

**Final Review Memorandum: Anascorp
OBE/DE Review for Pharmacovigilance Planning**

Subject : BLA STN 12533/0
Centruroides (Scorpion) Immune F(ab)₂ Intravenous (Equine), Instituto Bioclon
S.A. de C.V.
OBE/DE Final Review Memorandum

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Background

OBE/DE has completed an interim review of BLA STN 12533/0 for *Centruroides* (Scorpion) Immune F(ab)₂ Intravenous (Equine), Instituto Bioclon S.A. de C.V, hereafter referred to as Anascorp. The purpose of the review was to identify potential safety issues that may need to be addressed through post-marketing safety monitoring, studies, or other pharmacovigilance activities, should the product be licensed.

Centruroides (Scorpion) Immune F(ab)₂ Intravenous (Equine) is indicated for the management of patients with clinically important signs of scorpion envenomation. The proposed proprietary name is Anascorp®, and the proposed non-proprietary name is *Centruroides* (Scorpion) Immune F(ab)₂ Intravenous (Equine). In Mexico, the proprietary name is Alacramyn®.

Disease

Within North America, stings from *Centruroides* scorpions are found primarily in Southeastern California, Arizona, Nevada, Southern Utah, parts of New Mexico and in the western third of Mexico.¹ As of November 2008, a total of 13,000 stings have been reported in the USA, with the majority from the nonlethal scorpions; only 1 of 30 scorpion species found in the United States is dangerous to humans.² Sequelae can range in severity from trivial to life-threatening. Venom effects are caused by modification of cell membrane ion channels which results in the release of modulators and neurotransmitters, initiating cascades of immunological and inflammatory factors. These cascades can result in neuromotor hyperactivity, pulmonary edema, respiratory compromise, and occasionally death (Vol 21, pg 12).

Current therapy consists of supportive care that may include high doses of sedation administered in an intensive care setting (ICU) and prolonged hospitalization. Since scorpion stings often

¹ Curry SC, Vance MV, Ryae PJ, et al: Envenomation by the scorpion *Centruroides sculpturatus*. *J Toxicol Clin Toxicol* 1984;21:417-449.

² Cheng D, Dattaro JA, Yakobi R. Scorpion Envenomation [Internet]. Omaha: eMedicine; 2009 [updated 2007 Nov 8; cited 2009 Jul 17]. Available from: <http://emedicine.medscape.com/article/168230-overview>

occur in rural areas far from ICU facilities, a safe therapy is needed to treat patients in a timely manner and avoid clinical deterioration that can occur as a patient is being transported to a tertiary care facility (Vol 21, pg 12).

Product

Anascorp is an antivenom intended for intravenous infusion to patients presenting with scorpion envenomation. It contains Centruroides scorpion venom-specific binding antibody fragments, enzymatically derived from equine antiscorpion immunoglobulin. The antibodies are obtained from horses that have been (b)(4)immunized with venom of 4 scorpion species (*C. noxius*, *C.l. limpidus*, *C.l. tecomanus*, and *C.s. suffusus*). The antibodies are then cleaved by pepsin to form F(ab)₂ fragments. Studies using -----(b)(4)----- have shown high cross-reactivity of the Anascorp F(ab)₂ to toxins from eight different Centruroides species, including *C. exilicauda*, the most venomous species of scorpion in north America.³ At present, there is no FDA-approved agent for the treatment of systemic scorpion sting, including antivenom. This product and indication have been granted Orphan Drug Designation.

Clinical Studies

This review of clinical study data is based on the Clinical Summary (Vol 1, pg 129-146). The clinical development program of Anascorp in the United States and Mexico included 7 clinical studies of the product's safety and efficacy. Six of them are completed:

- AL-02/03: Double blind, pediatric study in Arizona, U.S.
- AL-02/04: Open label, adults in Mexico
- AL-02/05: Open label, pediatric in Mexico
- AL-02/06: Open label, pediatric in Arizona, U.S.
- AL-99/02: Open label, all patients in Mexico
- AL-03/06: Historical control in Arizona, U.S.

