

125488/0 Mid-Cycle Meeting Summary

STN: 125488/0

Product: Crotalidae Immune Fab2 Equine Injection

Applicant: Instituto Bioclon S.A. de C.V.

Short Summary: Management of patients with pit viper envenomation and prevention of late or recurrent coagulopathies

Reference IND 11275

August 22, 2013 from 1 pm to 3 pm

Woodmont Office Center in room 200 South

Meeting Chairperson: Howard Chazin, MD, Deputy Director, OBRR/DH

Application Chairperson: Michael Kennedy, PhD, OBRR/DH/LPD

Clinical Reviewer: Mitchell Frost, MD, OBRR/DH/CRB

Clinical Pharmacology Reviewer: Iftekhar Mahmood, PhD, OBRR/DH

Pharmacology/Toxicology Reviewer: Evi Struble, PhD, OBRR/DH/LPD

CMC Reviewers: Robert Fisher, PhD, OBRR/DH/LPD

Maria Luisa Virata, PhD, OBRR/DH/LPD

Yonggang Wang, PhD, OBRR/DH/LPD

Lilin Zhong, OBRR/DH/LPD

DMPQ Reviewer: Nancy Waites, DMPQ/OCBQ

Statistical Reviewer: Mary (Xue) Lin, PhD, OBE/DB

Epidemiologist Reviewer: Ravi Goud, MD, OMPT/CBER/OBE/DE/AEB

APLB Reviewer: Michael Brony, PharmD, OMPT/CBER/OCBQ/DCM/APLB

BIMO Reviewer: Erin McDowell, OMPT/CBER/OCBQ/DIS/BMB

Lot Release: Karen Campbell, OMPT/CBER/OCBQ/DMPQ/PRB

DSBQC Reviewer: Karen Campbell, OMPT/CBER/OCBQ/DBSQC/QAB

Veterinarian Consult: John Dennis, DVM, OM/DVS

RPM: Edward Thompson, OBRR/DBA/RPMB

Attendees:

Ginette Michaud, MD, Deputy Director, OBRR

Basil Golding, MD, Director, OBRR/DH

Mahmood Farschid, PhD, Deputy Director, OBRR/DH

John Eltermann, PharmD, Director, OBRR/DMPQ

Wei Hua, MD, Branch Chief, OBE/AEB

Carolyn Renshaw, Chief, OCBQ/DMPQ/BI

Renee Rees, PhD, Team Lead, OBE/TEB

Mark Shields, OBRR/RPMB

Betsy Jett, OBRR

Christopher Joneckis, PhD, CBER/ADRM

Erin McDowell, OCBQ/DIS/BMB

Agenda:

1. Reviewer Reports.

CMC – assay validation

Substantive Issues: Revision of the current (b) (4)

Corrective action: An Information Request will be sent by requesting revision to their (b) (4).

CMC – Raw Materials, Product Specifications, Adventitious Agents Testing

Key findings: (b) (4) product specifications proposed for Anavip are very similar to those used in the manufacture of their other equine F(ab')₂ product, Anascorp.

Substantive issues: Their (b) (4)

Revision of (b) (4)

The sponsor needs to demonstrate that Anavip is effective also in treating envenomation by (b) (4).

An Information Request will be sent for (b) (4).

CMC Stability

No substantive issue in assigned section has been identified to prevent approval or impact the review timeline.

The stability data for the final product will not be complete in the end of the review timeline, and a PMC will be proposed for this purpose.

CMC Process Validation

(b) (4)

(b) (4)

CMC – viral clearance

The firm conducted viral clearance studies in order to claim the manufacturing process's capacity of viral safety. The relevant manufacturing steps are 1) Pepsin Digestion; 2) Heat Inactivation of (NH₄)₂SO₄ precipitation step and 3) Nanofiltration. The model viruses used are (b) (4)

Preclinical Pharm/Tox

There is no need for additional animal studies.

The specification for cresol (process impurity) is set at 0.99 mg/vial. This specification is 3x higher than the specification for the same impurity in Anascorp. The specification raises concerns given the adverse reporting associated with cresol (myalgias) seen for this class of compounds.

Depending on the sponsor's response to an IR that will be sent, the application, if approved, (b) (4).

The sponsor will be asked to justify the specification and submit a toxicologic assessment on the safety of cresol at the amounts present in Anavip. (b) (4)

CMC/Facility

I have not completed my preliminary review for the Drug Product for the following sections of the application:

3.2.A Appendices

3.2.A.1 Facilities and Equipment for Drug Product

3.2.R Regional Information

My primary discipline review will be completed and ready for primary discipline review on 01 September 2013.

