Summary Basis for Regulatory Action

Date:	February 25, 2017
From:	Laurence Landow, MD
BLA/ STN#:	STN 103788/5341
Applicant Name:	BTG International Inc.
Date of Submission:	July 8, 2016
PDUFA Goal Date:	May 8, 2017
Proprietary Name/ Established Name:	CroFab® ®/ Crotalidae Polyvalent Immune Fab (Ovine)
Indication:	CroFab® ® is a sheep derived antivenin indicated for the management of adult and pediatric patients with North American crotalid envenomation
Recommended Action:	**Approval**
Signatory Authorities Action:	**Approval**

Offices Signatory Authority: Tejashri Purohit-Sheth, M.D., Director, DCEPT/OTAT/CBER

☒ I concur with the summary review.

☐ I concur with the summary review and include a separate review to add further analysis.

☐ I do not concur with the summary review and include a separate review.

Material Reviewed/ Consulted Reviewer Name – Document(s) Date	**Specific documentation used in developing the SBRA**
Clinical Review	Laurence Landow, MD
Clinical Pharmacology Review	N/A
Statistical Review	Judy Li, PhD
CMC Review	N/A
Pharmacology/ Toxicology Review	N/A
Bioresearch Monitoring Review	N/A
Establishment Inspection Report	N/A
Advisory Committee Transcript	N/A

Epidemiology	N/A
Promotional Labeling Review	Loan Nguyen, PharmD

1. Introduction

Crotalid snakes are a family of venomous snakes found in North America that include many types of rattlesnakes, as well as copperheads and water moccasins. STN 103778/0 was approved in October 2000 for the treatment of mild-moderate crotalid envenomation. Two supplements were submitted subsequently, one in 2009 for inclusion of subjects with severe envenomation (in addition to mild-moderate envenomation) and the second (current) for inclusion of pediatric and geriatric subcohorts.

Since approval in October 2000, CroFab® has been widely used to treat crotalid snakebites. The American Association of Poison Control Centers' National Poison Data System (NPDS) reported 2,768 cases of crotalid snake envenomation treated in health care facilities in 2006, including 1,528 cases with moderate or severe outcomes, 1,235 with lesser or unknown severity outcomes, and 5 deaths. These data represent only snakebite cases reported to NPDS by poison centers. In 2006, 1,359 patients reported to NPDS received Fab fragment antivenom for the treatment of their envenomation. CroFab® is recommended as first-line therapy for crotalid snakebites of all severity, including severe envenomations, in all major US medical toxicology textbooks. Treatment of severe envenomations with CroFab® is specifically advocated on the websites of several major U.S. medical centers and poison control centers. Treatment of severely envenomated patients with CroFab® is also endorsed the American College of Emergency Physicians and the American Academy of Pediatrics in their Advanced Pediatric Life Support curriculum.

2. Background

Two prospective clinical trials using CroFab® were submitted for the original BLA. They were prospectively defined, open label, multi-center trials conducted in otherwise healthy subjects 11 years of age or older who had suffered from minimal or moderate North American crotalid envenomation that showed evidence of progression. Progression was defined as the worsening of any evaluation parameter used in the grading of an envenomation: local injury, laboratory abnormality or symptoms and signs attributable to crotalid snake venom poisoning. Both clinical trials excluded subjects with Copperhead envenomation.

In the first clinical study, 11 subjects received an intravenous dose of 4 vials of CroFab® over 60 minutes. An additional 4-vial dose of CroFab® was administered after completion of the first CroFab® infusion, if deemed necessary by the investigator. At the 1-hour assessment, 10 out of 11 subjects had no change or a decrease in snakebite severity score (SSS). Ten of 11 subjects also were judged to have a clinical response by the investigator's clinical assessment. Several subjects, after initial clinical response, subsequently required additional vials of CroFab® to stem progressive or recurrent symptoms and signs. No subject in this first study experienced an anaphylactic or anaphylactoid response or evidence of an early or late serum reaction as a result of administration of CroFab®.

The second clinical study compared two different dosage schedules. Subjects were given an initial intravenous dose of 6 vials of CroFab® with an option to retreat with an additional 6

vials, if needed, to achieve initial control of the envenomation syndrome. Initial control was defined as complete arrest of local manifestations, and return of coagulation tests and systemic signs to normal. Once initial control was achieved, subjects were randomized to receive additional CroFab® either every 6 hours for 18 hours (Scheduled Group) or as needed (*prn* Group). In this trial, CroFab® was administered safely to 31 subjects with minimal or moderate crotalid envenomation. All 31 subjects enrolled in the study achieved initial control of their envenomation with CroFab®, and 30, 25 and 26 of the 31 subjects achieved a clinical response based on the investigator's clinical assessment at 1, 6 and 12 hours, respectively, following initial control. Additionally, mean SSS was significantly decreased across the subject groups by the 12-hour evaluation time point (p=0.05 for the Scheduled Group; p=0.05 for the *prn* Group). There was no statistically significant difference between the Scheduled Group and the *prn* Group with regard to the decrease in ES.

