Summary Basis for Regulatory Action Template

Date: October 19, 2017

From: Megha Kaushal M.D., Chair of the Review Committee

***BLA*/ STN#: 125444/225**

Applicant Name: Bioverativ Therapeutics, Inc.

Date of Submission: May 5, 2017

Goal Date: November 4, 2017

Proprietary Name/ Established Name: ALPROLIX® / Coagulation Factor IX (Recombinant), Fc Fusion Protein

Indication:

ALPROLIX, Coagulation Factor IX (Recombinant), Fc Fusion Protein, is a recombinant DNA derived coagulation factor IX concentrate indicated in adults and children with hemophilia B for:

- **On-demand treatment and control of bleeding episodes,**
- **Perioperative management of bleeding,**
- **Routine prophylaxis to reduce the frequency of bleeding episodes.**

Recommended Action:

The Review Committee recommends approval of this product.

Review Office(s) Signatory Authority:
Tejashri Purohit-Sheth, M.D./Director/Division of Clinical Evaluation and Pharmacology/Toxicology/OTAT/CBER/FDA

☐ 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.

The table below indicates the material reviewed when developing the SBRA

Document title	**Reviewer name, Document date**
CMC Review(s) • *CMC (product office)* • *Facilities review (OCBQ/DMPQ)* • *Establishment Inspection Report (OCBQ/DMPQ)*	Nancy Kirschbaum, Natalya Ananyeva – 22 July 2016
Clinical Review(s) • *Clinical (product office)* • *Postmarketing safety epidemiological review (OBE/DE)* • *BIMO*	Megha Kaushal 2 November 2017 L. Ross Pierce 11,24 August 2016 Bethany Baer – 06 April 2016 Dennis Cato- 30 August 2016
Statistical Review(s) • *Clinical data* • *Non-clinical data*	Shuya Lu 24 October 2017 Judy Li 26 August 2016
Pharmacology/Toxicology Review(s) • *Toxicology (product office)* • *Developmental toxicology (product office)* • *Animal pharmacology*	La'Nissa Brown 22 August 2016
Clinical Pharmacology Review(s)	Iftekhar Mahmood 23 October, 2017
Labeling Review(s) • *APLB (OCBQ/APLB)*	Kristine Khuc – 28 April 2016
Other Review(s) • *additional reviews not captured in above categories* • *consult reviews*	N/A
Advisory Committee summary	N/A

1. INTRODUCTION

ALPROLIX brand Coagulation Factor IX (Recombinant), Fx Fusion Protein (rFIX-Fc) was approved in the United States on 28 March 2014 and was commercially available starting on 05 May 2014. The product has orphan designation and is approved in adults and children for (1) on-demand treatment and control and prevention of bleeding episodes, (2) perioperative management of bleeding, and (3) routine prophylaxis to reduce the frequency of bleeding episodes. This labeling Prior Approval Supplement (PAS), was submitted in fulfilment of Post-Marketing Commitment (PMC) #1 to complete and report the results of the then ongoing pediatric phase 3-4 trial. This PAS, in addition to including the final study report for the pediatric study, Study 9HB02PED and an interim analysis report of ongoing extension Study 9HB01EXT, updates data in the ADVERSE REACTIONS and CLINICAL STUDIES sections. This is based on the 1) completed pediatric on-demand treatment and routine

prophylaxis PMC trial, Study 9HB02PED, in children under 12 years of age with severe to moderately severe hemophilia B (n = 30 enrolled) and the 2) extension study, Study 9HB01EXT, which enrolled 116 subjects from both the pivotal PTP trial in adults and adolescents with severe to moderately severe hemophilia B that studied on-demand treatment, routine prophylaxis, and perioperative management.

2. BACKGROUND

Hemophilia B, also called Christmas disease, is a genetic disease characterized by clotting factor IX deficiency, which leads to spontaneous and trauma-induced bleeds in joints and soft tissue. Recurrent joint bleeds can lead to hemophilic arthropathy, severe disability, and need for joint replacement surgery. Inheritance is recessive, via the X chromosome, so the disease occurs predominantly in males. Prevalence is estimated to be ~ 4000 affected individuals in the United States and ~ 80,000 individuals worldwide.

