Summary Basis for Regulatory Action Template

Date: September 21, 2018

From: Jay Lozier, MD, PhD, FACP, Chair of the Review Committee

STN#: BLA 125506/46

Applicant Name: BioProducts Laboratory, Limited

Date of Submission: March 23, 2018

Goal Date: September 21, 2018

Proprietary Name/ Established Name: COAGADEX®/coagulation factor X, human

Indications:

- Routine prophylaxis to reduce the frequency of bleeding episodes
- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding in patients with mild and moderate hereditary Factor X deficiency

Recommended Action:
The Review Committee recommends approval of this product.

Review Office Signatory Authority: Tejashri Purohit-Sheth, MD, Director, Division of Clinical Evaluation and Pharmacology/Toxicology, Office of Tissues and Advanced Therapies

X 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) • *Establishment Inspection Report (OCBQ/DMPQ)*	Angela Chica, MPA

Clinical Review(s) • *Clinical (product office)* • *Postmarketing safety epidemiological review (OBE/DE)* • *BIMO*	Jay Lozier, MD, PhD September 18, 2018 Faith Barash, PhD August 28, 2018 Carla Jordan
Statistical Review(s) • *Clinical data* • *Non-clinical data*	Boris Zaslavsky, PhD August 20, 2018
Clinical Pharmacology Review(s)	Iftekhar Mahmood, PhD August 1, 2018
Labeling Review(s) • *APLB (OCBQ/APLB)*	Kristine Khuc, PharmD July 16, 2018

1. INTRODUCTION

In December of 2015, Bio Products Laboratory, Limited (BPL) was granted approval for its product COAGADEX (coagulation factor X, human) to treat adults and adolescents (aged 12 years and above) with hereditary factor X deficiency for (1) on-demand treatment and control of bleeding episodes and (2) perioperative management of bleeding in patients with mild hereditary factor X deficiency. Hereditary factor X deficiency is a rare bleeding disorder for which no specific coagulation factor replacement therapy is currently available in the US. FDA granted this product Orphan Drug Status (No. 07-2469) on November 8, 2007.

BPL now submits a BLA efficacy supplement for the additional indication of routine prophylaxis to reduce the incidence of bleeding, and asks to remove the age restriction in the original approval. They provide data from one prospective study of routine prophylaxis in nine children < 12 years of age, and a retrospective survey of its use for routine prophylaxis, on-demand treatment, and perioperative management of bleeding in factor X deficiency in adults, children < 12 years of age, and adolescents 12-17 years of age.

This review considers the adequacy of the data from the two studies to determine the safety and efficacy of COAGADEX in factor X deficient subjects of all ages, with emphasis on routine prophylaxis in children < 12 years of age.

Documents pertinent to the review of COAGADEX were provided in BLA supplement 125506/46, received on March 23, 2018. The review team determined that the supplement could be filed on May 18, 2018. Data in the efficacy supplement, the proposed label, and an establishment inspection report for two of the clinical sites in which routine prophylaxis in pediatric subjects < 12 years of age was studied were evaluated in the course of the review. BPL has satisfactorily addressed all major issues, and we recommend approval of this BLA efficacy supplement for COAGADEX.

2. BACKGROUND

Factor X deficiency is an autosomal recessive bleeding disorder similar to hemophilia A and B. Unlike hemophilia A or B, which are sex linked diseases due to defects in factor VIII or factor

IX on the X chromosome, factor X deficiency affects males and females equally, due to the position of the gene for factor X on chromosome 13, and affects only ~1:1,000,000,000 people. The bleeding phenotype is similar to hemophilia A and B, though mucosal bleeding is more common in factor X deficiency. Severe disease is associated with factor X activity levels of less than 2% of normal, and the disease is mild if the factor X levels are >5% of normal.

Factor X is a vitamin K dependent protein that is synthesized in the liver hepatocyte and secreted in the blood stream as an inactive zymogen, that is cleaved and activated by either tissue factor/factor VIIa, or by factor IXa/factor VIII. After cleavage of an activation peptide, it becomes fully activated and subsequently cleaves and activates prothrombin with assistance of factor V, to generate the key active enzyme of hemostasis, thrombin, which clots fibrinogen and is an important platelet agonist. Factor Xa activity is attenuated by antithrombin, tissue factor pathway inhibitor, and protein Z-dependent inhibitor.

Prior to licensure of COAGADEX, factor X for replacement therapy has been provided in the United States by infusions of fresh frozen plasma and various prothrombin complex concentrates; in Europe a factor X/factor IX concentrate is also available. Prior to licensure, COAGADEX was studied under IND 14235 in formal studies leading to licensure, and was used under provisions of compassionate use in other patients, whose experience is reported in a retrospective survey of all such use for routine prophylaxis, on-demand therapy, and for perioperative management in patients with factor X deficiency.