Quality Control (Testing Plan & Lot Release Protocol)

The draft testing plan has been sent to the chair and RPM, this cannot be completed until other review items, including labeling have been completed.

The review of the lot release protocol template has not started; it was not submitted to the BLA.

DBSQC is not performing any review beyond the drafting of the testing plan and review of the lot release protocol template.

If all required information is available the testing plan and review of the lot release protocol could be complete by 18 January 2013.

Clinical

The review of the two clinical trials (phase 2 and phase 3) is ongoing.

The clinical development plan and pivotal clinical trial for Anavip was designed to show superiority of Anavip over CroFab with regard to recurrent coagulopathy (a late occurring event after initial treatment has been effective). There was no prespecified hypothesis testing for efficacy of Anavip in the initial treatment of pit viper envenomation, particularly with regard to the tissue injury caused by envenomation.

The phase 3 pivotal trial failed to meet statistical significance of the primary endpoint at the 0.05 level (p-value was 0.0605); however, 10% of the cohort treated with Anavip for initial control and maintenance dosing exhibited recurrent coagulopathy versus 30% of the cohort treated with CroFab for initial control and maintenance dosing.

The pooled Anavip cohorts (one cohort who received Anavip for initial control and maintenance dosing, and one cohort who received Anavip for initial control and placebo for maintenance dosing) were statistically superior to CroFab with regard to recurrent coagulopathy with a p-value of 0.0099. Pooling the two Anavip cohorts to test for superiority versus CroFab was not part of the statistical analysis plan.

There was a large amount of missing data in all three cohorts.

The substantive issues will preclude Anavip from a labeling claim of superiority versus CroFab with regard to recurrent coagulopathy. However, it appears that the data will support approval of the product for the treatment of pit viper envenomation. The indication may be limited to the coagulopathy of envenomation.

The review of the clinical data is ongoing. Further internal analyses of the data, including secondary endpoints, is needed to assess the indication(s) for which the product may be approved. If the sponsor wishes to seek the claim for superiority versus CroFab with regard to recurrent coagulopathy, this can be done in the postmarketing period.

Clinical Pharmacology

The pharmacokinetic study submitted by the applicant is well designed. However, the applicant has not provided the pharmacokinetic results of the drug following the second dose. The applicant should modify clinical pharmacology labeling as suggested by the FDA.

The following questions will be sent to the applicant and after the receipt of the response the review of this submission will be finalized.

1. Please provide the results of the pharmacokinetic study following the second dose of antivenom administered to healthy subjects.
2. Please provide the description of analytical method for the measurement of antivenom concentrations used in the pharmacokinetic study.

Epidemiology

Integrated risk assessment

Most AEs associated with administration of Anavip are mild or moderate in nature. The most frequently reported AEs are pruritus and nausea. Many of the other reported AEs are expected sequelae of crotaline envenomation. These reactions are listed in the proposed package insert that was submitted as part of this BLA.

The allergic reactions, anaphylaxis, serum sickness and hypersensitivity reactions, are well-characterized and recognized serious AEs associated with heterologous immune

globulins. These reactions are listed in the proposed package insert submitted as part of this BLA, and occur at a potentially lower rate than the already FDA-approved crotaline antivenin.

OBE/DE agrees with the safety profile proposed by Instituto Bioclon. Data submitted by the sponsor as part of the application, available published medical literature, and data collected by CBER for similar products identified no new safety concerns beyond the Safety Specification provided by Instituto Bioclon.

Recommendations

Based on the review of the pre-licensure safety data and the sponsor's proposed pharmacovigilance plan, OBE/DE recommends the following routine safety surveillance activities: Routine pharmacovigilance: Adverse event reporting in accordance with 21 CFR 600.80

Statistics

The sponsor reported that the pivotal study failed to show statistical significance of the primary efficacy comparison. This reviewer has asked the sponsor to provide additional primary efficacy analyses and these are under review by this reviewer.

The percentage of missing data is high (16% overall, and 20% in two of the three groups) in the pivotal study. This reviewer has asked the sponsor to investigate the reason for such a high percentage of missing data and provide sensitivity analyses to assess the impact of the missing data.

The Anavip/Anavip group and CroFab group tend to have more AEs than the Anavip/Placebo group. For example, about 65% in Anavip/Placebo group had at least 1 AE, and about 80% subjects in the other two groups had AEs. The two groups also reported more SAEs.

Since the primary efficacy endpoint failed statistical significance, the requested additional analyses will provide supportive information for potential product approval.

BIMO inspections

Inspections of Sites #10 Loma Linda University Adventist Health Sciences Center, and #16 Banner Good Samaritan Medical Center have been completed. No sponsor or monitoring issues were noted at these sites. Final inspection classification for both sites 10 and 16 was NAI. The Bioresearch Monitoring inspection report for Site #20 is still pending.

