

CLINICAL REVIEW
Division of Hematology Clinical Review
Office of Blood Review & Research

DATE: February 18, 2016

TO: File of 125582/0; Edward Thompson, RPMS/OBRR

FROM: Lisa Faulcon, MD, Team Lead, HPRB/DHCR/OBRR

THROUGH: Bindu George, MD, Branch Chief, CRB/DHCR/OBRR
Howard Chazin, MD, Deputy Director, DHCR/OBRR

APPLICANT: CSL Behring

PRODUCT: Coagulation Factor IX (Recombinant), Albumin Fusion Protein (rIX-FP)

INDICATION: IDELVION, Coagulation Factor IX (Recombinant), Albumin Fusion Protein (rFIX-FP) is indicated in children and adults with hemophilia B (congenital Factor IX deficiency) for:

- On-demand control and prevention of bleeding episodes
- Perioperative management of bleeding
- Routine prophylaxis to reduce the frequency of bleeding episodes

SUBJECT: ADDENDUM clinical memo

Recommendation: Approval is recommended by this clinical reviewer. No postmarketing studies are required; routine pharmacovigilance is suggested. The sponsor has agreed to implement a Dear Healthcare Provider Letter within 60 days of BLA approval. IDELVION is an orphan designated product and therefore does not trigger PREA.

EXECUTIVE SUMMARY

Note to the reader: During the IDELVION BLA review cycle, the clinical review was initiated and conducted by Peter Waldron, MD, CDER Medical Officer on detail to OBRR/Division of Hematology Clinical Review (DHCR) and continued by this clinical reviewer, Lisa Faulcon, MD, CBER Medical Officer/Team Leader in DHCR. Reviewer comments, further clarifications, Risk Benefit considerations and final recommendations were added to Dr. Waldron's clinical review by Howard Chazin, MD, Deputy Director, DHCR. This memo is an addendum to Dr. Waldron's clinical review memo and addresses only those aspects of the review that I reviewed.

CSL Behring (CSLB) submitted a Biologics License Application (BLA) (No. 125582) for Coagulation Factor IX (Recombinant), Albumin Fusion Protein (rIX-FP; albutrepenonacog alfa) on 05 December 2014 to support the following proposed indications in adults and children with congenital factor IX deficiency:

- On-demand control and prevention of bleeding episodes
- Perioperative management of bleeding
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes

The active ingredient of IDELVION, rIX-FP, is a purified protein derived from a Chinese Hamster Ovary (CHO) cell line and produced by recombinant DNA technology. It is produced by the genetic fusion of recombinant albumin to recombinant coagulation factor IX (FIX). The recombinant FIX portion is identical to the Thr148 allelic form of human plasma-derived FIX. The cleavable linker between the recombinant FIX and albumin molecules is derived from the endogenous “activation peptide” in native FIX. rIX-FP remains intact in the circulation until FIX is activated and upon activation of FIX, albumin is cleaved off and activated FIX (FIXa) is released. The final drug product is provided as a lyophilized powder in single-use glass vials containing nominally 250, 500, 1000 or 2000 international units of the active ingredient. The potency in international units is determined using an in vitro thromboplastin time (aPTT)-based one-stage clotting assay calibrated against the World Health Organization International Standard for FIX concentrate. Besides the active ingredient rIX-FP, each single use vial contains tri-sodium citrate, polysorbate 80, mannitol, and sucrose as excipients. For application by intravenous injection, the lyophilized drug product is reconstituted using 2.5 mL or 5 mL (for 2000 IU) of sterile water for injection, using a needleless Mix2vial device.

As discussed in Dr. Waldron’s memo, the efficacy and safety of IDELVION for the proposed indications were established in five open-label, prospective clinical trials of 111 unique subjects with hemophilia B (FIX activity $\leq 2\%$). Two of these studies were conducted under IND 14978. The submission does not trigger PREA because IDELVION is orphan designated for “treatment of patients with congenital FIX deficiency (hemophilia B)” (designated 04/27/2012). No post-marketing studies are required for this product.

DISCUSSION OF KEY ISSUES IDENTIFIED DURING THE REVIEW

I. Potential Safety Concern of Proteinuria

Background

Subjects in the phase 3 study CSL654_3001 (hereafter Study 3001) underwent routine urinalysis testing to assess for asymptomatic hematuria. Hematuria, both macroscopic and microscopic, is a

common problem in the management of hemophilia. Urinalysis was conducted by each local laboratory at all study centers in 10 countries according to local standard practice.

