)
Thrombocytopenia	1 (2.0%)	0	1 (1.2%)	3 (6.4%)

Source: ISS Table 5.1

Hypersensitivity/allergic AEs

From clinical studies and spontaneous reports, *Anavip related adverse events are type 1 and type 3 hypersensitivity reactions (acute allergic and serum sickness), whereas adverse reactions assessed as not being related to Anavip are venom effect of the snakebite (PVP 5).*

Twelve patients had serum sickness, anaphylaxis, or hypersensitivity reactions. Four patients had serum sickness, 2 receiving Anavip® and 2 receiving Crofab®, all recovered. Four patients had anaphylaxis, 3 with Anavip, and one with Crofab®, all recovered. The cases of anaphylaxis responded well to treatment, and symptoms resolved promptly, with three patients completing treatment with the antivenom. Four patients had milder hypersensitivity reactions such as urticaria and itching, 3 of these received Anavip, while one received Crofab®. All of their symptoms resolved. Rates of allergic reactions in all three treatment arms were comparable.

AE data collection focused on signs of serum sickness showed that rates for the AE terms pruritus, arthralgia, rash, and serum sickness were lower for Anavip® compared to Crofab® (ranged from 2.3 to 43% compared to 4.3 to 53%, respectively; no p values were provided).

Deaths

There was one death in the clinical studies, but this was not due to treatment. This patient was in the ANA/ANA arm; he was discharged from the hospital following treatment, but died on study day 5 in a motor vehicle accident.

i. Phase 4 Study YA-07/01

This is an ongoing Phase 4 study in Mexico comparing two dosing regimens of Antivipmyn® (Anavip's equivalent in Mexico). This study was a randomized, open-label trial, and limited data are currently available. Treatment Arm A received 20 vials of Antivipmyn® in one dose, while treatment Arm B received 4 doses of 5 vials of Antivipmyn® every 2 hours. Additional dosing of 5 or 10 vials of Antivipmyn® could be administered at the investigator's discretion. The study had 26 subjects when the original submission was written. Fifty percent of these patients (13) reported AEs, and 4 were serious, but only one of these was not attributable to envenomation. This case resulted in a death, and is reviewed below. All other AEs were of mild or moderate severity. Limited data from the study was presented in the integrated summary of safety report, and the number of patients with allergic reactions is not provided.

Death report: 7 year old male, who was admitted to the hospital in Mexico with grade 3 snakebite envenomation. His initial presentation included extensive ecchymosis and swelling of the bitten leg, and spontaneous bleeding of the gums. He was randomized to Treatment Arm B of the Phase 4 study. After the second dose of Antivipmyn®, the patient developed rash and hypotension, which was successfully treated with intravenous antihistamines and corticosteroids. During the third infusion, the patient again developed rash and hypotension, along with pruritus and amaurosis. The infusion was discontinued and the patient again received intravenous antihistamines and corticosteroids. A fourth dose of Antivipmyn® was administered and the spontaneous bleeding had stopped and the local lesion had ceased to progress. Approximately 16 hours after the first dose of Antivipmyn®, the local lesion worsened, and the patient underwent a fasciotomy for compartment syndrome. He also received fresh frozen plasma, platelets, and red blood cell transfusions. Despite the surgery and the transfusions, his envenomation worsened, with signs of hypovolemia. The patient then was given 15 vials of another equine-based snake antivenom, Birmex. Anaphylactic shock ensued, and the patient died despite CPR and treatment with intravenous vasopressors (epinephrine, dobutamine, and atropine). Death occurred 31 hours after the patient was admitted to the hospital.

b. Safety concerns

i. Important identified safety issue: Allergic reactions

The most frequently reported serious AEs following receipt of Anavip® are allergic reactions; this is consistent with the observed AEs associated with other previously licensed antivenoms. These reactions include anaphylactic reactions, serum sickness and hypersensitivity reactions. These reactions were observed in the clinical trials, but

rates of allergic AEs were lower than in the arm receiving the currently approved antivenom, Crofab® (p-values comparing the rates were not available).

Only one death was potentially attributable to Anavip, and this was observed in the phase 4 study for Antivipmyn® in Mexico. The death was due to severe envenomation, and presumed anaphylaxis secondary to the administration of another antivenom (non-U.S. licensed Birmex) prior to the anaphylaxis episode, attribution to Antivipmyn®/Anavip® is unlikely.

ii. Important potential safety issue: Myalgia due to Cresol

The Chemistry, Manufacturing, and Controls (CMC) review of the Anavip® submission identified a higher specification limit for Cresol than is utilized for a similar product, the scorpion antivenom, Anascorp®. This compound is utilized as (b) (4) and is also present in insulin injections, although the amount in an expected dose of Anavip® is greater than in the usual daily dose of insulin, per the CMC review.

