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Bioclon SA de CV Instituto
To: ----------(b)(4)---------
Information Request: STN 125335/0
June 10, 2009

The Center for Biologics Evaluation and Research is continuing to review your biologics license application for Centruroides (Scorpion) Immune F(ab)2 Intravenous (Equine) submitted on January 21, 2009. We have the following request for additional information:

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.

Information provided by[Reviwer Initials]_ Date ES/_____ Transmitted byDLC __ Date:6/10/09

Number of pages (including cover sheet) _2____

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a) The use of cresol has been associated with myalagia and elevated creatine kinase activity[1], and malignant hyperthermia[2]. 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.

The review of this submission is on-going and issues may be added, expanded upon, or modified as we continue to review this submission. Please submit this information as an amendment to this file no later than June 17, 2009. Please do not send an advance copy of the response by email unless requested to do so by FDA. If you anticipate you will not be able to respond by this date, please contact the Agency immediately. The action due date for this file is July 24, 2009.

Thank you for your assistance,

Debbie Cordaro
Regulatory Project Manager
FDA/CBER/DBA/OBRR/RPMB

References:

[1]Bach 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