Several different plasma-derived and recombinant FIX clotting factor products are licensed and available in the United States.

ALPROLIX brand rFIX-Fc was evaluated in patients with severe, previously treated hemophilia B in a Phase 1-2a trial in subjects 18 years of age and older, and in a Phase 3 study, in subjects 12 years and older prior to its licensure in March, 2014. Interim data from the pediatric trial in hemophilia B subjects under 12 years of age was also available at the time of original licensure. It has also been marketed overseas.

There was no pre-submission meeting for this PAS. No agreed iPSP was included in the original BLA because, as an orphan designated product, it was not subject to PREA. Pediatric data needed to include pediatric subjects in the indication was discussed in FDA preliminary responses to a Type C meeting dated 12 September 2011 and at the pre-BLA meeting held 14 June 2012.

Upon review of Study 9HB02PED, FDA Bioresearch monitoring (BIMO) inspections revealed several instances at two of four inspected study sites in which the values recorded in submitted data listings from the BLA did not match source documents for the actual doses of rFIX-Fc administered. Due to these inaccuracies, a complete response (CR) letter for this BLA supplement was sent to the applicant.

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

The scope of the CMC review was limited to (1) the evaluation of product-related information in the revised Full Prescribing Information (FPI) for ALPROLIX, and (2) assessment of validity of immunogenicity assays used to monitor formation of antibodies to Recombinant Coagulation Factor IX Fc Fusion Protein (rFIXFc) in the Pediatric Study 9HB02PED.

The information for validation of the immunogenicity assays that were used to monitor development of antibodies to rFIXFc in clinical studies, as described in Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods, Section 1.2.3, Immunogenicity Assays, were reviewed and found to be acceptable.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

In the present supplement, the Applicant submitted a pharmacokinetic study conducted in pregnant, genetically modified FIX-deficient (HemB) mice to measure placental transfer via the Fc portion of ALPROLIX, and the fetal Fc receptor (FcRn) expressed on placental tissue.

Pregnant, genetically-modified, FIX-deficient mice (HemB mice) were injected intravenously at the end of pregnancy on Gestation Day (GD) 18 or GD18 and GD20 with a single dose of approximately 3.3 to 6.6 -fold greater than the recommended clinical dose of ALPROLIX. Maternal blood samples, and blood from fetuses delivered by Caesarean section were collected 3 to 4 hours later, and FIX activity was measured in both maternal and fetal plasma using a FIX one stage assay. Detectable FIX activity was present in fetal plasma samples from 3 of 3 litters of HemB mice after ALPROLIX, dosing, with FIX activity ranging from 8 mU/mL to 19 mU/mL (equivalent to 0.8 to 1.9% of normal plasma FIX level). By contrast, there was no detectable FIX activity present in fetal plasma from 3/3 litters dosed with an equivalent amount of a recombinant, FIX as a comparator control. Additionally, after dosing pregnant HemB mice with ALPROLIX, FIX activity in fetal blood was approximately 2.6% of the maternal blood levels (range, 1.7% to 3.3% of maternal blood levels), suggesting that low levels of placental transfer of ALPROLIX, may occur. The relevance of these findings to patients with Hemophilia B is unknown.

5. CLINICAL PHARMACOLOGY

This supplement included a pharmacokinetic (PK) study that was conducted in pediatrics. There were 11 children <6 years of age (2-4 years) and 13 children 6 to <12 years of age (6 to 10 years) in the PK study. The children received a single 50 IU/kg dose of ALPROLIX via a 10 minute intravenous infusion. Blood samples were collected prior to dosing and at 7 time points up to 168 hours (7 days) after dosing. PK parameters for ALPROLIX were estimated based on the plasma FIX activity using non-compartmental analysis.