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

a) Product Quality

BPL is a plasma fractionator and manufacturer of many plasma-derived products including concentrates of coagulation factors VIII, IX and XI, human albumin and various immune globulin products. The manufacturing process for COAGADEX is a modification of the process used for another BPL product, a purified plasma-derived factor IX concentrate, which is currently licensed in the United Kingdom (UK) but not in the U.S. BPL produces COAGADEX in Elstree, UK, from source plasma obtained in the United States at FDA-licensed facilities. The bulk drug substance is subjected to viral inactivation by solvent/detergent extraction, nanofiltration, and dry heat treatment. The final drug product consists of a sterile, freeze-dried concentrate packaged in two nominal dose size vials (250 IU and 500 IU), to be reconstituted immediately prior to use with sterile water for injection, using a 510(k)-cleared device (Mix2Vial, K031861) to transfer the sterile water into the lyophilized COAGADEX product for reconstitution, and to transfer the reconstituted product into a syringe for administration. The reconstituted product contains factor IX and factor II as impurities in amounts not to exceed 1 IU/mL. Factor Xa content is controlled in the final product with a non-activated partial thromboplastin time release specification. In addition, several manufacturing steps, such as prothrombin complex purification and viral inactivation (solvent/detergent treatment and terminal heat inactivation), are used in the manufacture of other BPL products.

b) CBER Lot Release (only applicable for BLAs)

The lot release protocol template was submitted to CBER for review of the original BLA for licensure and found to be acceptable after revisions. COAGADEX samples were submitted to

CBER in support of the BLA, tested by CBER and found to be acceptable. For routine lot release, the applicant submits final container samples together with the respective lot release protocols. A lot release testing plan was developed by CBER is used for routine lot release.

c) Facilities review/inspection

Not applicable

d) Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 5.31(c). The FDA concluded that this request is justified as the manufacturing of this product will not alter significantly the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

e) Product Comparability

Not applicable.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

FDA approved COAGADEX in December of 2015. The BLA review at the time of approval indicated the Pharmacology/Toxicology reviewer found the data submitted at that time adequate to characterize the pharmacology and pro-thrombotic activity of COAGADEX. Specific reference was made to single dose toxicity studies in rats in which a no-observed-effect-level (NOEL) of >2400 IU/kg body weight was established (>40-fold safety margin), and repeat dose toxicity studies in rats, with repeated administration every 2 days, established a NOEL at 30 IU/kg body weight, a greater than 6-fold safety margin.

Thrombogenicity testing in rabbits demonstrated that thrombogenicity at doses of 100-400 IU/kg body weight, not significantly different to that of the physiological saline negative control.

5. CLINICAL PHARMACOLOGY

The clinical pharmacology program consisted of the following two studies.

1. Pharmacokinetics (PK) in adults and adolescents:
The PK study of COAGADEX was conducted in 16 patients (12-58 years of age) with moderate to severe factor X deficiency (<5 IU/dL). The patients received COAGADEX intravenously at a dose of 25 IU/kg every two weeks. The PK assessment was done after the first dose and at month 6. Blood samples were taken at baseline and month 6 at 0.25, 0.5, 1, 3, 6, 24, 48, 72, 96, 120 and 144-hour post-dose. Concentrations of COAGADEX were determined by clotting assay and the PK parameters were assessed by non-compartmental analysis. The half-life and clearance of COAGADEX were 32 ± 9 hours and 1.4 ± 0.3 mL/hour per kg, respectively. The PK of COAGADEX was comparable between first dose and at month 6.

2. Determination of in-vivo Incremental Recovery (IVR) in children:

The study was conducted in 9 children with severe or moderate factor X deficiency. Four subjects were between the ages of 2.3 and 3.3 years and 5 subjects were between 8.6 to 11 years. The study assessed the efficacy, safety, and in-vivo incremental recovery of COAGADEX in children under the age of 12 years following routine prophylaxis (at least 50 exposure days) over at least 6 months (26 weeks). No specific PK study of COAGADEX was conducted in children <12 years of age. The subjects received their first dose of 50 IU/kg of COAGADEX and underwent a 30-minute post-dose in-vivo incremental recovery assessment. The mean incremental recovery for children >5 years of age was 1.83 ± 0.24 IU/dL per IU/kg whereas, the mean incremental recovery for children <5 years of age was 1.45 ± 0.17 IU/dL per IU/kg. The in-vivo incremental recovery in adults was 2.04 IU/dL per IU/kg. As compared with adults, in children <5 years and >5 to <12 years of age, the IVR of COAGADEX was lower by 29% and 10%, respectively.