During his review, Dr. Waldron identified a potential safety concern of proteinuria in four subjects (4/63; 6%) who were enrolled in Study 3001 and had negative urinalyses at baseline. Because of the novelty of the product and the fact that proteinuria is recognized as an independent risk factor for renal disease and as a predictor of end-organ damage, a consult from the Center for Drug Evaluation and Research, Division of Cardiovascular and Renal Products, Aliza Thompson, MD was obtained (hereafter CDER CardioRenal consultant; Appendix I). Although this issue was not identified in other trials of IDELVION, Trial CSL654_2004 was the only other study that included routine urinalysis testing; this study included only 17 subjects who were on study for up to 20 weeks. In response to FDA inquiry (June 1, 2015; amendment 16), CSLB noted that the “out of range urine results were reviewed in each of the five Independent Data Monitoring Committee meetings throughout the study” and no action was taken by the Committee. The four cases of proteinuria are summarized below:

1. Subject (b) (6) was a 15-year-old white male who had a urinalysis that was positive for protein at weeks **12, 28, 44, 60** and **at the end-of-study visit**. As indicated in Table 1 below, the results of the urinalysis were reported as “+”; the applicant states that this corresponds to approximately 30 mg of protein per dL. The urinalyses were negative for blood. During the screening period, the subject experienced multiple trauma-induced severe bleeding episodes that required hospitalization; he received the first dose of rIX-FP eight months after the first urinalysis. After the pharmacokinetic (PK) analysis, the subject received 50 IU/kg as weekly prophylaxis throughout the study for a total of 78 weeks (18 months), and continued a routine prophylaxis regimen during the extension study. A review of the serum chemistries revealed normal serum albumin measurements and no pattern of increasing serum creatinine. There were no reports of hypertension. The CDER CardioRenal consultant concluded that interpretation of these findings are limited by the fact that the screening/baseline value was made almost one year prior to the measurement at 12 weeks.

Table 1: Subject (b) (6) Urinalysis Results

	Urine specific gravity	Urine protein (site source)	Other findings in the urine
Screening	1.011	negative	
W12	1.017	+	
W28	1.021	+	
W44	1.026	+	Leukocytes 2+
W60	1.022	+	
EoS	1.015	+	

2. Subject (b) (6) was a 54-year-old Asian male with a history of hepatitis C and

hypertension with a urinalysis that was positive for protein at weeks **12 and 44** and negative for protein at weeks 28, 60, 76, 92 and the end-of-study visit (Table 2). The subject received 36 IU/kg rIX-FP weekly until he switched to 75 IU/kg every 14 days by Week 40 for a total of 72 doses during the 24 months study period; he continued a routine prophylaxis regimen during the extension study. The CDER CardioRenal consultant concluded that the finding was intermittent and was not seen at later time points in the trial and that the patient had underlying conditions (e.g., hypertension) that could cause proteinuria.

Table 2: Subject (b) (6) Urinalysis Results

	Urine specific gravity	Urine Protein (site source)	Corresponding to (confirmed by PI)
Screening	1.021	Negative	2+ urine protein prior to study entry (2008)
W12	1.033	±	trace
W28	1.023	Negative	
W44	1.034	1+	
W60	1.017	Negative	
W76	1.025	Negative	
W92	1.018	Negative	
EoS	1.016	Negative	

- Subject (b) (6) was a 43-year-old white male with a history of hepatitis C and urinalysis that was negative for protein at baseline, weeks 12 and 28 and positive at week **44** with a value of 1 g/L (normal range: 0.0-0.3 g/L) listed for the **end-of-study visit**, which occurred more than 6 months after the 28 week visit (Table 3). The subject received rIX-FP 50 IU/kg on a weekly prophylaxis regimen until Week 44, was switched to 75 IU/kg every 10 days and then extended the treatment interval to once every 14 days at Week 68 until EoS for a total 79 doses during the ~20 month period; he continued a routine prophylaxis regimen during the extension study. A review of the serum chemistries revealed that the serum albumin measurement at week 12 was above the reference range (55 g/L; normal range 35-52 g/L); all other measurements were within the reference range. The subject reportedly had two urinary tract infections during the study (from week 16 to week 40) and syphilis (from week 56 to week 68), and was treated with several agents that could have caused or contributed to the proteinuria, including the concomitant use of the fluroquinolone ofloxacin which has a labeled adverse event of proteinuria.

