

CLINICAL PHARMACOLOGY REVIEW

Division of Hematology
Office of Blood Review & Research

STN 125506

Applicant: Bio Products Laboratory

Product: Coagulation Factor X (Human)

Indication: Treatment of hereditary factor X deficiency for coagulation Factor X product

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INTRODUCTION

Factor X is one of the vitamin-K-dependent serine proteases and plays a crucial role in blood coagulation in both the intrinsic and extrinsic pathways of the clotting cascade. Factor X deficiency is rare hemophilia due to inherited lack of coagulation factor X. The prevalence of severe factor X deficiency in the general population is approximately 1 in 1 million which puts it between 1/100 and 1/20 of the prevalence of hemophilias A and B, respectively. Although hereditary factor X deficiency is very rare, acquired factor X deficiency is even rarer.

The genes for FVIII and FIX reside on the X chromosome; therefore, only males are affected by the FVIII and FIX deficiencies. The gene for factor X, however, is on the long arm of chromosome 13. Thus, unlike hemophilias A and B, both genders can be carriers of the genetic mutation responsible for factor X deficiency and/or develop the condition.

Severe factor X deficiency refers to the endogenous concentration of factor X of <1% (< 1 IU/dL); moderate factor X deficiency refers to the factor X functional activity of 1-5%; and mild factor X deficiency refers to factor X activity of >5% compared to the factor X activity in the general population of 65-120 IU/dL.

Hereditary factor X deficiency is currently treated using either fresh frozen plasma (FFP) or a prothrombin complex concentrate (PCC). Factor X concentration in FFP is extremely low, and large volumes of FFP have to be administered in factor X deficient patients to provide sufficient factor X to stop bleeding.

Three types of PCC products are available: 3-factor complex containing factors II, IV, and X; 4-factor complex containing factor VII in addition to the above; and a complex combining factor IX and X. PCC products have the advantage over FFP as the coagulation factors in PCC are concentrated, thus requiring smaller infusion volumes (approximately 50 mL).

Bio Products Laboratory Ltd (BPL) is currently developing a new, high-purity, plasma-derived factor X concentrate, known as FACTOR X. FACTOR X is purified from pooled human blood plasma collected from healthy US donors who have been subjected to medical examinations, laboratory tests, and a review of their medical history before the donation. Each donation must be nonreactive for hepatitis B surface antigen (HBsAg), anti-HIV-1 and anti-HIV-2 antibodies, and anti-HCV antibodies. Furthermore, plasma minipools (512 donations per pool) have undergone screening for HIV, HBV, HCV, HAV, and Parvovirus B19. Fractionation pools are tested for HBsAg and HIV and HCV antibodies. In addition, HCV and Parvovirus B19 are tested using (b) (4)

The clinical pharmacology review consists of a phase III pharmacokinetic trial of factor X in severe and moderate factor X deficient patients.

CLINICAL PHARMACOLOGY LABELING COMMENTS

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Factor X is an inactive zymogen, which can be activated by factor IXa (via the intrinsic pathway) or by factor VIIa (via the extrinsic pathway). Factor X is converted from its inactive form to the active form (factor Xa) by the cleavage of a 52-residue peptide from the heavy chain. Factor Xa associates with factor Va on a phospholipid surface to form the prothrombinase complex, which activates prothrombin to thrombin in the presence of calcium ions. Thrombin then acts upon soluble fibrinogen and factor XIII to generate a cross-linked fibrin clot [See Module 4.2.1.1.1].

12.2 Pharmacodynamics

Replafacten is derived from human plasma and used as a replacement for the naturally existing coagulation factor X in patients with hereditary factor X deficiency [See Module 2.7.2, Section 1].

12.3 Pharmacokinetics

In a clinical study of Replafacten in subjects with severe or moderate factor X deficiency (basal FX:C <5 IU/dL), the pharmacokinetics of Replafacten were assessed after intravenous infusion (please describe the infusion time) administration of a nominal dose of 25 IU/kg Replafacten dose. Pharmacokinetic (PK) parameters were calculated from plasma factor X:C activity measurements after subtraction of the pre-dose value. The PK parameters for 13 subjects at the baseline visit are summarized in Table 3. The PK assessment was repeated at least 6 months post-baseline. The PK parameters for 8 subjects at the repeat PK assessment were compared with the first dose for the same 8 subjects at the baseline visit after the first and are summarized in Table 3. The PK assessment was repeated at least 6 months after the first dose. The PK parameters following a single and repeat dose are summarized in Table 3. The pharmacokinetics of Replafacten were similar following the single and repeat dosing.