6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE

A detailed formal pharmacovigilance plan was submitted as amendment 125506/46/2 (Effective date February 27, 2018, submitted to FDA April 19, 2018) to the BLA supplement. In that amendment, BPL Limited committed to routine pharmacovigilance activities, to include (from the amendment):

- Maintain systems and processes that ensure that information about all suspected adverse reactions that are reported to the personnel of the company is collected and collated in an accessible manner.
- Prepare reports for regulatory authorities:
    - Expedited Adverse Drug Reaction (ADR) reports
    - Periodic Safety Update Reports (PSURs)
- Conduct continuous monitoring of the safety profile of approved products including signal detection, issue evaluation, updating of labelling and liaison with regulatory authorities.

Pharmacovigilance activities will be conducted through the main pharmacovigilance site at Elstree, in the UK. At that site, individual case safety report forms from UK and overseas distributors, periodic safety update reports, trend analysis, and global safety-related inquiries from EMA, FDA, and other regulatory authorities will be processed.

Areas of concern to be monitored include hypersensitivity/infusion reactions, inhibitor antibody development, viral transmission, TSE transmission, and use in special populations (geriatrics, and pregnant/lactating females). Of these, the use in special populations remains an outstanding concern, going forward, as there is empiric evidence of no infusion reactions or inhibitor development with the clinical data at hand, and the manufacturing process excludes human source plasma from regions where BSE has occurred, and incorporates screening and robust viral inactivation procedures against likely important blood borne pathogens (HIV, hepatitis A/B/C, parvovirus).

The pharmacovigilance measures described in amendment 125506/46/2 are sufficient to address outstanding concerns.

a) Clinical Program

There were no discussions of the BLA efficacy supplement with the Applicant prior to its submission. Review of this efficacy supplement was conducted on an accelerated (6 month) review clock). Since COAGADEX is for the treatment of an orphan disease, review and approval of this supplement was not subject to the provisions of PREA, though the major study done in support of the routine prophylaxis indication was done in children < 12 years of age.

- Two studies were submitted in support of routine prophylaxis and removal of age restrictions for the current indications of on-demand treatment and perioperative management of factor X deficiency. One was a prospective, single arm, open-label trial of COAGADEX for routine prophylaxis against bleeding in nine factor X deficient children < 12 years of age; the other was a retrospective survey of use of COAGADEX in fifteen patients under provisions of compassionate use prior to licensure, in patients of all ages. The retrospective study of the 15 patients also included a) three subjects < 12 years of age who were received treatment for perioperative management with mild-moderate deficiency b) adult and adolescent subjects who received routine prophylaxis and on-demand treatment of bleeding.

Efficacy Results:

Routine Prophylaxis in children < 12 years

The overall efficacy rating by the Investigators of the routine prophylaxis study in children < 12 years of age was "Excellent" (highest possible rating) in all subjects (100%). In the retrospective study the overall efficacy rating was "Excellent" in 14 of 15 subjects (93%), and "Good" in the one remaining subject. The pediatric study of routine prophylaxis in children < 12 years of age showed that routine prophylaxis reduced the frequency of bleeding to 2.2 bleeds per year, per subject, and 7 of the nine subjects in the trial had no bleeding in the six months while on prophylaxis. Similar results (ABR = 2.1) were demonstrated in factor X deficient subjects of all ages on routine prophylaxis in the retrospective study of COAGADEX use in 15 subjects of various ages (ranging from 1-43 years). The ABR for the seven subjects in the retrospective survey treated only on-demand was 9.5, indicating the efficacy of routine prophylaxis. The combined experience for treating breakthrough bleeding during routine prophylaxis and bleeding on-demand showed that 76 of 83 bleeding episodes were successfully treated with no more than one infusion of COAGADEX (91.5%).

Perioperative management of children < 12 years

Three subjects < 12 years received treatment for perioperative management of bleeding. Of the three subjects, two subjects had severe factor X deficiency and underwent treatment for minor procedures with concomitant use of antifibrinolytics. The third subject with moderate factor X deficiency underwent treatment for a more invasive procedure, without concomitant administration of antifibrinolytics and adequate post treatment factor replacement levels of 61%. The efficacy outcomes in all three subjects were assessed as excellent by the investigators. The data from the third subject, given the absence of concomitant use of antifibrinolytic medications

and adequate replacement levels following treatment with COAGADEX was the primary basis to support the recommendation for perioperative management of children < 12 years of age and include the treatment of subjects with moderate factor X deficiency. In addition, extrapolation of data from adult subjects who underwent major surgery was an additional consideration for this recommendation.