Compared to adults, incremental recovery was lower and body weight adjusted clearance was higher in children under 12 years of age, particularly in children under 6 years of age. Incremental recovery in children 2 to 4 years and 6 to 10 years was lower by 41% and 27%, respectively. Compared to adults, body weight- adjusted clearance in children 2 to 4 years and 6 to 10 years was higher by 36% and 11%, respectively. The half-life of ALPROLIX in children 2 to 4 years and 6 to 10 years was shorter by 19 hours and 15 hours, respectively.

The results of the PK study indicate that clearance of ALPROLIX (based on per kg body weight) is higher and half-life is shorter in children <12 years of age as compared to adults. The difference in clearance between children <12 years of age and adults indicates that the dose of ALPROLIX should be increased in children <12 years of age compared to the recommended adult dose.

6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE

a) Clinical Program

The final study report for the pediatric trial, Study 9HB02PED and an interim analysis report of ongoing extension trial, Study 9HB01EXT were reviewed, in addition to pooled analyses of cases of perioperative management in major surgeries and of adverse events and adverse reactions across all three completed phase 3 and phase 3-4 studies.

The completed pediatric study, Study 9HB02PED, of PTP male children < 12 years of age with at least 50 EDs to a FIX product at the time of study start enrolled 15 subjects < 6 years of age and 15 subjects 6 to < 12 years of age. Subjects were administered ALPROLIX for routine prophylaxis at a starting dose of 50 to 60 IU/kg once weekly and investigators were permitted to adjust the dose up to 100 IU/kg, and the frequency up to twice weekly based on breakthrough bleeds and trough FIX activity levels in relation to a minimum target of 1 IU/dL (1%).

By the end of the trial, the median weekly prescribed dose in both age cohorts was 60 IU/kg (range 40 to 70 IU/kg). One subject in the age 6 to < 12 years of age cohort received 100 IU/kg every 5 days as his final prescribed dose. Three subjects discontinued the trial prematurely (not due to AEs). Ten subjects < 6 years of age had 50 or more exposure days (EDs) to ALPROLIX during the trial. Thirteen subjects age 6 to < 12 years had 50 or more EDs to the product during the trial. The median annualized bleeding rates during routine prophylaxis with ALPROLIX brand rFIX-Fc were 1.09 (SD 1.93) bleeds per subject-year in the <6 years of age cohort and 2.13 (SD 3.17) in the 6 to < 12 years of age cohort. The mean ABRs in the two age cohorts were 1.72 and 2.80 bleeds per subject-year, respectively. The mean/median (SD) annualized spontaneous bleeding rates rate during routine prophylaxis were 0.47/0.0 (SD 0.89) bleeds per subject-year in the < 6 years of age cohort and 0.79/0.0 (SD 0.99) in the 6 to < 12 years of age cohort. The mean/median (SD) annualized joint bleeding rates rate during routine prophylaxis were 0.23/0.0 (SD 0.65) bleeds per subject-year in the < 6 years of age cohort and 1.87/1.1 (SD 2.64) in the 6 to < 12 years of age cohort.

Analysis of PK data revealed that, in children in the < 6 years of age cohort (whose actual ages ranged from 2-4 years of age), there was a 33% increase in body weight adjusted clearance, a 41% decrease in IR, and a 19 hours shorter half-life than in adults. The Applicant was asked to identify a specific modified starting dose for routine prophylaxis in children < 6 years of age and to recommend that an in-vivo recovery (IVR) of 0.6 IU/dL/IU/kg be used to calculate doses for bleeding and perioperative management in this age group. The Applicant was initially resistant to modifying the existing starting dosage recommendation for routine prophylaxis for children under 6 years of age, and

