

## Clinical Memo Summary

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| Application Type                                 | Original Application   |
| STN  | 125488/0   |
| CBER Received Date                               | March 18, 2013   |
| PDUFA Goal Date                                  | March 18, 2014   |
| Division / Office                                | DH /OBRR   |
| Priority Review                                  | No   |
| Reviewer Name(s)                                 | Nisha Jain   |
| Review Completion Date /<br>Stamped Date         |  |
| Applicant  | Instituto Bioclon, S.A. de C.V.  |
| Established Name                                 | Crotalidae (pit viper) Immune F(ab') <sub>2</sub><br>(Equine) Injection  |
| (Proposed) Trade Name                            | Anavip   |
| Pharmacologic Class                              | Equine derived Crotalidae (Pit-Viper)<br>Immune F(ab') <sub>2</sub> antivenom  |
| Formulation(s), including<br>Adjuvants, etc      | Each vial contains no more than 120 mg of<br>protein of <i>Bothrops asper</i> and <i>Crotalus</i><br><i>durissus</i> venom<br><br>Each vial contains 25.2-56.8 mg of sodium<br>chloride, 18.2-85.8 mg of sucrose, and 16.2-<br>51.8 mg of glycine as stabilizers and trace<br>amounts of pepsin, cresol (< 0.99 mg/vial),<br>borates (<1 mg/vial), and sulfates (<1.7<br>mg/vial). |
| Dosage Form(s) and Route(s) of<br>Administration | Lyophilized Powder for Injectable<br>Suspension, Intravenous   |
| Dosing Regimen                                   | 10 vials   |
| Indication(s) and Intended<br>Population(s)      | Management of coagulopathy in patients with<br>North American pit viper envenomation   |
| Orphan Designated (Yes/No)                       | Yes  |

**Recommendation:**

There are no outstanding clinical issues for the CR letter. Anavip can be approved for management of coagulopathy in patients with North American pit viper envenomation.

**Summary Review:**

Anavip [Crotalidae (Pit-Viper) Immune F(ab')<sub>2</sub> (Equine) Injection] is a sterile, lyophilized, polyvalent preparation of equine immunoglobulin F(ab')<sub>2</sub> fragments, manufactured from the plasma of horses immunized with venom of *Bothrops asper* and *Crotalus durissus*. Anavip contains venom-specific F(ab')<sub>2</sub> fragments of immunoglobulin G (IgG) that bind and neutralize venom toxins, facilitating redistribution away from target tissues and elimination from the body.

Antivipmyn, a product similar to Anavip is registered in Mexico since 1984. Approximately (b) (4) vials has been sold in last nine years (2004 to 2012). Crofab, another crotalidae polyvalent ovine Immune Fab has been licensed 2000 in the US. The rationale for the development of Anavip is based on longer elimination half-life of F(ab')<sub>2</sub> (mean 133 h vs. 12 to 23 h for CroFab) thereby leading to a possible decreased incidence of recurrent envenomation symptoms, specifically recurrent coagulopathy

To support the indication of management of coagulopathy in patients with North American pit viper envenomation, data from a healthy volunteer PK study and two randomized, controlled, open-label clinical trials have been submitted in the biologic licensing application STN 125488.

In fourteen healthy volunteers who received a single vial of Anavip intravenously (IV), the mean elimination half- life was 133 hours.

The phase 2 trial (AN03/02) was designed as a randomized, controlled, multicenter, open-label study. Twelve subjects aged 18-70 years were randomized in 1:1 ratio to receive either Anavip or the licensed product. The subjects were dosed until initial control was achieved, followed by maintenance doses. Initial control was considered to be achieved if the leading edge of local injury was not progressing more than 1 inch/hour and platelet count, fibrinogen level, PT and PTT were either in or returning to the normal range. The maintenance dosing was initiated 6 hours after the last dose required to achieve the initial control and was continued every 6 hours for 3 doses. All patients in both treatment groups achieved initial control of local injury and coagulopathy following treatment. In the control group, at the end of maintenance dosing, 5 of 6 subjects had platelet counts above 150,000/mm<sup>3</sup>, and all 6 had fibrinogen levels above 150 mg/dL. However, during the follow-up phase, 2 subjects showed laboratory findings of recurrent coagulopathy with platelets below 150,000/mm<sup>3</sup> and fibrinogen below 150 mg/dL leading to inpatient management with administration of additional doses (one subject received an additional 6 doses (12 vials) and one subject received an additional 4 doses (8 vials). In the Anavip arm, at the end of maintenance dosing, 5 of 6 subjects had platelet counts above 150,000/mm<sup>3</sup>. One subject's platelets were 114,000/mm<sup>3</sup> and were trending upward and all 6 had fibrinogen levels above 150 mg/dL. During the follow-up phase, 5 of 6 subjects had platelet counts above 150,000/mm<sup>3</sup>, with no downward trend; 1 subject's platelet counts was 127,000/mm<sup>3</sup> on follow-up Day 1, reached 160,000/mm<sup>3</sup> on Day 4 and continued trending upward. All 6 subjects in Anavip group had fibrinogen levels above 150 mg/dL during the

follow-up phase. None in the Anavip group required rehospitalization or retreatment with Anavip. The clinical outcomes of this study provided preliminary evidence of effectiveness of Anavip on management of coagulopathy in subjects with North American pit viper envenomation.