Anavip® use is not chronic, so its Cresol content would cause Acute AEs, and myalgia is the AE of concern. Data comparing the rate of myalgias in the clinical studies demonstrated a lower rate of this AE in Anavip when compared to Crofab (8.2% and 5.4% vs. 17%).

The CMC reviewer has (b) (4)

iii. Important missing information

Patients between the ages of 2 to 80 years old were enrolled in pre-approval clinical studies; no safety information is available for infants and children less than 2 years of age. In addition, no safety information is available for pregnant patients. Due to the rarity of crotaline envenomation, the morbidity and mortality associated with these bites, and the lack of a hypothesis suggesting a greater risk in these populations, specific studies in these populations are not warranted at this time.

c. Sponsor proposed action and timeline

The sponsor proposes to carry out routine or standard pharmacovigilance activities which include:

- *Passive surveillance comprised of the receipt of AEs from various sources (spontaneous, literature, etc.) collected in a centralized and validated company safety database.*
- *Reception, verification, and follow-up of AEs.*
- *Identification of unexpected, serious and special cases (occurring during pregnancy and lactation).*
- *Reporting of AEs to FDA as required by regulations, including the reporting of 15-Day expedited serious and unexpected AEs to FDA*
- *Training staff in pharmacovigilance practices.*
- *Preparation of periodic safety reports as required by regulations.*
- *Searches of AE reports in the scientific literature.*
- *Signal detection, trending, and analysis of all AEs reported will be performed by the Risk Management and Safety Review Committee on a regular basis (PVP 13) .*

3. CBER safety review

At the time of this memo, CBER's clinical review and statistical review are not yet available.

4. Postlicensure Safety Review

Anavip® is an original BLA in the US, but this product has been used in Mexico under the name Antivipmyn®. The sponsor has received very few AE reports globally with less than 30 reports since 2004 including: generalized rash (11), pruritus (5), edema (4), erythema (2) and one each of angioedema, bradycardia, facial erythema, facial flushing, forearm rash, palpebral edema, and uvular edema. These AE reports do not indicate any new safety concerns as these AEs are similar to those reported in the clinical trials, and represent conditions of limited

morbidity when compared to the potential harms associated with envenomation. These AEs may not completely characterize possible adverse reactions, however, as passive surveillance frequently collects less AEs than may actually occur due to its voluntary reporting.

In addition, an ovine-derived crotaline antivenom, Crofab®, is currently approved in the US. Review of FDA collected post-licensure data in FAERS for this antivenom, identified no new safety concerns.

Review of the medical literature did not reveal any new safety issues.

5. Integrated risk assessment

Most AEs associated with administration of Anavip® are mild or moderate in nature. The most frequently reported AEs are pruritus and nausea. Many of the other reported AEs (e.g. bruising, bleeding) are expected sequelae of crotaline envenomation. These events are listed in the proposed package insert that was submitted as part of this BLA.

Allergic reactions, anaphylaxis, serum sickness and hypersensitivity reactions, are well-characterized and recognized serious AEs associated with heterologous immune globulins. These reactions are listed in the proposed package insert submitted as part of this BLA, and occur at a potentially lower rate than the already FDA-approved crotaline antivenom, Crofab®, but statistical comparisons of rates of AEs were not made. Routine pharmacovigilance is sufficient to monitor these AEs.

Cresol content in Anavip® is potentially higher than levels expected in another antivenom product from the same company. The acute AE, myalgia, is of concern, and the CMC reviewer (b) (4), routine pharmacovigilance is sufficient to monitor this adverse event, as: rates are lower in the Anavip arms of clinical trials when compared to Crofab; the risk-benefit when considering envenomation favors treatment with Anavip, the AE and association with cresol is conveyed in the product insert; and this AE would be difficult to evaluate given confounding due to the indication being treated, i.e. association of crotaline envenomation with rhabdomyolysis and compartment syndrome.

Data submitted by the sponsor as part of the application, available published medical literature, and data collected by CBER for similar products identified no new safety concerns.

Final determination of the safety profile of the product used in the studies submitted to this BLA is pending the final clinical, statistical and product reviews.

	Conditions	Action Plan
Identified Risks	Hypersensitivity reactions (e.g. serum sickness, anaphylaxis)	<ul style="list-style-type: none">• Routine pharmacovigilance• AEs are mentioned in the warnings and precautions portion of the proposed product insert
Potential Risks	Myalgias due to Cresol	<ul style="list-style-type: none">• Routine pharmacovigilance• AE is mentioned in the warnings and precautions portion of the proposed product insert
Missing Information	Children less than 2 years old	<ul style="list-style-type: none">• Routine pharmacovigilance

6. Recommendations

Based on the review of the pre-licensure safety data and the sponsor's PVP, OBE/DE recommends the following routine safety surveillance activities:

- 1) Routine pharmacovigilance: Adverse event reporting in accordance with 21 CFR 600.80