Routine Prophylaxis and On-demand treatment of Adults and Adolescents
Four adult subjects and two adolescent subjects received routine prophylaxis and/or treatment of on-demand treatment. These six subjects received a mean dose of 26.4 IU/kg once weekly for routine prophylaxis. Based on these results and the pharmacokinetic assessments, the recommended dose of 25 IU/kg twice weekly is considered adequate for routine prophylaxis in adults and adolescents. Eleven subjects, majority of whom had severe factor X deficiency received on-demand treatment for 79 breakthrough bleeding or spontaneous/traumatic bleeding episodes of which 5 were considered major bleeding events. All of the bleeding events were considered to have effective outcomes as assessed by the investigator.

CBER Bioresearch Monitoring (BIMO) inspections were conducted at two clinical study sites that participated in the conduct of Study Ten02: A Phase III open-label multicenter study to confirm the safety, pharmacokinetics and efficacy of BPL's high purity factor X in the prophylaxis of bleeding in factor X deficient children under the age of 12 years (Ten02). The inspections did not reveal significant problems that impacted the data submitted in this application.

b) Pediatrics

PREA does not apply to this product and the indications that are sought due to the Orphan Designated Status. However, the key prospective study of routine prophylaxis to reduce bleeding in patients with factor X deficiency was done entirely in children < 12 years of age, and supporting data from the retrospective study of compassionate use included data on the use of COAGADEX in two children under 12 years of age and five adolescents 12-17 years of age.

c) Other Special Populations

The use of COAGADEX was not studied in pregnant/lactating females, immunocompromised, or geriatric populations.

7. SAFETY

COAGADEX was well tolerated, with no adverse events attributable to the product observed in the course of the routine prophylaxis study in children < 12 years of age or in the retrospective survey of its use under provisions of compassionate use in factor X deficient patients of all ages (range 1-43 years old). There were no deaths, no drug-related adverse events, no infusion reactions, no development of neutralizing antibodies ("inhibitors"), or thromboembolic events observed in either trial (2989 exposure combined exposure days). Many of the adverse events that were seen were unrelated to COAGADEX use and were typical events seen in children (URI, nasopharyingitis, influenza A, etc.). These did not signify any safety concern for use of the product.

8. ADVISORY COMMITTEE MEETING

No Advisory Committee Meeting was deemed necessary for the review of this efficacy supplement, as no novel issues were presented by its use for in patients with congenital factor X deficiency, in particular, in the study of prophylaxis in children <12 years of age or for routine prophylaxis, on-demand treatment or perioperative management in children < 12 years of age in the retrospective survey of compassionate use of COAGADEX.

9. OTHER RELEVANT REGULATORY ISSUES

Not applicable

10. LABELING

The COAGADEX label approved in 2015 conformed to the Physician Labeling rule. All issues negotiated in the course of review stem from proposed language in support of the indication for routine prophylaxis and use in children < 12 years of age. During negotiations over the revised label/package insert the Applicant argued for use of the word "prevent" in the proposed routine prophylaxis indication. FDA conveyed that as a regulatory term, the word "prevent" required complete elimination of bleeding in the context of routine prophylaxis, which was not observed in either of the clinical trials submitted as part of this efficacy supplement. Final language in the label agreed upon during the course of review described the routine prophylaxis indication as "Routine prophylaxis to reduce the frequency of bleeding episodes"

The APLB found the prescribing information (PI) to be acceptable from a promotional and comprehension perspective.

11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

The review team recommends approval of this BLA for the proposed indication of routine prophylaxis, removal of the age restriction for on-demand and perioperative management of factor X deficiency, and extension of the perioperative indication to moderate factor X deficiency. Efficacy and safety clinical data for COAGADEX supported a favorable benefit/risk determination for the proposed indication. No post-marketing commitment or risk mitigation strategy is recommended.

b) Risk/ Benefit Assessment

COAGADEX is a highly purified factor X concentrate derived from pooled plasma. It is manufactured with robust viral inactivation procedures against the most important blood-borne pathogens. There has been no evidence of inhibitory antibodies to factor X, no evidence of thromboembolic complications of its use, and no hypersensitivity to the product manifest by anaphylaxis or local infusion reactions. Subjects on prophylaxis have ABRs of 1-2 events per year, which is consistent with successful prophylaxis demonstrated during use of other factor concentrates for bleeding prophylaxis in hemophilia A or hemophilia B. Effective control of breakthrough bleeding or on-demand bleeding is achieved with one dose of the product in 91.5% of the time. Surgical procedures have been completed under coverage with COAGADEX with no excessive bleeding and favorable assessments of hemostasis.

The risk-benefit relationship suggests a high degree of benefit with no discernable risk.

c) Recommendation for Postmarketing Activities

The lack of any safety signal from either study, and the extreme rarity of factor X deficiency led us to conclude that there was no new studies of the safety of use of COAGADEX as part of a Post-Marketing Commitment or Requirement. The sponsor's proposed pharmacovigilance plan, which includes continuous monitoring of the safety profile and adverse event reporting to FDA in accordance with 21 CFR 600.80, is adequate.