was also initially reluctant to recommend using an age-specific IVR value of 0.6 IU/dL per IU/kg for children under 6 years of age, stating that having more than one recommended dosage regimen depending on age of the patient would be confusing to physicians. The review team held a teleconference with the Applicant on 14 July 2016, explaining that, going forward, FDA intended to ask sponsors to recommend age-specific doses for children when there was a 30% or greater difference in clearance or IVR in the pediatric age stratum compared to adults. FDA pointed out that the second option of the existing recommendation to use a starting dose of 50 IU/kg once weekly or 100 IU/kg once every 10 days was not justified in children less than 12 years of age, because of the paucity of data in children using a prophylaxis regimen involving a frequency of less often than weekly. No subjects in the pediatric PMC trial had a last prescribed dosage regimen less frequent than once weekly and only four pediatric subjects from this trial received ALPROLIX for routine prophylaxis in the extension trial at a frequency less often than once weekly. In consideration of the actual dose regimens used at the end of the pediatric trial, FDA revised its recommendation to a starting dose of 60 IU/kg once weekly for children under 12 years of age to be consistent with the regimens used during the last 3 months and at the end of the pediatric trial.

The extension trial, Study 9HB01EXT, enrolled 116 subjects with pre-treatment FIX levels of < 2% or with medically important FIX gene mutations who completed the pediatric PMC trial, Study 9HB02PED, and adult and adolescent phase 3 trial, Study 998HB102.

Efficacy endpoints for the extension trial included assessment of annualized bleeding rates (ABRs) during routine prophylaxis and assessment of response to bleeding episodes. All pediatric subjects < 12 years of age were required to remain on routine prophylaxis, but when subjects reached 12 years of age, they were permitted to switch to on-demand (episodic) treatment. Ninety-two subjects remained on weekly or individualized prophylaxis during the trial, of which 90 used a dosing frequency of at least 7 days. ABRs during prophylaxis were in a range similar to those observed during the phase 3 and PMC pediatric trial. Approximately 90% of bleeding episodes resolved with a single injection of rFIX-Fc in the cohort of subjects under 6 years of age. One hundred percent of subjects in the age cohort 6 to less than 12 years had their bleeding episodes resolved after one or 2 injections of ALPROLIX. Perioperative management was evaluated in eight subjects who had surgery during the extension trial who underwent 14 major surgical procedures. Hemostatic efficacy was rated excellent in 12 major surgeries, good in one surgery, and was considered not evaluable in one surgery.

The additional data from the submitted studies continues to support the efficacy of the ALPROLIX for the proposed indications.

b) Pediatrics

As an orphan designated product, the product was not subject to PREA, and as such, no agreed iPSP was required or included in the original BLA.

Nonetheless, thirty pediatric subjects under 12 years of age were studied in the phase 3-4 pediatric PMC trial (15 subjects age less than six years of age, and 15 subjects six to less

than 12 years of age). Pharmacokinetic data were available for 11 children age 2 to 4 years, 13 children age 6 to 10 years, and 11 adolescents age 12 to 17 years.

Review of data confirmed that children under 12 years of age on average have higher Factor IX body weight-adjusted clearance and lower recovery as compared to adults (and adolescents). More frequent or higher doses may be needed in children < 12 years of age. When calculating target peak doses for treatment of bleeding or surgery, the package insert was revised to recommend using the average in vivo recovery value of 0.6 IU/dL per IU/kg, or individually determined in vivo recovery, for children under 6 years of age. For children under 12 years of age, the recommended starting routine prophylaxis dose was revised to 60 IU/kg per week from 50 IU/kg per week.

c) Other Special Populations

Not applicable

7. SAFETY

The Safety Set in Study 9HB02PED comprised 30 subjects who received at least one dose of the product. The 30 subjects were followed for a total of 26.1 subject-years.