One of the studies is ongoing:

- AL-03/07: Open label, treatment of all patients in Arizona, U.S.

Study AL-02/03:

AL-02/03 was a prospective, randomized, double-blind, multi-centered, controlled study of Anascorp versus placebo in pediatric patients in Arizona who had systemic signs of scorpion sting envenomation. The trial included a saline placebo arm (n=7) and an Anascorp arm (n=8). Ages ranged from 6 months to 18 years old. The main purpose of this study was to demonstrate the efficacy and safety of Anascorp in the treatment of systemic manifestations of scorpion sting. Secondary endpoints were: 1) decrease in venom blood levels within 1 hour after initiation of Anascorp treatment while controls continue to have elevated venom blood levels for several hours, and 2) Anascorp-treated patients require significantly less benzodiazepine sedation for control of agitation than controls.

Male and female patients who presented for emergency treatment of clinically important systemic signs of scorpion sting envenomation within 5 hours of a scorpion sting were randomized in the

³ DesertUSA.com [Internet]. San Diego: Digital West Media, Inc.; c1996-2009 [cited 2009 Jul 17]. Scorpion Sting; [about 4 screens]. Available from: http://www.desertusa.com/oct96/scorpion_sting.html

study in a 1:1 treatment ratio of Anascorp to placebo. If pathological agitation was severe enough for the treating physician to decide that sedation was necessary, midazolam sedation was initiated. At 7 and 14 days after discharge, outcome and occurrence of any adverse events were assessed by telephone interview.

In the Anascorp recipients, 100% of patients experienced clinical resolution of symptoms within 4 hours versus 14.3% of placebo recipients. The average time from baseline until the last dose of midazolam for Anascorp patients was 22.5 minutes compared with 534 minutes for placebo patients.

No patient experienced a serious adverse event (SAE), withdrew due to an adverse event (AE), or died during the study. One patient in the placebo group and two patients in the Anascorp group experienced one or more AEs, all of which were of mild intensity. One patient experienced an AE that was considered possibly related to Anascorp during the time of the study, and three patients experienced one or more AEs that were considered not related to Anascorp. Among Anascorp recipients AEs included diarrhea and vomiting, and among the placebo group, AEs included pyrexia, respiratory acidosis, and rash. No patient had symptoms suggestive of serum sickness during follow-up calls seeking signs of delayed reactions. There were no reports of acute serum reaction to Anascorp. (Vol 1, pg 129-132)

Study AL-03/06:

AL-03/06 was a retrospective control study to assess the duration of clinically important systemic signs of scorpion envenomation in the absence of antivenom treatment in pediatric patients at two hospitals in Arizona. A secondary objective was to establish the time from sting to resolution of signs of envenomation.

Hospital records at two participating sites in Arizona were reviewed for pediatric patients 6 months to 18 years old who were admitted for the management of scorpion envenomation during the period of 1990 to 2003. The study analysis included 97 cases. (Vol 1, pg 133- 135)

Studies AL-02/04, AL-02/05, and AL-02/06:

AL-02/04, AL-02/05, and AL-02/06 were open label, controlled studies of Anascorp in patients with scorpion stings. In AL-02/04 the study subjects were adult patients, and in both AL-02/05 and AL-02/06, the study subjects were pediatric patients. The objectives of these studies were to assess the resolution of clinically important systemic signs of scorpion envenomation within four hours after Anascorp treatment and to demonstrate that blood venom levels decreased within one hour following Anascorp treatment. A total of 23 adult patients and 78 pediatric patients were enrolled in the 3 studies. (Vol 1, pg 136-139)