Please describe Baseline Visit as ‘First Dose’ in the footnote of Table 3. Please delete column 3 in Table 3. Please delete Tmax, Cmax, and C0 values.

Table 3 Summary of Mean PK Parameters at the Baseline Visit

	Baseline Visit (n=13)	Repeat PK Assessment (n=8)	Repeat PK Assessment (n=8)
	mean (CV)	mean (CV)	(% Baseline Visit)
T _{max} (hr)	0.367 (0.233, 1.20)*	0.417 (0.250, 3.00)*	ND
C _{max} (IU/mL)	0.508 (19.1)	0.465 (23.7)	96.4
Half-life (hr)	30.9 (24.8)	29.2 (17.8)	93.2
AUC _{0-144h} (IU.hr /mL)	17.6 (21.9)	16.0 (27.2)	96.6
AUC _(0-∞) (IU.hr /mL)	18.5 (21.5)	16.8 (28.7)	ND
C ₀	0.488 (20.1)	0.453 (43.0)	102
V _{ss} (mL/kg)	53.3 (28.7)	58.2 (14.8)	102
CL (mL/kg/hr)	1.23 (24.1)	1.43 (23.8)	110
MRT _(0-∞) (hr)	43.2 (21.0)	40.7 (20.0)	ND
Incremental recovery (IU/dL per IU/kg) [§]	2.22 (22.1)	1.93 (22.3)	91.1

* Presented as median and range

[§] Using peak increment within 1 hour post-dose

ND Not done

~~Repeat/baseline ratios for all PK parameters were within the range of 90% to 110% [See Module 2.7.2 Section 2.1.5.1].~~

Deleted because this information is in Table 3

~~Incremental recovery at the repeat PK assessment was statistically equivalent to that at baseline. Combining incremental recovery values at the baseline visit and repeat PK assessment gave an overall mean incremental recovery of 2.1 IU/dL per IU/kg [See Module 2.7.2, Section 2.1.6].~~

~~There is no anticipated effect.~~ Studies were not conducted to evaluate the impact of gender or renal/hepatic function on the pharmacokinetics profile of Replafacten.

RECOMMENDATION

The pharmacokinetic study report is acceptable. The sponsor should modify the clinical pharmacology labeling as suggested by the FDA.

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Study Title: A Phase III open, multi-center study to investigate the pharmacokinetics, safety and efficacy of BPL's high purity factor X in the treatment of severe and moderate factor X deficiency.

This was an open, multi-center, nonrandomized, prospective study in subjects with severe and moderate factor X deficiency to assess the pharmacokinetics (PK), safety, and efficacy of FACTOR X. After an initial dose and PK assessment at the baseline visit, subjects received FACTOR X for spontaneous or traumatic bleeds or for specific short-term preventative use. The duration of the study for each subject was at least 27 weeks: at least 1 week between the screening visit and the baseline visit to allow for analyses, at least 25 weeks through the 6-month visit, and an end-of-study visit at least 1 week after the 6-month visit.

Subjects requiring any surgical or invasive procedure during the course of the trial, whether planned or emergency, could do so using FACTOR X if the local laboratory at the main investigational site or other hospital at which the surgery was performed.

There were 13 and 8 subjects in single and repeat dose study, respectively. The mean age was 29.9 years with a range of 14 to 58 years (2 subjects aged 14 and 17 years). There were 4 males and 9 females in the study. Of the 13 subjects in the study, 12 had severe factor X deficiency with FX:C level <1%, and 1 subject had moderate disease with FX:C level in the range of 1% to <5%. The subjects were diagnosed with factor X deficiency for a mean duration of 22.8 years. Before entering this study, all 13 subjects had been treated with replacement factor concentrates, and 11 had been treated with fresh frozen plasma. In addition, 12 subjects had experienced spontaneous bleeding in the past.

Subjects received 25 IU of factor X per kg body weight (25 IU/kg) by intravenous infusion at a rate of 10 mL/min but no more than 20 mL/minute. In addition, the dosage of FACTOR X for subjects requiring surgical or invasive procedure during the study was calculated based on the subject's factor X level and body weight and a nominal recovery of 1.5 IU/dL per IU/Kg. Factor X dose of 25 IU/kg was based on the empirical finding that 1 IU/kg of factor X can raise a patient's factor X level by 1.5% of normal (expected to raise the factor X level by approximately 35-40% of normal).

The loading dose was calculated to raise the subject's factor X level to 70% to 90% of normal. The post-surgery maintenance dose was calculated to maintain the subject's factor X level at least 50% of normal. Each subject received 1 dose of FACTOR X at the baseline visit and additional doses of FACTOR X to treat spontaneous or traumatic bleeds or for short-term preventative use as needed for at least 6 months. If a subject did not experience a bleed that required FACTOR X treatment within the first 5 months, the study could be extended at 3-month intervals for the subject, until a bleed occurred, for up to a total duration of 2 years.

