



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

To: BLA STN 125335/0

Cross Reference: IND 10371

From: Evi Struble, Ph.D.

Through: Dorothy E. Scott, M.D.

CC: Debra Cordaro, RPM, HFM-370

Applicant: Instituto Bioclón S.A. de C.V.'s

Product: Anascorp®, Centruroides (Scorpion) Immune F(ab')₂ Intravenous (Equine)

Subject: Final Memo, Nonclinical Pharmacology/Toxicology

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1. Brief Description of BLA Submission

Anascorp is a lyophilized F(ab')₂ fragment of immunoglobulin G (IgG) made from the blood of horses immunized with the venom of four different *Centruroides* scorpions. The BLA submission contains data from one GLP animal study conducted in rats and five clinical trials.

2. Proposed indication

For “the management of patients with clinically important signs of scorpion envenomation”.

3. Dose

3 vials, each vial reconstituted with 5 mL sterile WFI (b)(4) then that volume diluted in 50 mL of 0.9% NaCl -(b)(4)- and delivered in a 10 min IV infusion. Further vials, up to a total of 5 can be administered at 1 vial/hour. Thus, maximum dose is -(b)(4)- or, assuming 75 kg human subject, --(b)(4)--.

4. Conclusions and Recommendation

1. Based on the potential for adverse reactions this reviewer recommends that a warning for cresol be included in the PI for Anascorp such as: “Localized reactions and generalized myalgias have been reported with the use of cresol as an injectable excipient”.
2. Due to deficiencies in the design of the acute toxicity animal study submitted, no conclusions can be drawn as to the safety and NOAEL of Anascorp in animals and no label claims to this regard can be made.

5. Letter Ready Comments:

The nonclinical safety assessment program submitted with this application contains deficiencies that do not allow for adequate interpretation of animal safety data, including NOAEL. The following is a list of data needed to be submitted to the Division for review and evaluation.

- 1) Regarding study number 1299-001 titled “Crotaline (Pit Viper) Equine Immune F(AB)₂: an Acute Intravenous Toxicity Study in Rats”,
 - a) Please submit the clinical pathology, necropsy analysis data as well as the blood concentration of Anavip for the 4 dead males and one dead female rat. Please submit the pathologist evaluation regarding the cause of death for these animals.
 - b) Please explain the large variability in the blood concentration levels of Anavip at 1 hr post infusion. For example, the concentration of Anavip in group 2 subjects ranges from 1 to 3244 µg/ml (Appendix 1); large variability is also observed in the other study groups.
 - c) Please explain the low systemic exposure achieved with Anavip which is substantially smaller than the dose administered. For example, male 1006 dosed with 500 mg/kg Anavip showed plasma concentration of 38 µg/ml at 1 hr post infusion. This concentration corresponds to about 2.4 mg/kg Anavip circulating in the blood, assuming blood volume of 64 mg/ml. Similarly, low exposures were observed in other subjects and study groups.

- d) Please explain the difference between the dilution concentration and plasma concentration values for Anavip for subjects number 11013 and 11014 (data reported in Appendix 1). After taking the dilution into account, the numbers do not correspond.
- 2) Regarding the safety of the excipients and impurities present in the final formulation of Anascorp the following issues need to be evaluated.
- a) The use of cresol has been associated with myalgia and elevated creatine kinase activity¹, and malignant hyperthermia². Please conduct a toxicity assessment for cresol and adjust the labeling for Anascorp to include a warning to address this issue.
- b) To what extent is (b)(4) present in the final formulation of Anascorp? Please submit a toxicity assessment for this compound.

6. Complete Review

Contents:

- I. Review of the animal studies submitted with the BLA
II. Review of the excipients and impurities contained in the formulation

I. Review of animal studies submitted with the BLA

Title: Crotaline (Pit Viper) Equine Immune F(AB)₂: an Acute Intravenous Toxicity Study in Rats

Study Number: 1299-001

Aim: Acute toxicology Study in Rats

Performing Lab: -----(b)(4)-----

Test item: Anavip Crotaline (pit viper) equine immune F(ab')₂

Stability data not available

GLP study

Test Model: n=20 M and 20 F --(b)(4)- rats, 6 weeks old

Design: block randomized 5M, 5F/ group receiving either vehicle or test article at 500, 2000 and 5000 mg/kg IV for up to 60 minutes via the tail vein. The rats were observed for 14 days and then sacrificed and necropsied.

