



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology**

Pharmacovigilance Plan Final Review Memorandum

From:	Faith Barash, MD MPH Medical Officer
To:	Mikhail Osanesov, PhD Visiting Scientist, Principal Investigator Laboratory of Hemostasis / Division of Hematology / OBRR
Through:	Chris Jankosky, MD MPH Chief, Pharmacovigilance Branch Michael Nguyen, MD Acting Director, Division of Epidemiology
Subject:	Pharmacovigilance Plan Review Memo
Applicant:	BioProducts Laboratory
Product:	Coagulation Factor X (Human)

Proposed Indication:

Control and prevention of bleeding episodes in adults and children (aged 12 years and above) with hereditary factor X deficiency.

Perioperative management in adults and children (aged 12 years and above) with hereditary factor X deficiency.

Submission type: BLA 125506

Submission date: July 11, 2011

PVP Submission date: September 9, 2013

Action Due Date: March 11, 2014

1. Introduction

a. Product Description

Coagulation Factor X (Human) was granted orphan drug status by the U.S. FDA (No. 07-2469, 08 Nov 2007) for the treatment of hereditary factor X deficiency. Coagulation Factor X (Human) was developed as a replacement therapy to treat hereditary factor X deficiency, an extremely rare bleeding disorder with a prevalence of 1 in 1,000,000. There is no specific coagulation factor replacement therapy currently available.

b. Regulatory History

Request for Priority Review in accordance with Section 506 of the FDA&C Act for the product Coagulation Factor X was presented with the license application. As of the writing of this Pharmacovigilance Plan review memorandum, the product is not licensed in any country. As such, there is no post- marketing safety data to review.

c. Objectives

This memorandum is in response to a request from the Office of Blood Research and Review (OBRR) to the Office of Biostatistics and Epidemiology (OBE) to review the Pharmacovigilance Plan/Risk Management Plan submitted by BioProducts Laboratory. The BLA is seeking initial licensure of the product coagulation factor X (Replafacten) for the indication of (b) (4) for hereditary factor X deficiency. The purpose of this review is to identify potential safety issues that may need to be addressed through post-marketing safety surveillance or studies should the product be approved.

2. Materials Reviewed

- a. BLA 125506 Pharmacovigilance Plan (dated 9/9/2013)
- b. BLA 125506 Clinical Overview Review of Safety (2.5.5)
- c. BLA 125506 Summary of Clinical Safety (2.7.4)
- d. Labeling and Proposed Package Insert
- e. Other – Literature Review
- f. There are no data in FAERS, no PSUR's and no Section 915 or 921 postings. There is no Advisory Committee review.

3. Pharmacovigilance Plan Review

Epidemiology:

Hereditary Factor X Deficiency is a rare type of hemophilia due to an inherited lack of Coagulation Factor X. The prevalence in the general population is approximately 1 in 1 million (Uprichard and Perry, 2002; Peyvandi et al, 2002). The gene for factor X is located on chromosome 13, so unlike sex linked hemophilias, both genders can be carriers of the mutation and/or develop the condition. Only 89 patients with this condition have been identified in the US, but this may underestimate the true prevalence.

Hereditary Factor X Deficiency can vary in severity. Bleeding patterns may be similar to those of male patients with hemophilia, with joint and muscle bleeds being common. Patients may also experience significant bleeding from mucus membranes such as nose, lungs and gastrointestinal tract. Females of child-bearing age may experience menorrhagia. Bleeding from the umbilical cord in neonates is also common (Herrmann et al, 2006)

Safety Concerns and Planned Pharmacovigilance Actions (from Table 14 of sponsor provided PVP)