Table 3: Subject (b) (6) Urinalysis Results

	Urine Specific Gravity	Urine protein (eCRF)	Urine protein (site source)
Screening	1.010	Negative	negative
W12	1.010	Negative	negative
W28	1.010	Negative	negative
W44	1.005	+	+ and 0.3g/L
EoS (W80)	1.000	1 g/L	++ and 1g/L

4. Subject (b) (6) was a 26-year-old white male with a urinalysis that was positive for proteinuria at weeks **12 and 28 and the end-of study visit**, which was approximately 3 months later (Table 4). Leukocytes were also identified in the urine samples from Week 12 and EoS of Study 3001, which may indicate sample contamination or pyuria. He was treated with rIX-FP episodically (on-demand only), at a dose of 50 IU/kg, and accumulated only 14 doses during the 10 month study period in Study 3001. This subject was enrolled in the extension study but was withdrawn since March 26, 2015 due to lost follow-up and noncompliance. There were no significant differences in urinary concentration at each of the time points and serum albumin measurements were all within the reference range. The applicant stated that a dose of paracetamol (acetaminophen) taken 48 hours prior to the Week 28 visit and an elevated, but within range (1.001 to 1.035), specific gravity which suggested dehydration likely contributed to the observed proteinuria, which is highly speculative.

Table 4: Subject (b) (6) Urinalysis Results

	Urine specific gravity	Urine protein (site source)	Other findings in the urine
screening	1.025	negative	
W12	1.030	trace	+ Leukocyte
W28	1.025	0.3g/L (1+)	+ Ketones (0.4g/L)
EoS	1.020	trace/negative	+ Leukocyte

Analysis of Submitted Data:

After review of these data, this reviewer noted that a causal relationship could be established in each of the four cases: based on the protocol-defined categories on page 81/121 of Protocol Amendment 3, the first three cases would be considered at least possibly related (event or laboratory test abnormality with reasonable time relationship to intake of the investigational product but could also be explained by disease or other drugs); subject (b) (6) had an unexplained observation of proteinuria, therefore this finding could be considered related to the product. Although urinalysis is useful for screening for proteinuria, a systematic review showed that the protein:creatinine ratio on a random urine specimen had a strong correlation with 24-hour protein excretion and might be used

to rule out the presence of significant proteinuria as defined by a quantitative measure of the 24-hour protein excretion¹.

In an information request sent on July 13, 2015, CSLB was informed that additional information was needed to further evaluate the possible association between proteinuria and rIX-FP. Because urine protein:creatinine ratio was considered more informative, CSLB was asked to obtain and submit follow-up data (spot urine protein/creatinine ratio, dipstick urinalysis, serum chemistry and hematology testing) for the three subjects with proteinuria that were enrolled in the extension study. CSLB was advised that these findings may be included in the label and that additional data in a larger cohort may be needed to assess the risk and to further inform the label. CSLB was advised that the protocol for the extension study would then need to be revised to include urinalysis and spot urine protein/creatinine ratio testing in a pre-specified number of naïve subjects. The recommended changes were:

- Testing should be done every 6 months, and at the end of the trial as per recommendations from the CDER CardioRenal consultant.
- The protocol should also be revised to specify a clinical work up for subjects with increased protein creatinine ratios. As per the CDER CardioRenal consultant, a threshold of >0.2 mg protein/mg creatinine in children greater than two years of age and ≥ 500 mg/g in adults would trigger further evaluation.
- The revised extension study would be considered a postmarketing commitment study. There was insufficient evidence for product relatedness (i.e., strength of association, consistence of the finding across several trials, and biological plausibility) to support a postmarketing requirement study based on a potential safety signal.