Efficacy supplement 103788/5144 was received on May 11, 2009. Approved on March 11, 2010, it expanded the indication to include treatment of severe crotalid envenomations. The supplement was a retrospective medical chart review (Protocol MC03/03/05) of cases abstracted for the calendar years of 2002-2004. This review comprised subjects (N=247) at 18 study sites in the U.S. and used a modified 7-point snakebite severity score (SSS) based on a previously validated SSS to assess outcomes. Subjects were further classified as having mild, moderate, or severe envenomation based on their SSS. Subjects with a severity score of 5 or 6 at the start of antivenom therapy were a priori defined as severe envenomations; those with a score of 3 or 4 were defined as moderate envenomations and those with a score of 1 or 2 were defined as mild envenomations. Subjects who were bitten but did not manifest signs/symptoms of envenomation at presentation (score of 0) could still receive antivenom.

Supplement 103788/5341 was received on July 8, 2016 and is based on Protocol MC03/03/05, except that it compared subject outcomes stratified by age as well as severity. The objective was to compare the efficacy and safety of CroFab® in the MC03/03/05 dataset (N=247) *for whom sufficient data were available to calculate a baseline SSS* (N=207), i.e., designated as the intention-to-treat (ITT) population.

3. Chemistry Manufacturing and Controls (CMC)

N/A

4. Nonclinical Pharmacology/Toxicology

N/A

5. Clinical Pharmacology

N/A

6. Clinical/ Statistical

a. Clinical Program

Trial #1

The population studied in supplement 103788/5341 comprised two subgroups, a pediatric cohort aged ≤16 years and geriatric cohorts aged >65 years and >75 years. Each subgroup was compared with the adult cohort aged >16 and ≤65 years. The ITT population (N=207) included

pediatric (N=72), adult (N=128) and geriatric subjects aged >65 years (N=9) and geriatric subjects aged >75 years (N=4).

The primary endpoints as defined in Protocol MC03/03/05 were as follows:

- Snakebite Severity Score (SSS) change from start of treatment to 3 different time points: initial control or receipt of last loading dose, worst condition post-treatment and final assessment
    - Number and percentage of subjects with improved SS
    - Minimum, median and maximum for change in SS
    - Change in SS between age groups
- Achievement of initial control
    - Number and percentage of subjects who achieved initial control
    - Achievement of initial control compared between age groups
- Recurrence
    - Number and percentage of subjects who had recurrence
    - Comparison between age groups

These endpoints were analyzed as follows:

- Change in SSS from start of treatment to initial control/last loading dose
- Change in SSS from start of treatment to final assessment
- Percent of subjects who achieved initial control of venom effects
- Percent of subjects who had a recurrence of venom effects

Efficacy Summary

Compared with adult subjects aged >16 to ≤65 years, CroFab® conferred similar benefit to pediatric subjects and to geriatric subjects for treatment of North American crotalid envenomation, although none of the geriatric experienced severe envenomation.

7. Safety

Safety was assessed by the percentage of subjects with immediate and delayed AEs. The Safety Population (N=247) consisted of pediatric subjects (N=78), adult subjects (N=156), geriatric subjects aged >65 years (N=13) and geriatric subjects aged >75 years (N=6).

The aggregate population experienced a low incidence of both immediate AEs [15/247 (6.1%)] and delayed AEs [2/247 (0.8%)] across all age groups. For pediatric *vs.* adult subjects, respectively, no statistically significant differences were found with respect to immediate AEs (6.4% vs 5.1%, p=0.764) or delayed AEs (1.3% vs 0.6%, p=1.000). Similarly, for geriatric *vs.* adult subjects, no statistically significant differences were found with respect to immediate AEs (15.4% vs 5.1%, p=0.173) or delayed AEs (0% vs 0.6%, p=1.000).

Safety Summary

Safety profiles for the pediatric *vs.* adult cohort and for the geriatric *vs.* adult cohort were similar. No new safety patterns or concerns were identified.

8. Advisory Committee Meeting

N/A

9. Other Relevant Regulatory Issues

NA

10. Labeling

The applicant submitted an amended version of the package insert to include data from the pediatric and geriatric subpopulations.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

I recommend an approval action be taken for this BLA supplement.

b) Risk/ Benefit Assessment

Although the efficacy data are somewhat limited due to lack of a control group, post hoc nature of the analysis, absence of significance testing, a substantial amount of missing data and use of a modified 7-point severity scale that has not been validated, the benefit-risk profile of CroFab® is greater than the benefit-risk profile associated with untreated envenomation.

c) Recommendation for Postmarketing Risk Management Activities

NA

d) Recommendation for Postmarketing Activities

NA