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
Adverse reactions such as infusion site irritation, fatigue and back pain	Routine Pharmacovigilance	Listed as Adverse Reactions in section 6.1 of the proposed Prescribing Information.
Lack of effect	Routine Pharmacovigilance	Warning in section 2.1 of the proposed Prescribing Information that patients may vary in their pharmacokinetic and clinical responses to REPLAFACEN
Hypersensitivity or allergic reactions, including anaphylaxis	Routine Pharmacovigilance	Section 4 of the proposed Prescribing Information contra-indicates use in patients with a history of hypersensitivity to any of the product components. Warning in section 5.1 of the proposed Prescribing Information regarding risk of allergic reactions.
Inhibitor development	Routine Pharmacovigilance	Warning in section 5.2 of proposed Prescribing Information regarding risk of inhibitor development.
Virus transmission	Routine Pharmacovigilance	Warning in section 5.3 of proposed Prescribing Information regarding risk of transmissible infectious agents.
TSE transmission	Routine Pharmacovigilance	Warning in section 5.3 of proposed Prescribing Information regarding risk of transmissible infectious agents
No clinical data in labor or delivery	Routine Pharmacovigilance	Warning in section 8.2 of proposed Prescribing Information that no studies have investigated use during labor or delivery.
No clinical data in subjects aged less than 12 years	Routine Pharmacovigilance	Section 1.2 of the proposed Prescribing Information states that the product is indicated for adults and children (aged 12 years and above). Section 8.4 of the proposed Prescribing Information states that safety and effectiveness in patients aged under the age of 12 years have not been established.
No clinical data in subjects aged 65 years or over	Routine Pharmacovigilance	Warning in section 8.5 of proposed Prescribing Information that clinical studies did not include sufficient patients aged 65 or more to determine whether they respond differently from younger subjects.

a. Summary of Clinical Safety (2.7.4)

The overall safety evaluation of Replafacten, Factor X, is based on safety data from two clinical trials: Ten01 and Ten03 studies.

Ten01 is a phase III open, multicenter study to investigate the pharmacokinetics, safety and efficacy of BPL's high purity Factor X in the treatment of moderate and severe factor X deficiency. In an interim analysis of data collected through 10 Aug 2012, 13 subjects were enrolled and received at least 1 dose of Factor X for treatment of bleeds or for controlling bleeding in surgical cases.

The 13 subjects were from 8 sites in 5 countries. There were 2 sites in UK, 2 sites in Spain, 1 site in USA, 1 site in Germany and 2 sites in Turkey.

Ten03 is a phase III open, multicenter study to investigate the safety and efficacy of Factor X for prophylaxis in Factor X deficient subjects undergoing surgery. In an interim analysis, 1 subject received Factor X.

Neither study included a control group because of the rarity of the disease and for ethical considerations.

Both studies are currently ongoing.

The total number of infusions received in study Ten01 was 258, and the total exposure days were 257. The total number of infusions received in study Ten03 was 15.

Table 1. Extent of exposure to Factor X per subject in Ten01 and Ten03 studies:

Variable Per Subject	Ten01	Ten03
N	13	1
Time on Study (subject-months)	145.4	0.5
Total Dose by cut-off date (International Units)		13,338 IU
Mean Total Dose (IU)	37,337.3 IU	
SD	42,321.007 IU	

Minimum	46,55.6 IU	
Median	19,178.6 IU	
Maximum	133,224.0 IU	
Total unit dose IU/kg		151.9 IU/kg
Mean	514.28 IU/kg	
SD	532.09 IU/kg	
Minimum	50.0 IU/kg	
Median	296.9 IU/kg	
Maximum	1,665.2 IU/kg	
Total number of infusions by cut off		15
Mean	19.8	
SD	20.83	
Minimum	2	
Median	11.0	
Maximum	67	

Nominal dose based on labeled FX content (570 IU/vial)

Factor X (Replafacten) human dose of 60 IU/kg is the recommended pre-surgical bolus to increase Factor X levels to 70-90 IU/dl.

IU – International Units

Table 2. Number of Factor X infusions given per indication by subject:

Subject number	No. infusions on demand	No. infusions treat bleeds	No. infusions for any prevent.	No. infusions before surgery	No. infusions PK assessment	Total
Ten01						

(b) (6)	0	0	0	1	1	2
(b) (6)	26	18	8	0	2	28
(b) (6)	1	1	0	0	1	2
(b) (6)	21	4	17	0	2	23
(b) (6)	65	11	54	0	2	67
(b) (6)	27	13	14	0	1	28
(b) (6)	9	8	1	0	2	11
(b) (6)	2	2	0	0	1	3
(b) (6)	10	10	0	0	2	12
(b) (6)	7	7	0	0	2	9
(b) (6)	6	6	0	0	2	8
(b) (6)	6	6	0	0	2	8
(b) (6)	54	34	20	1	2	57
Total	234	120	114	2	22	258

Ten 03						
(b) (6)	0	0	14	1	0	15

Demographics:

Of the 12 subjects who received Factor X to treat a bleed, the age range was 12-58 years. Three subjects were male, nine were female. Nine subjects were Caucasian, two were Asian, and two were African-American.