In response to that information request (August 10, 2015, amendment 31), CSLB clarified that the “contribution of albumin from the rIX-FP drug product to the total protein in the blood is small. The drug product has a minimum of (b) (4) and albumin constitutes approximately (b) (4) of the total protein. Each 1 IU of rIX-FP contains (b) (4) albumin. Therefore, there is only (b) (4) of albumin in 10,000 IU of rIX-FP, which is a very small fraction of total albumin content of 34-54 g/L of blood. An average adult male (70 kg, approximately 5.5L blood volume) on a prophylaxis regimen of 75 IU/kg rIX-FP would receive a dose of 4,900 IU, containing only (b) (4) albumin. The introduced albumin from the IMP is only (b) (4) of total albumin. Therefore, the proteinuria should not be due to the albumin-containing rIX-FP.”

In amendment 43, CSLB provided the requested follow-up information for the three subjects enrolled in the extension study:

1. (b) (6) the 15-year-old white male who had a urinalysis that was positive for protein at weeks 12, 28, 44, 60 and at the end-of-study visit, was 18 years old at the time of follow-up. He had a negative urinalysis and normal urine protein-to-creatinine ratio

¹ Price CP, Newall RG and Boyd JC. Use of Protein:Creatinine Ratio Measurements on Random Urine Samples for Prediction of Significant Proteinuria: A Systematic Review, Clinical Chemistry 2005;51:9 1577–1586.

and serum chemistry values for kidney function (albumin, blood urea nitrogen, creatinine, and serum protein).

2. Subject (b) (6), the 54-year-old Asian male with a history of hepatitis C and hypertension with a urinalysis that was positive for protein at weeks 12 and 44 and negative for protein at weeks 28, 60, 76, 92 and the end-of-study visit, was 57 years old at the time of follow-up. He had a negative urinalysis and normal urine protein-to-creatinine ratio, serum chemistry values for kidney function and serum hematology studies.
3. Subject (b) (6) was a 43-year-old white male with a history of hepatitis C and urinalysis that was negative for protein at baseline, weeks 12 and 28 and positive at week 44 with a value of 1 g/L (normal range: 0.0-0.3 g/L) listed for the end-of-study visit. He had a negative urinalysis and normal urine protein-to-creatinine ratio. Albumin was not reported but serum protein was high and creatinine was low; all other serum chemistry values for kidney function were within normal range.

Reviewer Comment: In this reviewer's opinion, these findings do not raise significant concerns for renal safety and are not sufficient to support a request for a postmarketing study or a Risk Evaluation and Mitigation Strategy as:

- 1) a clear biologically plausible reason why this product should cause proteinuria (the albumin load and clearance should not result in proteinuria) is not evident,
- 2) none of the cases were reported as adverse events and no associated clinical sequelae was documented, and
- 3) based on expert opinion from the CDER CardioRenal consultant and consultation with OBE, there is insufficient evidence to suggest that this is a safety signal.

Although there are limitations to the safety database, namely it was derived from small observational studies of subjects with confounding comorbidities that could make interpretation of a possible clinically significant signal difficult, the submitted follow-up data from the three subjects enrolled in the extension study suggest that persistent proteinuria is not an issue even after continued exposure to the product.

The utility of including these findings in the label was discussed with Dr. Chazin and the CDER CardioRenal consultant and all agreed that these findings do not need to be included in the package insert (PI).

II. (b) (4)

[REDACTED]

(b) (4)

III. Potency and Pharmacokinetic Assays

Result of CSLB's field study revealed that IDELVION demonstrates considerable variability by approximately 50% in measured FIX activity levels in clinical pharmacology assays and potency assays calibrated using plasma-derived FIX activity standards. Per Mikhail Ovanesov (CMC reviewer), the variability is caused by the known biochemical differences between IDELVION and naturally occurring FIX. Differences in assay reagents and instruments may increase the variability in measured FIX activity. Because CSLB developed a product-specific standard that is not commercially available, concerns were raised about the ability of treating physicians to monitor patients. Without access to IDELVION product-specific standard, clinical labs may over- or under-estimate FIX activity in PK samples from IDELVION-treated patients. Overestimation of FIX trough levels could result in patients receiving less product (i.e., underdosing), which may lead to increased bleeding events. This would be problematic in instances where FIX trough levels are used to adjust dosing for routine prophylaxis and post-operative management because patients may be started and/or maintained on a lower than optimal dose; this could potentially result in increased incidence of bleeding in these patients. Although we anticipate that in most cases of "under-dosing" resulting from overestimation, the physicians would likely increase the dose for routine prophylaxis based on observed increased bleeds, the threshold for determining when to make this change would be based on practice guidelines which could expose patients to unnecessary risks of bleeds. The assay variability would also be problematic in instances where a lack of effect is noted in a bleeding patient due to overestimation of the FIX levels. .