According to the sponsors, in over 90% of patients evaluated, Anascorp treatment effectively reduced circulating scorpion venom by 90% or greater within one hour of administration. Baseline signs and symptoms of envenomation and subsequent sequelae at time of discharge were effectively reduced by Anascorp in 100% of the patients. (Vol 1, pg 139)

No deaths or SAEs were associated with Anascorp administration. Of the intention to treat (ITT) population, 20% (20/101) experienced at least one AE, and only 3% (3/101) had an AE that was considered to be possibly related to the study drug. One AE was considered to be moderate in severity and possibly related to Anascorp administration. The most frequent AEs were reported only in pediatric patients: pyrexia (4%), vomiting (3%). No patient had any sign of acute hypersensitivity reaction or possible serum sickness. There was no clinically significant laboratory abnormality. (Vol 1, pg 138-139)

Study AL-99/02:

AL-99/02 was a randomized, double-blind, variable dose comparison conducted in Mexico of Anascorp versus Birmex, an antivenom produced by the Mexican government, in patients with scorpion sting.

Nearly all patients experienced clinical recovery within 3 hours after the start of Anascorp treatment, and 90% recovered after receiving 3 or fewer vials. Anascorp was well tolerated by the patients who participated in this study, and few AEs were reported. Out of 105 patients, only 3 Anascorp-treated patients experienced transient AEs. In this study, there were no case report forms. Therefore, no further details about the nature of these AEs are known. (Vol 1, pg 140-141)

Study AL-03-07:

Ongoing study AL-03/07 is an open treatment protocol for use of Anascorp in patients with scorpion sting envenomation in Arizona. The objective was to assess the time to resolution of systemic signs of scorpion envenomation and to evaluate the AE profile following Anascorp treatment when administered in the anticipated clinical setting. A total of 554 patients ages 0 to 90 years old with scorpion stings have been treated with Anascorp. Although all patients in the study were treated with Anascorp, the ----(b)(4)---- used to prepare Anascorp was not the same throughout the duration of the study.

13% of Anascorp-treated patients reported an AE. The most common AEs were rash (2.5%) and vomiting (2.5%). Only 1 patient who received Anascorp reported a serious AE related to treatment. (Vol 1, pg 141-144)

Safety Specification

The Sponsor's submitted Safety Specification and pharmacovigilance plan (PVP) were reviewed. Anascorp is indicated for the management of patients with clinically important signs of scorpion envenomation. It is contraindicated in patients with a known history of hypersensitivity to horse proteins unless the anticipated benefits outweigh the risks (Vol 1, pg 53). In clinical trials, age range was from 6 months to 90 years old (Vol 21, pg 110). Important identified risks include hypersensitivity and serum sickness reactions. 80% of the subjects were less than 18 years of age. Of the 27 subjects who were >65 years of age, 10 experienced an adverse event, but none was considered to be a serious adverse event (SAE). Adverse events were similar to those experienced by younger subjects, except for one patient who needed a partial pneumectomy for squamous cell carcinoma and another with a history of coronary artery disease who experienced a syncopal episode after standing up. One of the subjects had possible serum sickness.

In the clinical trials, a total of 776 subjects received Anascorp: 8 were normal volunteers, and the rest were patients who presented for emergency treatment of clinically important signs of scorpion stings. Of the 768 patients, 105 participated in study AL-99/02 where there were no case report forms, and all that is known about their AEs is that they were transient (Volume 23, p. 111). Of the remaining 663 patients, 34% reported at least one treatment-emergent AE.

No patient ceased participation in a study due to AEs. Study investigators suspected an acute allergic reaction following Anascorp use in only one patient. This patient (Patient #---(b)(4)---) developed hives on both eyelids and labored breathing 5 minutes after infusion of Anascorp had been completed. He was treated with diphenhydramine, epinephrine, and Solumedrol. Within 34 minutes of treatment, his symptoms resolved, and he was observed overnight in the ICU. The

patient was diagnosed with having had a possible acute allergic reaction to Anascorp. (Vol 21, p. 149).