Outcome measurements: Cageside observations, clinical observations at 1, 2, 4 hrs post infusion and on day 1 and daily thereafter, body weight, urinalysis, (b)(4) of blood collected at 1 hr post-dose, clinical pathology on all animals, necropsy.

No histopathology was performed.

Results:

The local and systemic toxicities of Anavip are as follows:

4/20 deaths 2 M in the middle and 2 M in the high dose

Major irritation at the injection sites at all doses

Dose dependent injection site tissue necrosis, including tail shedding at all doses, especially the high dose.

These toxicities could be related to the very high concentration of the test article injected, namely 180 mg/ml, resulting to a very highly viscous liquid.

The NOAEL for systemic toxicity was determined at 500 mg/kg. There was no safe dose for local toxicity.

Reviewer Conclusions:

1. Due to the very high concentration as well as the high viscosity of the administered test item the intended systemic exposure was not achieved. The table below shows the discrepancy between Anavip injected dose (last column) and the plasma amount (column shaded gray) as determined by (b)(4) at 1 hr post injection.
2. Protein concentration analysis presented in Appendix B shows differences in protein concentration in administered samples with one sample having no protein present.

Table 1

Group	Anavip Plasma Concentration (µg/ml) ^a	Anavip Plasma Amount (mg/kg) ^b	Anavip Dose (mg/kg)
2m	38	2.432	500
2m	94	6.016	500
2m	3205	205.12	500
2m	791	50.624	500
2m	1	0.064	500
2f	928	59.392	500
2f	1954	125.056	500
2f	1331	85.184	500
2f	3244	207.616	500
3m	109	6.976	2000
3m	3558	227.712	2000
3m	216	13.824	2000
3m	316	20.224	2000
3m	7383	472.512	2000
3f	283	18.112	2000
3f	13154	841.856	2000
3f	2226	142.464	2000
3f	176	11.264	2000
3f	4182	267.648	2000
4m	201	12.864	5000
4m	49	3.136	5000
4m	8778	561.792	5000
4m	20211	1293.504	5000
4m	21261	1360.704	5000
4f	2813	180.032	5000

4f	197	12.608	5000
4f	29869	1911.616	5000
4f	121	7.744	5000
4f	9730	622.72	5000

^a Study Report, Appendix 1

^b Calculated by the reviewer using 64 ml/kg as the rat blood volume (See Karl-Heinz Diehl *et al*)

In conclusion, due to the lack of consistent exposure in each group no conclusions can be drawn as to the safety and NOAEL of Anavip.

II. Review of the excipients and impurities contained in the formulation

Table 2 shows the excipients and impurities in Anascorp (based on the certificate of analysis; the maximum exposure is calculated from the maximum dose as described in the PI).

Table 2

Compound	Amount	Maximum Exposure
Glycine	-----(b)(4)-----	(b)(4)
Sucrose	----(b)(4)-----	(b)(4)
Sodium Chloride	45 - 80 mg/vial	400 mg
Borates	NMT 1.0 mg/vial	5 mg
Sulfate	---(b)(4)-----	(b)(4)
Cresol	----(b)(4)----	(b)(4)

With the exception of cresol and borates, all the other compounds are commonly found in IGIV products.

Cresol

Cresol is present in many insulin and insulin analogs, as well as growth hormone preparations where it is used a preservative; f. e. Apidra (insulin glulisine [rDNA origin] injection) contains 3.15 mg/ml cresol or 3.15 mg for each 100 U of insulin. An injection of 50 units of insulin analog with Apidra would deliver about --(b)(4)-- of cresol as Anascorp.