No FIX inhibitors were reported for either age group in the pediatric PMC trial, Study 9HB02PED. Review of safety data from this trial did not reveal unusual findings or new safety signals for this product. No deaths were reported. No subjects discontinued treatment prematurely due to an AE. Four subjects (13%) reported at least one serious adverse event (SAE), with a total of 11 SAEs. No SAEs were considered related to administration of Alprolix by either the investigator or the FDA clinical reviewer. Three subjects reporting SAEs were in the < 6 years of age cohort and one subject was in the age 6 to < 12 years of age cohort. Twenty-six subjects (87%) reported at least one adverse event (AE). Twelve subjects (80%) reported at least one AE each in the < 6 years of age cohort and 14 subjects (93%) reported at least one AE each in the 6 to < 12 years of age cohort. The most common AEs were nasopharyngitis (7 subjects, 23%), viral infection (4 subjects, 13%), falls (6 subjects, 20%), head injury (4 subjects, 13%), face injury (3 subjects, 10%), and pyrexia (4 subjects, 13%). Only one subject (in the < 6 year age cohort) had one or more AEs considered suspected adverse reactions (SARs) by the investigator. This subject had decreased appetite starting the same day as the first dose of rFIX-Fc and recurring on each subsequent day of administration of rFIX-Fc and always resolving the following day. The FDA clinical reviewer agreed that this AE may have been related to test product administration.

The primary endpoint of the extension trial, Study 9HB01EXT, was development of FIX inhibitors. No subject in the interim analysis of the extension trial reported herein was reported to have developed an inhibitor. The safety dataset included 116 subjects, of which 113 (97.4%) were evaluated after at least 26 weeks and 96 (82.2%) were evaluated after at least 52 weeks. No vascular thrombotic events or serious hypersensitivity events were reported. No significant safety signals were evident from review of the trial data.

Overall, the submitted data support a favorable benefit: risk assessment for use of the product in all studied populations in all the currently approved indications.

8. ADVISORY COMMITTEE MEETING

No advisory meeting was held in conjunction with this CR response to this supplement, given that no issues regarding safety or efficacy arose that were judged to benefit from advisory committee input.

9. OTHER RELEVANT REGULATORY ISSUES

Not applicable.

10. LABELING

Many edits to the DESCRIPTION and HOW SUPPLIED sections of the package insert (PI) were recommended and accepted by the Applicant. The description of the product class in the INDICATIONS AND USAGE section of the PI was revised to strike "Human" to reduce the potential to confuse this recombinant fusion protein product with human plasma-derived FIX products, notwithstanding the Established Pharmacologic Class (EPC) Text Phrase for coagulation factor IX recombinant human products. The PI and carton label were revised to indicate that the product vial and diluent syringe/components do not contain natural rubber latex.

Several information requests were sent to the Applicant to make edits to the submitted draft package insert. The use of a higher weekly starting dose of 60 IU/kg is now recommended for children under 12 years of age. The use of an age-specific IVR value of 0.6 IU/dL per IU/kg is now recommended for calculating initial doses for bleeding and perioperative management in children less than 6 years of age, in view of the 40 % lower mean IVR in this age group compared to adults. Additional edits to the PI originating from the APLB review, the clinical review, the pharmacology-toxicology review, the product review, and the statistical review were conveyed to the Applicant and accepted. The Applicant was requested to make corrections to the clinical data in the package insert relating to the actual doses of rFIX-Fc administered during the pediatric trial to be consistent with source documents. This request was made as a consequence of observations at two of four study sites that underwent BIMO inspections in which discrepancies were noted between source documents and CRFs on the one hand and the Applicant's data listings on the other hand. After reviewing the data, no change in dose was required to be made to the package insert.

The final PI was submitted on 11/2/2017.

11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

Approval of the PAS is recommended.

b) Risk/ Benefit Assessment

The clinical reviewer concludes that the benefit: risk balance remains favorable after review of the submitted data for the three existing indications. No other reviewing disciplines disagreed with this view. The risk of under-treatment with less-than-expected therapeutic effect and increased breakthrough bleeds during routine prophylaxis is expected to be lessened using a higher weekly starting dose of 60 IU/kg for children under 12 years of age. The use of an age-specific IVR value of 0.6 IU/dL per IU/kg is recommended for calculating initial doses for bleeding and perioperative management in children less than 6 years of age, in view of the 40 % lower mean IVR in this age group compared to adults.

c) Recommendation for Postmarketing Activities

No PMRs or PMCs are recommended.