Reviewer Comment: Per the CMC reviewer and Chair, potency assignment is not significantly impacted since the applicant was able to demonstrate that the same amount of protein/activity was there at every stage of clinical development and postlicensure. Therefore, this issue impacts patient monitoring. The following regulatory actions were considered:

- **A Postmarketing Requirement (PMR) or Risk Evaluation and Mitigation Strategy (REMS) to evaluate the potential safety issue related to possible underdosing and resultant increased bleeding episodes in patients.**
- **Warn the public through education (e.g., Dear Healthcare Provider Letter (DHCP), FDA Webposting)**
- **Describe the issue in the Prescribing Information (PI). (This approach was used for the Alprolix PI.)**

The review team determined that a PMR or REMS was not warranted because, based on results of the clinical trials, the majority of patients that will be treated with this product are unlikely to be adversely affected by the variability in assay results. However, these

trials were not adequately designed to address this issue; therefore the risk in the hemophilia population at large cannot be accurately assessed. Therefore, the following steps were put in place to warn treating physicians of the issue:

1. The issue was described in the PI. The following language was included in the *Monitoring Laboratory Tests (5.5) subsection of Warnings and Precautions*:

Factor IX in vitro results may vary with the type of activated partial thromboplastin time (aPTT) reagent used in the assay system. For example, kaolin-based aPTT reagents along with other reagents designed to exhibit low responsiveness to lupus anticoagulant have shown to result in lower than expected recovery based on labeled potency.

A specific monitoring schedule was not proposed as this is considered practice of medicine. The review committee, in consultation with the Advertising and Promotional Labeling Branch (APLB) determined that listing specific reagents that are optimal for assay monitoring would be considered promotional.

2. CSLB committed to developing an Important Prescribing Information DHCP letter related to laboratory monitoring tests, in accordance with the FDA guidance, to be distributed within 60 days of the BLA approval.
3. CSLB committed to including a contact number in the DHCP letter for CSL Behring Medical Information if additional guidance regarding the impact of reagents and reference standards on aPTT is needed.
4. The DHCP letter will be posted on the FDA website and distributed via various social media outlets (e.g., twitter, CBER What's New, etc).

This mitigation strategy discussed with and concurred by OBRR management (Drs. Epstein and Michaud).

IV. Labeling

a) *Proprietary Name*

The proposed proprietary name for the product, IDELVION, was reviewed by the Advertising and Promotional Labeling Branch (APLB) and was recommended to be acceptable on February 10, 2015. IDELVION was found acceptable as the proprietary name for the product by the agency on March 3, 2015.

b) *Conclusion of APLB and Committee Review of Draft Prescribing Information and Other Labeling*

The product labeling (i.e., prescribing information, patient package insert, and instructions for use) and the product package and container labels were reviewed, commented, and/or revised by the appropriate discipline reviewers before APLB conducted its review from a promotional and comprehension perspective. FDA comments and recommendations regarding the product

labeling and labels were initially conveyed to CSLB on July 16, 2015, and negotiated throughout January, February, and March 2016.

c) *Discussion of Labeling Issues*

i. **Request for Revised Language for Indication And Usage Claims**

In an information request sent on July 16, 2015, CSLB was informed of FDA's efforts to harmonize labeling for blood coagulation products and was asked to revise the language for their proposed indications from the stated claims of:

- Routine prophylaxis
- Control and prevention of bleeding episodes
- Prevention and control of bleeding in perioperative settings (perioperative management)

to the proposed claims of:

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

CSLB responded (July 30, 2015; amendment 26) with a request to retain the word "prevent" stating, "the change FDA has proposed to remove the word "prevent" from the on-demand and prophylaxis indications is unacceptable as it puts CSLB at a competitive disadvantage, as current marketed products (including one approved 15 May 2015) contain the word "prevent" or "prevention" in their indication statements. CSLB is willing to implement this proposed change when all affected marketed coagulation products implement the change." CSLB proposed the following language:

- On-demand control and prevention of bleeding episodes
- Perioperative management of bleeding
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes

Reviewer Comment: The proposed language and the justification for not conforming to the harmonized language are acceptable. Applicant compliance with the Agency's harmonizing efforts is voluntary at this point. We will continue to encourage CSLB to consider revising the labeling during labeling negotiations. FDA is planning to issue a guidance to improve compliance with the harmonizing efforts.

ii. **Labeling Claim for 14-day Dosing Regimen for Adolescents and Adults**

On December 29, 2015 FDA advised CSLB that the design of Study 3001 did not support a 14-day dosing regimen for the general hemophilia population since subjects treated with this

regimen on study were selected from a population that met pre-specified criteria for switching from the 7-day regimen to the 14-day regimen. CSLB responded that:

During the Type C meeting on November 15, 2011 (see BLA Module 1.12.1 FDA meeting minutes 06DEC2011), elements of the pivotal 3001 protocol study design were reviewed and specifically addressed an approach to achieve a labeling claim for both 7- and 14- day dosing regimens. Per FDA recommendations, CSLB amended Study 3001 (Amendment 1, 30 Nov 2011; see BLA Module 5.3.5.2) to include a “criteria for switching subjects to a higher dose cohort”. Criteria for switching stated, the subject must:

- 1. be on a stable dose in the previous month (no dose adjustment),*
- 2. not have experienced spontaneous bleeding event in the previous month,*
- 3. currently be on a weekly prophylaxis dose of ≤ 40 IU/kg rIX-FP, and*
- 4. be willing to switch to a 14-day treatment interval.*

Overall, the criteria did not account for the patients’ bleeding history coming into the clinical study, the annualized bleeding rate experienced during the 7-day prophylaxis period, nor the individual patient’s PK profile. The protocol switching criteria recommended by FDA in the 15 November 2011 meeting is in line with typical individualized care for hemophilia patients when adjusting dose and interval for factor replacement therapy. In Study 3001, in conjunction with clinically relevant switching criteria, the majority (21 out of 38) of subjects were successfully switched to a 14-day regimen, including three adolescents. Of 21 subjects who originally switched regimens in Study 3001, the subject with the highest reported ABR/AsBR (6 and 4.5 respectively) during the 7-day treatment period switched to the 14-day regimen successfully and has remained on the 14-day prophylaxis regimen since Dec 2012. The general observation during Study 3001 and continuing in Study 3003 (extension study that started in the beginning of 2014) is that the large majority of patients switched to an extended treatment interval. Of the 52 subjects from Study 3001 that enrolled in Study 3003, only 9/52 (<20%) continued on the 7-day dosing schedule, and 43 (>80%) patients have received prophylaxis at 10-day (n=10) or ≥ 14 -day (14- and 21-day, n=33) dosing intervals.

The population and observed PK supports that a large majority of patients (95%) would be able to continue their prophylaxis successfully with FIX activities remaining above 1% for greater than 14 days. All patients had a favorable PK profile, with each patient tested for PK of 50 IU/kg having residual activity at day 14. Overall, data supports a generalized dosage and administration regimen for both 7- and 14-day.

Reviewer Comment: After review of the population and observed PK data from clinical trials, Dr. Iftekhar Mahmood (CBER Clinical Pharmacologist reviewer) concluded that there were insufficient data to support a 14-day regimen for the general hemophilia population. Based on review of the clinical data, this clinical reviewer and Dr. Chunrong

Cheng (Biostatistical reviewer) also concluded that the 14-day regimen was not generalizable because the population that was treated on the 14-day regimen was selected based on the pre-specified criteria above. The review team determined that, for patients ≥ 12 years of age, a 14-day regimen would be appropriate for patients who meet the pre-specified switching criteria after being treated for at least one month on the 7-day regimen. This was based on both clinical data and observed FIX trough level data. The data (as discussed in Dr. Waldron's memo) show that for the 21 subjects that switched to the 14-day regimen for an additional median duration of 10 months, the annualized spontaneous bleeding rate (AsBR) remained low with a mean (SD) of 1.07 (2.1) and median of zero (range 0 to 7.3). In response to an information request, CSLB submitted data that showed that FIX trough levels were maintained at or above 3% for the 21 subjects that switched to a 14-day regimen.