In the phase 3 (YA07/02) randomized, controlled, double blind, multi-center study, two Anavip regimens were compared with a licensed product at 16 sites in US. A total of 121 subjects aged 2-80 years with signs and symptoms of envenomation were randomized in three groups: Group 1: Anavip with maintenance therapy (N = 42), Group 2: Anavip with Placebo (normal saline) maintenance therapy (N = 37), Group 3: CroFab with maintenance therapy (N = 41). The primary objective of this trial was to confirm the effectiveness of Anavip in management of coagulopathy. The study had an in-hospital Acute Treatment Phase that included screening and baseline assessments, initial and maintenance dosing, and an outpatient Follow-up (Subacute) Phase that included 4 follow-up visits on Days 5, 8, 15 and 22. Initial dosing consisted of sequential IV doses infused to achieve initial control. If initial control of envenomation was not achieved, treatment was repeated until initial control was attained. Maintenance dosing (4 vials of Anavip or placebo [normal saline], or 2 vials of licensed product) was initiated 6 hours after the start of the last dose required to achieve initial control, and continued every 6 hours for 3 doses. The Follow-up (Subacute) Phase began immediately after the third maintenance dose. Patients returned to the clinical site on Days 5, 8, and 15 for scheduled follow-up visits. Patients with ongoing signs of envenomation received 4 vials of Anavip or 2 vials of licensed product. Dosing was continued as needed until the patient was stabilized.

The primary efficacy endpoint was the proportion of patients experiencing coagulopathy as measured on Study Day 5 or 8. Patients were assessed as experiencing coagulopathy if they had any one of the following: absolute platelet levels  $< 150,000/\text{mm}^3$  as measured on either Study Day 5 ( $\pm 1$  day) or 8 ( $\pm 1$  day); absolute fibrinogen levels  $< 150$  mg/dL as measured on either Study Day 5 ( $\pm 1$  day) or 8 ( $\pm 1$  day); or clinical coagulopathy between end of maintenance dosing and Study Day 5 requiring additional antivenom. The comparison of coagulopathy proportions between treatment groups, was tested using an exact logistic regression model with terms for treatment and region. Comparisons of the proportion of coagulopathy for two levels of Anavip versus licensed product were performed in the following order: Anavip with Anavip maintenance dose versus licensed product; then Anavip with Placebo maintenance dose versus licensed product. The efficacy analysis did not meet the pre-specified statistically defined superiority criterion. However, the number of subjects showing pre-specified criteria for coagulopathy on either Study Day 5 or 8 were 10.3% and 5.3% in the Groups 1 and 2 when compared to 29.7% in Group 3 indicating efficacy of Anavip in management of coagulopathy in patients with North American crotalid envenomation.

Review of literature reveals that presence of baseline coagulopathy in subjects with North American crotalid envenomation is an important prognostic factor. Subjects with baseline coagulopathy are more likely to either worsen the coagulopathy or remain coagulopathic at Day 5 or 8. If the laboratory findings of coagulopathy returned to normal after treatment with the antivenins, then the data would be considered supportive of efficacy. FDA conducted a posthoc analysis to assess the outcomes of the patients who presented with or without baseline coagulopathy in the three treatment groups. Using the pre-specified criteria for coagulopathy, it was found that Anavip/Anavip (Group 1) had the highest percentage of baseline coagulopathic subjects among the three groups [41.5% compared with 17.5% and 32.5% for the Anavip/Placebo (Group 2) and CroFab/CroFab (Group 3), respectively]. Thirty-three percent (33%) of all baseline coagulopathic subjects continued to experience coagulopathy on either Day 5 or 8, compared to only 6% for baseline non-coagulopathic subjects. Only 18% of the subjects with baseline coagulopathy in Group 1 continued to remain coagulopathic at Days 5 or 8 compared to 58% in Group 3. An exact logistic regression analysis adjusting for baseline coagulopathy and region was conducted and showed that treatment effect for both Groups 1 and 2 is statistically significant. This analysis provides supportive evidence of efficacy of Anavip.

Safety was assessed in all subjects who received at least one dose of Anavip or licensed product. Seventy six percent (65/86) of patients receiving Anavip reported at least one adverse reaction. The most common adverse reactions ( $\geq 2\%$ ) in the clinical studies were: pruritus, nausea, rash, arthralgia, peripheral edema, myalgias, headache, pain in extremity, vomiting, and erythema. A total of nine subjects, including six (14.0%) subjects in Group 1, one (2.7%) subject in Group 2, and two (4.9%) subjects in Group 3 experienced at least one SAE. Most SAEs were assessed as severe and not related to study drug. The only treatment-related SAE was severe swelling in Group 1 and was considered possibly related to study drug. One subject in Group 1 died from multiple injuries sustained during a motor vehicle accident and the death was reported to be unrelated to study drug. Serum sickness was not reported in the clinical trials.

In conclusion, the pivotal trial failed to meet its pre-specified statistically defined superiority criterion (p value 0.06) however, based on clinically meaningful criteria of laboratory findings of coagulopathy, the data show that only 10% of the Group 1 subjects (Anavip/Anavip) experienced coagulopathy at Day 5 or 8 compared to 30% in Group 2 (CroFab/CroFab). The effectiveness of Anavip is further supported with only 18% of the subjects with baseline coagulopathy remaining coagulopathic at Days 5 or 8. The safety profile of the Anavip is acceptable. Overall, the data supports the safety and efficacy of Anavip for management of coagulopathy in patients with North American pit viper envenomation.