APLB

Completely reviewed.

Review memo completion: Impossible to say, as there are other competing projects and deadlines. Maybe by August 31, 2013.

2. Will Discipline Review Letters be issued (for PDUFA V Program submissions).

Pending

3. If the application will be discussed at an Advisory Committee, potential issues for presentation.

No BPAC

4. Determine whether Postmarketing Commitments (PMCs), Postmarketing Requirements (PMRs) or a Risk Evaluation Mitigation Strategy (REMS) are needed.

- i. Will there be a Title IX PMR requiring SWG review?

Not discussed in the meeting

- ii. If the determination is made that a PMC, PMR or REMS is needed, begin the development of the language for the approval letter.

Not discussed in the meeting

5. National Drug Code (NDC) assignments to product/packaging.

Submitted under amendment 15 dated June 11, 2013.

NDC for (b) (4) .

6. Proper naming convention.

Crotalidae Immune Fab2 Equine Intravenous

7. Status of inspections (GMP, BiMo, GLP) including issues identified that could prevent approval.

GMP inspection of the (b) (4) facility, manufacture of drug product, occurred (b) (4) (b) (4) The EIR is in the process of being written. The inspection for the Tlalpan facility, manufacture of drug substance, was waived.

BIMO Inspections of Sites #10 Loma Linda University Adventist Health Sciences Center, and #16 Banner Good Samaritan Medical Center have been completed. No sponsor or monitoring issues were noted at these sites. Final inspection classification for both sites #10 and #16 was NAI. The Bioresearch Monitoring inspection report for Site #20 St. Joseph's Regional Health Center is still pending. A two item 483 was issued to Site #20 for items related to drug accountability records.

Confirm

8. Components Information Table was obtained and notification to the Data Abstraction Team (DAT) if discrepancies were found per *SOPP 8401.5: Processing Animal, Biological, Chemical Component Information Submitted in Marketing Applications and Supplements*. If not complete, indicate date it will be completed.

Not discussed in the meeting

9. New facility information is included in the application, requiring implementation of regulatory job aid *JA 910.01: Facility Data Entry*. If not complete, indicate date it will be completed.

Sent to Jeff McGuire on April 23, 2013

The Tlalpan facility is entered into the EDR.. The (b) (4) facility is not entered since it does not have an FEI number. Bioclon applied for an FEI number a few months ago and have not received one to this date. According to Jeff, no partial facility information can be entered into the EDR so until we get the FEI number we will not be able to enter this information.

10. Status of decisions regarding lot release requirements, such as submitting samples and test protocols and the lot release testing plan.

See Reviewer Report section (Quality Control (Testing Plan & Lot Release Protocol))

11. Unique ingredient identifier (UNII) code process has been initiated. See regulatory job aid *JA 900.01: Unique Ingredient Identifier (UNII) Code* for additional information.

Sent request to SRS on August 19, 2013

12. PeRC presentation date is set, and the clinical reviewer has addressed waiver/deferral/assessment of the PREA decision.

Not Applicable to the product

13. Reach agreement on information to be included in the Mid-cycle communication with the applicant (see section below). The Mid-cycle communication is only for applications that qualify under the PDUFA V Program.

Conduct meeting on September 4, 2013.

No discussion on information to the applicant in this meeting.

14. Major target and mile stone dates from RMS/BLA.

Request initial labeling review	Aug 16, 2013	
Mid-Cycle Review Meeting	Aug 22, 2013	Due 1-Sep-13
MidCycle Communication with Applicant	Sep 4, 2013	Due 5-Sep-13
External Late-Cycle Meeting	Nov 21, 2013	Due Sun, 12/01/13
Advisory Committee Meeting, if needed	Pending	Due: 12/17/13
Labeling Review	Pending	Due: 12/18/13
Final Labeling Target	Feb 16, 2014	
Complete PMC Study,		
Labeling Review, Review Addenda	Feb 14, 2014	Due: 02/16/14
Send FDA Action Letter	Mar 18, 2014	Due: 03/18/14

15. The status of the review for each discipline, inspection, EIR. If any primary reviews have not met the target date, provide the date the review will be completed. Include any consult disciplines. *Note: Individual reviewer requesting consult is responsible for reporting on status if the consultant is not present*

Not discussed in the meeting.

16. Discuss pending dates of targets and milestones (e.g. late-cycle meeting, Advisory Committee, labeling discussion).

See item #14.

17. Establish a labeling review plan and agree on future labeling meeting activities.

RPM proposes December 12, 2013 for a labeling meeting by email.

Drafted: Edward Thompson
Revisions: Nancy Waites
Erin Mcdowell
Evi Struble