

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

BLA STN 12533/0

Centruroides (Scorpion) Immune F(ab)₂ Intravenous (Anascorp®)

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I. Introduction

OBE/DE/TBSB has completed a pharmacovigilance planning review of BLA STN 12533/0, Centruroides (Scorpion) Immune F(ab)₂ Intravenous, hereafter referred to as Anascorp®. The purpose of this review is to identify potential safety issues that may need to be addressed through post-market safety monitoring, studies, or other pharmacovigilance activities, should this product be licensed.

Product Background

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

Within North America, stings from *Centruroides* scorpions are found primarily in the southwestern United States and in the western third of Mexico. 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.

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 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.

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. noxi*, *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*. At present, the FDA has not approved any agent for the treatment of systemic scorpion sting, including antivenom. This product and indication have been granted Orphan Drug Designation.

Clinical Studies

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, USA
- AL-02/04: Open label, adults in Mexico
- AL-02/05: Open label, pediatric in Mexico
- AL-02/06: Open label, pediatric in Arizona, USA
- AL-99/02: Open label, all patients in Mexico
- AL-03/06: Historical control in Arizona, USA

One of the studies is ongoing:

- AL-03/07: Open label, treatment all patients in Arizona, USA

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) venom blood levels decrease within 1 hour after initiation of Anascorp treatment while the placebo group continues to have elevated blood venom levels for several hours, 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 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 was 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. A mean dose of 0.1 mg/kg midazolam was administered to Anascorp recipients during the first hours after initiation of study drug infusion, but in no case was sedation continued beyond the first hour of study observation. In contrast, placebo recipients received a mean of 0.3 mg/kg midazolam during the first hour and continued to

receive midazolam up to 1.8 mg/kg during the 4-hour study observation with ongoing sedation between the time of study enrollment and hospital discharge. 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. Three patients experienced one or more AEs that were considered not related to the study drug; one patient experienced an AE that was considered possibly related to Anascorp during the time of the study. 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.

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 of 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. Out of 119 cases of scorpion envenomation reviewed, 22 were eliminated for failing to meet study inclusion/exclusion criteria which left 97 cases for study analysis.

In this pediatric population, documented medically important signs of scorpion envenomation persisted for an average of 764 minutes after scorpion sting with just 4% of the cases resolved by 4 hours after hospital admission. Intensive supportive care included intravenous infusion of midazolam to control pathological agitation in the absence of therapy with antivenom. Infusion of midazolam continued for an average of 607 minutes after hospital admission. Doses of midazolam in excess of conventional use for other indications were typically used to treat the neuromotor syndrome associated with scorpion stings.

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 clinical 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.

In over 90% of patients evaluated, Anascorp treatment effectively reduced circulating scorpion venom by 90% or greater from baseline values within one hour of Anascorp administration. Baseline signs and symptoms of envenomation and subsequent sequelae at time of discharge were effectively reduced by Anascorp in 100% of the patients.

No deaths or SAEs were associated with Anascorp administration. 20% (20/101) of the intention to treat (ITT) population experienced at least one AE, and only 3% (3/101) had an AE that was

considered to be possibly related to the study drug. Of those who experienced AEs, none was an SAE, and only 1% (1/101) 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.

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.

Safety was evaluated by the following events: 1) comparing the incidence of AEs related to antivenom use, 2) the use of corticosteroids, antihistamines, NSAIDs, or epinephrine to control an AE, or 3) hospital stays beyond scorpion intoxication to treat any adverse reaction. Nearly all patients experienced clinical recovery within 3 hours after the start of treatment, and 90% recovered after receiving 3 or fewer vials of Anascorp.

Anascorp was well tolerated by the patients who participated in this study, and few AEs were reported. Out of 105 patients, only 3 who received Anascorp experienced transient AEs. In this study, there were no case report forms. Therefore, no further details about the nature of these AEs are known.

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. Because the results of this study were not blinded and because it was an open label study, no formal statistical analysis was performed.

13% of the patients who received Anascorp 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.

II. Safety Assessment

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. 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 number --- (b)(6) ---, developed hives on both eyelids and labored breathing 5 minutes after infusion of Anascorp had been completed. He was treated with IV diphenhydramine, subcutaneous epinephrine, nebulized racemic epinephrine, and IV 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.

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 (3.7%), rash (3.9%), fatigue (3.3%), pruritis (2.9%), and myalgia (2.4%). These symptoms may have been related to the envenomation and/or use of sedative medication as opposed to the Anascorp. No deaths were reported in any study. There were no obvious patterns of AEs with increasing dose of Anascorp.

III. Pharmacovigilance Planning Assessment

When a new product is marketed, the exposed population may be larger or in other ways different from the population studied in pre-approval trials. Therefore, it is important to continue surveillance for AEs even after a product has been approved for marketing. For most products, compliance with applicable post market reporting requirements under FDA regulations, or routine pharmacovigilance, is sufficient for post-marketing risk assessment. As outlined in “Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment” (<http://www.fda.gov/Cder/guidance/6359OCC.pdf>), FDA believes pharmacovigilance plans may be appropriate when: 1) Serious safety risks have been identified pre- or post- approval, 2) at risk populations have not been adequately studied. The pharmacovigilance plan is developed by a product’s sponsor and is specifically focused on detecting new safety risks and/or evaluating already identified safety risks.

Possible Safety Concerns

Immunologic Reactions

There may be 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 size of the safety database in study AL02-03 was small (8 patients in treatment arm and 7 patients in placebo arm). Many AEs, particularly infrequent or rare AEs, would not likely have been detected. However, the overall safety database including all open label studies was large and consisted of a mixed age range of patients.

Special Populations

There is 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 penectomy 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.

There is limited information on safety in patients with pre-existing conditions, such as renal conditions, liver problems, diabetes, or other medical conditions.

Pharmacovigilance Activities

There is no documentation of a pharmacovigilance plan in the original submission. A pharmacovigilance plan has been submitted as an amendment to the BLA and a review is in progress.

Conclusion

In clinical trials, Anascorp was well tolerated when administered for the treatment of scorpion envenomation. Some immunologic type reactions were noted in the studies (e.g. rash, pruritis), however, these were mild, and relatively infrequent. There are no trends observed in SAEs that would constitute a significant safety risk to patients at this time.

In addition to routine pharmacovigilance monitoring, the sponsor should consider initiating a patient registry and submitting to the FDA all serious reports of hypersensitivity and allergic reaction as expedited reports, whether or not they are considered labeled events or related to the product.

Recommendations

- The sponsor has submitted a pharmacovigilance plan as an amendment to this BLA and review of this amendment is in progress. Assessment and recommendations will be forthcoming as needed.
- Establish and maintain a patient registry for monitoring potential AEs with attention to serum sickness and hypersensitivity reactions in patients receiving Anascorp for treatment of symptoms and signs of scorpion envenomation
- As part of the PVP, the sponsor should consider submission of all serious reports of immunologic reactions such as rash, pruritis, allergic/anaphylactic reactions, as expedited reports regardless of labeling.
- The sponsor should provide a timetable for the ongoing clinical trial, AL-03/07, and expected dates that results and AE data will be provided.

Letter-ready Comments

The Division of Epidemiology of the Therapeutics and Blood Safety Branch will provide letter-ready recommendations or questions after review of the recently submitted PVP.