Table 3. Subject demographics and disease history

Study	Ten 01	Ten 03

N	13	1
Age	29.9(+/-15.45;range 14-58)	55
No. adult subjects (>15yr)	11	1
No. adolescent subj. (12-<16 yr)	2	0
weight	69.59(+/-19)	88
Gender (%)		
Male	4(30.8%)	1(100%)
Female	9(69.2%)	0
Race (%)		
American indian, Alaska native	0	0
Asian	2(15.4%)	0
African american	2(15.4%)	0
Hawaiin, pacific islander	0	0
White, caucasian	9(69.2%)	1(100%)
other	0	0
Ethnicity		
Hispanic	4(30.8%)	0
Non-hispanic	9(69.2%)	1(100%)
Time since diagnosis	22.8(+/-11.95%)	27
Factor X activity at diagnosis	4.0(+/-3.74)	8

Time since lowest factor X activity recorded	7.6(+/-11.10)	27
Lowest factor X activity	0.92(+/-1.04)	8

Analysis of Adverse Events (2.7.4.2.1)

The table below summarizes all treatment emergent adverse events (adverse events that occur during the course of treatment) that occurred in at least 2 subjects. 12 of 14 subjects experienced at least one treatment emergent adverse event. The most common adverse event was headache, occurring in 28.6% of subjects.

Table 4. Treatment-emergent adverse events that occurred in at least 2 subjects:

Preferred Term	Number of Subjects	Percent (%)
Any AE	12	85.7
Headache	4	28.6
Nasopharyngitis	3	21.4
Nausea	3	21.4
Pain (extremity)	3	21.4
Anemia	2	14.3
Arthralgia	2	14.3
Back Pain	2	14.3
Constipation	2	14.3
Hypotension	2	14.3
Insomnia	2	14.3
Pyrexia	2	14.3

Of the 14 subjects who received Factor X, 1 subject ((b) (6)) died of pneumonia. The event was considered by the sponsor as unrelated to Factor X treatment.

Including the 1 death, a total of 5 serious adverse events were noted in 3 subjects. All SAEs occurred in Ten01. All were considered to be unrelated to treatment with Factor X. No SAE occurred in the Ten03 study.

The second subject (03002) with a SAE had a right forearm bleed, which became serious because the ((b) (6)) did not seek medical care until 3 days post commencement of the adverse event. On presentation to hospital, subject was treated with Factor X and hospitalized, triggering the report as a serious adverse event.

The third subject (subject ((b) (6)) with a SAE was reported to have menorrhagia and dysmenorrhea. This was considered unrelated to Factor X by the sponsor. This SAE is likely related to the underlying Factor X deficiency. (Reviewer's comment)

Important Identified Safety Issues:

Replafacten is a plasma derived product. As such, it carries the known risk of transmission of viral disease. Viral elimination processes include three well established steps: solvent detergent treatment, filtration through a 15nm virus retentive filter and terminal dry heat treatment. In Ten01, 4 subjects completed virology assessments. No seroconversion was seen for HAV, HCV, HIV, HBsAg, or Parvovirus. In Ten03, no seroconversion in any viral titer was seen in the subject.

Important Potential Safety Issues:

Replafacten has a high possibility of off-label use in Factor X deficient children, in Factor X deficient pregnant patients, in situations where there is necessity for rapid reversal of anti-coagulation or in other situations of uncontrollable bleeding.

Important Missing Information:

Safety and effectiveness in patients under the age of 12 years has not been established. There is the potential for off-label pediatric use in children with Factor X Deficiency. There is no clinical data to support this use, and the proposed labeling states that the product is indicated for use in patients age 12 years or older.

Because of orphan designation, PREA is not triggered. BPL had intended to complete a study to assess the safety and efficacy of BPL factor X in children < 12 years old. Pediatric safety data was to become available once the study was completed.

A protocol for Factor X (Human) pediatric study Ten02 was presented. However, the sponsor does not intend to proceed with this trial at this time. A waiver for the Ten02 pediatric study has been requested. Per the sponsor, the basis for the waiver is that while Factor X (Human) offers improvement in the clinical management of this bleeding disorder, a clinical study in children will not be of significant therapeutic benefit over the existing clinical data.

Use in Pregnancy and Lactation (2.7.4.2.5.4)

Neither clinical trial included subjects who were pregnant. Factor X is a naturally occurring protein derived from human plasma. It is not expected to be teratogenic, and is not likely to cross the placenta or be excreted into breast milk.

Development of inhibitor antibodies:

In the Ten01 and Ten03 studies, all subjects tested negative for Factor X inhibitors throughout the study period. When PK parameters for Factor X inhibitors were measured at the repeat visit, there was no indication of development of Factor X inhibitors.