Cresol at these doses when used as an injectable has been associated with with myalgia and elevated creatine kinase activity¹, and malignant hyperthermia². For this reason, the following warning is included in both classes of the injectables mentioned: “Localized reactions and generalized myalgias have been reported with the use of cresol as an injectable excipient”

National Toxicology Program (NTP) has evaluated the potential genetic toxicology of cresols in cell culture using Ames test as well as potential carcinogenicity of cresols *in vivo* in 2 year studies in rats and mice. Cresol was determined to be carcinogenic at doses in excess 230 mg/kg in rats and 300 mg/kg in mice or more than (b)(4) times the exposure from Anascorp use⁴.

Borates and Boron

A toxicity evaluation for borates was submitted by the sponsor (Amendment 0.21) containing document number EMEA/CVMP/025/MRL titled “Summary Report on Boric Acid and Borates” and a published paper titled “Boric acid single dose pharmacokinetics after intravenous administration to man”, Arch Toxicol (1984) 55: 64-67.

The EMEA report concludes that no Maximum Residue Limits are necessary for boric acid and boron and it could be used in all food producing animal species. It calculates that the maximal exposure to boron from eating animal products would be 39 mg/day and considered safe in humans. This exposure is lower than the maximal exposure from Anascorp.

Reviewer Conclusion:

Based on the potential for adverse reactions this reviewer recommends that a warning for cresol be included in the PI for Anascorp such as: “Localized reactions and generalized myalgias have been reported with the use of cresol as an injectable excipient”.

The other impurities and excipients present in Flebogamma final product are safe when used according to the PI.

7. Label

This reviewer recommends the following changes to the label printed in red typeface.

CONTRAINDICATIONS

- Anascorp should not be administered to patients with a known history of hypersensitivity to horse proteins unless the benefits outweigh the risks. (4)
- Localized reactions and generalized myalgias have been reported with the use of cresol as an injectable excipient. (Possible reference suggestions 1, 2)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, mutagenesis, impairment of fertility

Animal carcinogenicity and reproduction studies have not been conducted with Anascorp.

13.2 Animal Toxicology and/or Pharmacology

There were no animal studies performed with Anascorp.

~~A non-GLP acute toxicity study was conducted in mice receiving Anascorp by intravenous and intraperitoneal injection at doses of 1 to 5 g/kg. No death were observed at any dose or route. The LD₅₀ for both routes was greater than 5 g/kg. However, a GLP acute toxicity study in rats was conducted with Antivipmyn (Crotalidae (Pit Viper) Equine Immune F(ab)₂), an antisnake F(ab)₂ that has the same physicochemical characteristics as Anascorp. Under the conditions of this study, where rats received a single IV dose of, the no observed adverse effect level (NOAEL) for systemic toxicity was determined to be 500 mg/kg.~~

Rationale for the changes: Due to the lack of verifiable standards in performing the study, a non-GLP study cannot be used to make label claims. Due to deficiencies in design and lack of interpretable data, the study conducted with Anavip cannot be used to make label claims.

8. References

¹Bach MA, Blum DM, Rose SR, Charnas LR, J Pediatr. 1992 Oct; 121(4):650-1.

Myalgia and elevated creatine kinase activity associated with subcutaneous injections of diluent.

² Wappler F, Roewer N, Köchling A, Braune H, Reissinger T, Schulte am Esch J, Intensive Care Med. 1996 Aug; 22(8):809-12

Fulminant malignant hyperthermia associated with ketoacidotic diabetic coma.

³Karl-Heinz Diehl *et al*, J. Appl. Toxicol. 21, 15–23 (2001) “A Good Practice Guide to the Administration of Substances and Removal of Blood, Including Routes and Volumes”

⁴Natl Toxicol Program Tech Rep Ser. 2008, Jul(550):1-120. [National Toxicology Program technical report series] Toxicology and Carcinogenesis Studies of Cresols (CAS No. 1319-77-3) in Male F344/N Rats and Female B6C3F1 Mice (Feed Studies).