iii. Labeling Claim for Pediatric Regimen

For patients < 12 years of age, CSLB initially proposed a dosing regimen of 35-50 IU/kg every 7 days, which was the dose used in the pediatric clinical trial (3002); the dose could be adjusted to 75 IU/kg every 14 days for those patients who are "well-controlled" on a 7-day regimen. However, during the clinical trial the proposed pediatric dose of 35-50 IU/kg every 7 days was not adequate for 37% (10/27) of the subjects treated in trial 3002 as 42% (5/12) of subjects < 6 years and 33% (5/15) of subjects ≥ 6 to 12 years required doses of greater than 50 IU/kg for weekly prophylaxis. Furthermore, according to Listing 16.2.5.3, most (4/5; 80%) of the subjects < 6 years of age who were treated with doses of 35-40 IU/kg required a dose adjustment up to 50 IU/kg. In addition, subjects were not treated with a 14-day regimen. Despite this, page 74/695 of the clinical study report states that "the PK profile of rIX-FP, and mean FIX activity level of 2.81 IU/dL at 14 days after 50 IU/kg rIX-FP administration, suggest that a prolonged routine prophylaxis treatment interval of up to 14 days is a viable option for subjects < 12 years of age."

Reviewer Comment: Based on Dr. Mahmood's review, population and observed PK data did not support a 14-day regimen. Furthermore, based on review of the clinical data the proposed dosing of 35-50 IU/kg did not adequately reflect the dosing requirements observed in the clinical trial. Based on this assessment, CSLB agreed to revise the pediatric dose to 40-55 IU/kg every 7 days.

Appendix I. Division of Cardiovascular and Renal Products Consult

DRAFT

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(b) (4)

1 Page determined to be not releasable: (b)(4)



**Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products**

Date: May 14, 2015

Drug Name: Coagulation Factor IX (Recombinant), Albumin Fusion Protein (rIX-FP)

BLA: 125582

Applicant: CSL Behring LLC

From: Aliza Thompson, Medical Officer, Division of Cardiovascular and Renal Products, CDER

Through: Norman Stockbridge, Director, Division of Cardiovascular and Renal Products, CDER

To: Peter E. Waldron, Division of Hematology Clinical Review, CBER

Subject: Consult regarding four subjects with positive tests for urine protein

Background

On December 5, 2014, CSL Behring submitted BLA 125582 for Coagulation Factor IX (Recombinant), Albumin Fusion Protein (rIX-FP) for the following proposed indications in patients with congenital factor IX deficiency:

- Routine prophylaxis treatment
- Control and prevention of bleeding episodes
- Prevention and control of bleeding in perioperative settings

The product is a long-acting coagulation Factor IX. The increased half-life is achieved by fusion of Factor IX with albumin. When Factor IX is activated, the albumin is released from the fusion molecule.

The pivotal trial, CSL654-3001, was an open-label, multicenter clinical trial comparing episodic (on-demand) treatment to weekly routine prophylaxis and every 10 to 14 day routine prophylaxis in male patients with hemophilia B. According to the Clinical Reviewer, four subjects in this trial (out of a 63 subject safety population) had a normal screening urinalysis, and then developed a positive test for protein in the urine without blood on more than one sample. None of the four subjects had a pattern of increasing serum creatinine or hypertension. According to the applicant, no inhibitors to rIX-FP and no antibodies to rIX-FP or CHO host cell protein were detected in any subject in this trial.

Of the five trials submitted, only one other trial included urinalysis testing. This trial (CSL654-2004) included a smaller number of subjects (17), and a shorter observation time. No subjects in this trial fit the Clinical Reviewer's urine protein selection criteria.

The Division of Hematology Clinical Review has asked the Division of Cardiovascular and Renal Products to address the following questions:

1. What additional steps are recommended to characterize (a) the observed proteinuria including the cause of proteinuria and (b) any effect on renal function over time?

2. If the available data allow any conclusions on this issue, then please describe specific concepts that should be conveyed in the prescribing information.

Discussion of Four Cases¹

- Subject (b) (6) was a 15-year-old white male who had a urinalysis that was positive for protein at weeks 12, 28, 44, 60 and at the end-of-study visit. At screening, the subject had a creatinine of 79.6 µmol/L (0.9 mg/dL; eGFR of 74 using the (b) (4) equation), and a similar creatinine at the end of the study. No other medical history is provided and no other abnormalities were noted on other UA parameters. The proteinuria findings don't appear to be explained by differences in urinary concentration at the different time points (urine osmolality at baseline was 1.011 and ranged from 1.015 to 1.026 at the follow-up visits) and serum albumin measurements were all within the reference range. Of note, the screening value was made almost one year prior to the measurement at 12 weeks.