For pharmacokinetic study, blood samples were taken at 0.25, 0.5, 1, 3, 6, 24, 48, 72, 96, 120, 144, and 168 hours post dose. Factor X concentrations were measured by both the one-stage

clotting and chromogenic assays. The concentrations of FX:C and FX:Ag at pre-dose were subtracted from all subsequent post-dose concentrations. Pharmacokinetic parameters were calculated by non-compartmental analysis and are shown in Table 1. Plasma concentration-time profiles of Factor X are shown in Figures 1-2.

Table 1
Pharmacokinetic parameters (mean \pm SD) of Factor X following
25 IU/kg intravenous dose to subjects with severe and moderate factor X deficiency

Parameters	Clotting Assay		Chromogenic Assay	
	Single dose	Repeat dose	Single dose	Repeat dose
Sample size (n)	13	8	13	8
AUC _(0-inf)	18.9 \pm 4.1	17.3 \pm 4.8	23.2 \pm 5.8	20.2 \pm 6.1
CL (mL/h/kg)	1.27 \pm 0.31	1.47 \pm 0.36	1.15 \pm 0.39	1.29 \pm 0.38
Half-life (hrs)	32 \pm 9	30 \pm 5	34 \pm 7	30 \pm 5
MRT (hrs)	44 \pm 10	41 \pm 8	48 \pm 9	42 \pm 10
V _{ss} (mL/kg)	56 \pm 18	59 \pm 8	54 \pm 17	52 \pm 9
IR (IU/dL)/(IU/kg)	2.23 \pm 0.51	1.79 \pm 0.34	2.34 \pm 0.59	2.01 \pm 0.40

AUC = Area under the curve (Unit = IU x hr/mL); CL = Clearance; MRT = Mean residence time; V_{ss} = Volume of distribution at steady state; IR = Incremental recovery

Conclusions: Factor X is a low clearance drug with a half-life of 30 hours. Repeat dosing of Factor X does not accumulate in the systemic circulation as there is no difference in the PK parameters of Factor X between the first dose and the repeat dose.

Figure 1: Mean pre-dose-adjusted plasma concentrations of FX:C (**clotting**) following a single IV bolus dose of 25 IU/kg FACTOR X: Baseline and Repeat PK assessment

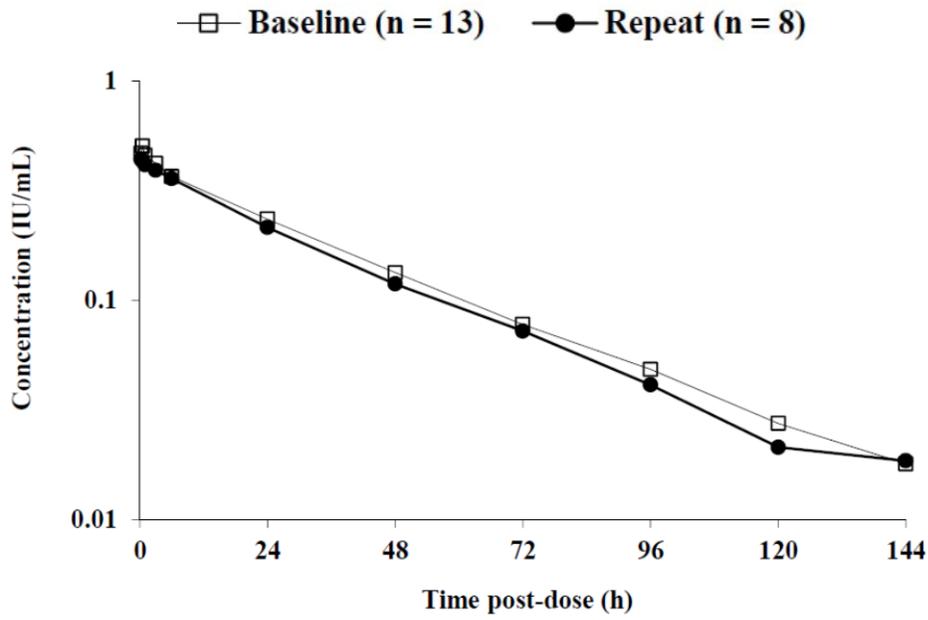


Figure 2: Mean pre-dose-adjusted plasma concentrations of FX:C (**chromogenic**) following a single IV bolus dose of 25 IU/kg FACTOR X: Baseline and Repeat PK assessment