Thrombogenicity Markers:

Thrombogenicity markers (D-dimer, TAT and F1+2) were reviewed by BPL for spurious data and significant pre-dose increases at baseline and repeat PK visits. After exclusion of spurious data, there were elevations in all three parameters in one of the 13 subjects ((b) (6)) at the baseline visit. Elevation was not observed at the repeat PK visit, suggesting that the results at the baseline visit may be the result of incorrect sample handling and does not appear to be reproducible. The thrombogenicity marker results are difficult to interpret given the subjects ongoing bleeding at the visit. No clinical signs or symptoms of thrombosis were noted in this or any other subject.

Factor X is not expected to have any abuse potential. No case of overdose was reported in the clinical trials. An overdose of Factor X may present theoretical risks of thrombosis.

Postmarketing Data (2.7.4.2.6):

Factor X has not been marketed in any country.

Sponsor's Proposed Actions:

BPL plans to conduct routine pharmacovigilance including the elements below:

- **Maintenance of systems and processes that ensure information about all suspected adverse reactions are reported**
- **Prepare reports for regulatory authorities, including expedited adverse drug reaction reports and periodic safety update reports (PSURs)**
- **Conduct continuous monitoring of the safety profile of approved products, including signal detection, issue evaluation, updating of labeling and liaison with regulatory authorities.**

Bio Products Laboratory Ltd (BPL) has one main pharmacovigilance site at Elstree in the United Kingdom, where data entry and preparation of Periodic Safety Update Reports are generated. Expedited submissions to regulatory authorities including FDA are managed at this site.

BioProducts Laboratory Ltd (BPL) has one overseas subsidiary based in Raleigh, North Carolina.

4. Other Information

There is no data retrieved from data mining.

A PubMed search for “factor x deficiency treatment” retrieved 193 papers. There were no articles specifically about Coagulation Factor X (human), Replafacten.

Selected publications listed below:

Martin-Salces M et al. Femur fracture in a woman with severe factor X deficiency- an experience using Factor X concentrate in surgery. Hemophilia 2013; 7:1-2

Menegatti M. Factor X Deficiency. Semin Thromb Hemost 2009; 35(4): 407-415

Brown DL et al. Diagnosis and treatment of inherited factor X deficiency. Hemophilia 2008 Nov; 14(6): 1176-82

Nance D et al. Factor X deficiency and pregnancy: preconception counseling and therapeutic options. Hemophilia 2012 May; 18(3)

Teixeira PS et al. Factor X deficiency and pregnancy: case report and counseling. Hemophilia 2012 Jan; 18(1)

Chiossi G et al. Plasma Exchange in a Case of Severe Factor X Deficiency in Pregnancy: Critical Review of the Literature. Amer J Perinatol 2008; 25(3): 189-192

Peyvandi F et al. Rare coagulation deficiencies. Hemophilia 2002; 8: 308-321

Factor X deficiency is typically treated with fresh frozen plasma or prothrombin plasma concentrates for acute bleeding episodes or in preparation for surgery. The disadvantages of FFP include the large volume of fluid required, allergic reactions and the variable half-life. Administration of prothrombin plasma concentrate is associated with a risk of thromboembolism. One article was retrieved outlining use of a factor X concentrate (CSL Behring, Marburg, Germany) which contains both Factor X and Factor IX.

There were no articles specifically addressing either Replafacten or Coagulation Factor X concentrate. The above articles provide perspective on the current standard of care treatment of this rare bleeding disorder.

5. Post-Licensure Safety Review

There are no post-licensure materials for review, as the product has not been marketed, and there is no product of the same class.

6. Integrated Risk Assessment

Factor X concentrate (Replafacten) appears to have a reasonable safety profile, but the clinical studies were very small. In this very small study, there did not appear to be significant risks of thrombogenicity, antibody formation, anaphylaxis or viral transmission. A concern exists about the probable off-label use in pediatric or pregnant populations.

BPL had previously stated that (b) (4)

Per sponsor, this decision does not conflict with the proposed indication submitted in the BLA. The product will likely be used in both the Factor X deficient pediatric population and the Factor X deficient pregnant population, and the sponsor should collect and analyze adverse event data if used off-label in these populations. (Reviewer comment)

7. Recommendations/Letter-ready comments

- **OBE has reviewed the sponsor's pharmacovigilance plan for BLA 125506, Replafacten, Factor X replacement.**
- **There were not apparent safety issues that would prevent approval of this BLA. However, the study size is small, making the detection of rare adverse events difficult.**