Reviewer's comment: The significant time lag between the screening measurement and subsequent urine measurements complicates the interpretation of the urine analysis findings.

- Subject (b) (6) was a 26-year-old white male with a urinalysis that was positive for proteinuria at weeks 12 and 28 and the end-of study visit (approximately 3 months later). At screening, the subject had a creatinine of 54 µmol/L (eGFR > 130 mL/min/1.73 m² based on the (b) (4) equation), and a similar creatinine (65 µmol/L) at the end of the study. No other medical history is reported in the submitted narrative and no other abnormalities were noted on UA parameters. The proteinuria findings don't appear to be explained by differences in urinary concentration at the different time points (urine osmolality at baseline was 1.025 and ranged from 1.02 to 1.03 at the follow-up visits) and serum albumin measurements were all within the reference range. The screening measurement was obtained < 4 months prior to the 12 week measurement.
- Subject (b) (6) was a 43-year-old white male with a history of hepatitis C and urinalysis that was negative for protein at baseline, weeks 12 and 28 and positive at week 44 with a value of "1" listed for the end-of-study visit (more than 6 months later). At screening, the subject had a creatinine of 48 µmol/L (eGFR ~130 mL/min/1.73 m² based on the (b) (4) equation), and the same creatinine at the end of the study. Urinalyses were all negative for blood. The proteinuria findings don't appear to be explained by differences in urinary concentration at the different time points (the urine was more dilute at the week 44 measurement than it was at the prior time points). One serum albumin measurement was above the reference range (55 g/L), but all other measurements were within the reference range. The applicant notes that the subject had 2 urinary tract infections during the study (from week 16 to week 40) and syphilis (from week 56 to week 68) and that "both diseases and the medications to treat the diseases can increase protein in the urine."

¹ On April 23, 2015, the applicant submitted a response to CBER's April 15, 2015 request for additional information on these cases. This review is based on the information provided in the applicant's April 23rd submission and the laboratory dataset for trial CSL654-3001.

- Subject (b) (6) was a 54-year-old Asian male with a history of hepatitis C and hypertension with a urinalysis that was positive for protein at weeks 12 and 44 and negative for protein at weeks 28, 60, 76, 92 and the end-of-study visit. At screening, the subject had a creatinine of 48.6 $\mu\text{mol/L}$ (eGFR $\sim 120 \text{ mL/min/1.73 m}^2$ based on the (b) (4) equation), and a similar creatinine at the end of the study.

Reviewer's comment: The finding was intermittent and was not seen at later time points in the trial. The patient also had underlying conditions that can cause proteinuria.

Responses to Consult Questions

1. What additional steps are recommended to characterize (a) the observed proteinuria including the cause of proteinuria and (b) any effect on renal function over time?

Response: In one of the four cases, the finding was intermittent and multiple subsequent urine measurements were negative for protein. In a second case, there was a significant time lag between the screening measurement and the 12-week measurement (when the abnormal finding was first noticed); hence, it is possible that proteinuria was present prior to treatment.

We think additional information is needed to assess the significance of the findings in the other two cases (Subjects (b) (6))::

- *In the laboratory dataset for trial CSL654-3001, the urinalysis is reported as "positive" for proteinuria in these subjects, but the protein reaction is often scored as trace, 1+, 2+, 3+, 4+. What were the actual test results in these subjects?*
- *In the applicant's laboratory dataset, the end-of-study value for urine protein is given as "1" for Subject (b) (6). The applicant should clarify what "1" means. The applicant should also provide additional information on the medications that were taken (names and dates of administration). It seems likely that the proteinuria seen in this subject was caused by other factors, but the applicant should provide the requested information.*
- *As far as we can tell, the applicant has not provided a possible explanation for the abnormal urine protein findings in Subject (b) (6). The applicant should be asked to provide additional information on the subject's course and a possible explanation for the finding.*

2. If the available data allow any conclusions on this issue, then please describe specific concepts that should be conveyed in the prescribing information.

Response: It is not obvious to us that there is a signal for proteinuria. We think it is premature to discuss including information on this finding in labeling.