Five patients who developed rash and one patient who developed pruritis were thought to have serum sickness. The most frequently reported AEs in patients treated with Anascorp were vomiting (6.9%), pyrexia (4.7%), rash (3.9%), fatigue (3.3%), pruritis (2.9%), and myalgia (2.4%). It is unclear if these symptoms were related to the envenomation, use of sedative medication, concurrent illness during the two weeks following treatment, or were a side effect of Anascorp itself. No death was reported in any study. There was no obvious pattern of AEs with increasing doses of Anascorp.

Pharmacovigilance Plan

The sponsor's pharmacovigilance plan (PVP) will utilize the same individual physicians and hospitals of southern Arizona who participated in the clinical studies. The sponsors anticipate that routine PVP practices will be sufficient to capture all incidences of AEs. The sponsor will develop a Pharmacovigilance Standard Operating Procedure and will maintain a world wide database for adverse experience reports for submission to the FDA. It will also be responsible for filing Postmarketing 15-day "Alert reports" and "Alert report" follow-up as well as preparation of Form FDA 3500A reports in compliance with 21CFR 314.80(c).

PVP Assessment and Recommendations:

Possible Safety Concerns

Immunologic Reactions

There is a risk of serum sickness or allergic reaction from use of Anascorp. Evidence for this risk includes cases of infrequent allergic type reactions in clinical studies in patients who received Anascorp. The risk would be expected with a horse antibody anti-venom product. The frequency of these reactions was low, they were mostly mild, resolved with treatment, and in some cases could be attributed in whole or in part to the envenomation itself.

Limited Randomized Study Population

The safety database in pivotal study AL02/03 was extremely small (8 patients in treatment arm and 7 patients in placebo arm) (Vol 1, p. 129). Many AEs, particularly infrequent or rare AEs, would not likely have been detected in this small study. However, the overall safety database including all open label studies was larger and consisted of a mixed age range of patients.

Special Populations

The large majority of patients included in the controlled studies were less than 18 years old (80%), ranging from less than one month to 17.5 years. Pediatric patients were essentially evenly distributed among infant/toddlers (<2 years old, 32%), toddler/early childhood (2 to 4 years, 36%), and children (5 to 17 years old, 32%). The sponsor states that the efficacy and safety of Anascorp is comparable in pediatric and adult patients.

There are limited data on elderly patients who received Anascorp. Out of the 27 who were >65 years old, 10 experienced an AE, but none was considered serious. One patient was considered to

have had possible serum sickness. AEs were similar to those experienced by younger patients, except for two patients. One was a 71 y/o male who needed a partial pneumectomy for squamous cell carcinoma. The other was a 79 y/o female with significant past medical history of coronary artery disease, hypertension, cerebrovascular accident, and hyperlipidemia. When she stood up to get a wheel chair, she became syncopal and was treated with 1 liter of IV fluids. After 1 hour of observation, she was discharged without symptoms or further sequelae.

In the BLA documents, no information was found on the safety of Anascorp in patients with pre-existing conditions, such as renal conditions, liver disease, diabetes, pregnancy, or other medical conditions.

PVP Recommendations:

1. Despite small numbers in the pivotal study, the overall safety database, including all open label studies, was large and consisted of a mixed age range of patients.
2. The relatedness of AEs to the product versus symptoms of envenomation is difficult to assess. Many reported AEs (pruritis, agitation, vomiting) are consistent with symptoms expected of envenomations.
3. The potential for immunologic adverse events exists, however, they were observed only rarely in trial patients. Immunologic reactions are included in the proposed label.
4. No additional serious safety issues have been identified from review of Anascorp's accumulated safety data. We have no recommendations for additional pharmacovigilance activities beyond those outlined in the proposed PVP at this time. Final assessment of pharmacovigilance planning needs will depend on responses to other deficiencies identified in CBER's Complete Response and review of any additional clinical data submitted in support of future evaluations of this product.