

**Summary Basis for Regulatory Action**

<b>Date</b>	January 24, 2013
<b>From</b>	Daniela J. Vanco, Committee Chair
<b>Subject</b>	Summary Basis for Regulatory Action
<b>BLA #</b>	STN 125385/30
<b>Applicant</b>	CSL Behring GmbH
<b>Date of Submission</b>	March 28, 2012
<b>PDUFA Goal Date</b>	January 26, 2013
<b>Proprietary Name / Established names</b>	Corifact <sup>TM</sup> Factor XIII Concentrate (Human)
<b>Dosage forms</b>	Lyophilized powder: each vial contains 1000 – 1600 IU of Factor XIII to be reconstituted with 20 mL of Sterile Water for Injection, USP, for intravenous administration
<b>Proposed Indication(s)</b>	For routine prophylactic treatment and peri-operative management of surgical bleeding in adult and pediatric patients with congenital FXIII deficiency
<b>Orphan Designation</b>	Yes
<b>Recommended Action:</b>	Approval
<b>Signatory Authorities Action</b>	<p><b>Basil Golding, M.D.</b> </p> <p><i>Offices Signatory Authority:</i></p> <p><input type="checkbox"/> I concur with the summary review</p> <p><input type="checkbox"/> I concur with the summary review and include a separate review or addendum to add further analysis</p> <p><input type="checkbox"/> I do not concur with the summary review and include a separate review or addendum</p>

**APPROVED**  
By Basil Golding at 8:28 am, Jan 24, 2013

<b>Material Reviewed/ Consulted SBRA</b>	<b>List of specific documentation used in compiling</b>
Clinical	Daniela J. Vanco
Bio-Statistics	Renee Rees
Advisory Committee	Not presented
Labeling	Loan Nguyen
Clinical Pharmacology	Iftekhar Mahmood
Epidemiology	Bethany Bear

## 1. Introduction

### Recommendation

The approval of this efficacy supplement for Factor XIII Concentrate (Human), Corifact®, to expand the existing indication of “routine prophylactic management in patients with congenital Factor XIII deficiency”, to include “peri-operative management of surgical bleeding”, is recommended. The PMR phase 4 study data, which was submitted in support of this supplement, has met its safety and efficacy endpoints, thus verifying the correlation between the surrogate endpoint of trough levels of FXIII and clinical efficacy. The surgical sub-study showed that the Factor XIII Concentrate (Human) is safe and effective in the peri-operative management of FXIII deficient patients.

### Summary

The Applicant, CSL Behring GmbH (hereafter CSLB), has submitted the efficacy supplement STN 125385/30, seeking labeling expansion to include peri-operative management of surgical bleeding. Original BLA approval of the Factor XIII Concentrate (Human), Corifact® (hereafter Corifact), on February 17, 2011, was based on accelerated approval with trough Factor XIII activity levels (5 to 20%) as the surrogate marker of efficacy in the pivotal pharmacokinetic (PK) Study BI71023\_2002 for the indication “routine prophylactic treatment of congenital Factor XIII deficiency”. The clinical benefit and safety of Corifact was to be demonstrated in the post-marketing requirement study (Study BI71023\_3001), a one-year, 41-subject study to verify the clinical benefit by showing a correlation between trough levels of FXIII (5% to 20%) and clinical efficacy, and also by comparing the incidence of bleeding with treatment to historical control. The final PMR Study No. BI71023\_3001 report was submitted in the supplement STN 125385/17 on December 20, 2011. CSLB thus fulfilled the Subpart E Postmarketing Study Requirement for accelerated approval.

On March 28, 2012, CSLB filed the efficacy supplement STN 125385/30 to expand the indication to include peri-operative prophylaxis.

In the phase 4 safety and efficacy study, out of 41 subjects on prophylactic FXIII treatment, five underwent surgical procedures; two subjects with scheduled surgeries (herniated disc, port placement). No treatment-related AEs were reported among the surgical sub-population subjects.

Additional safety data were obtained in the post-marketing study (Study BI71023\_3002) on 61-subjects with a long-term follow-up of two years.

## 2. Background

Corifact is presented as a lyophilized powder to be reconstituted in Sterile Water for Injection for intravenous administration. Factor XIII circulates in plasma as a glycoprotein consisting of two A-subunits and two B-subunits (A<sub>2</sub>B<sub>2</sub>) with a molecular weight (MW) of ~ 320 kDa. When the A-subunit is cleaved by thrombin in the presence of calcium ions, FXIII is activated to FXIIIa. FXIII is also present in platelets, monocytes, and macrophages as a homodimer of A-subunits (A<sub>2</sub>) with a MW ~ 166 kDa. The B-subunit (~ 77 kDa) in plasma has no enzymatic activity and functions as carrier molecules for the A-subunits. The B subunits stabilize the A-subunits and protect them from proteolysis. Activated FXIII is a transglutaminase that catalyzes the cross-linking of the  $\alpha$ - and  $\gamma$ -chains of fibrin, thus stabilizing fibrin clots by rendering them more elastic and resistant to fibrinolysis.<sup>1,2</sup> FXIIIa also cross-links  $\alpha$ 2-plasmin inhibitor to the  $\alpha$ -chain of fibrin, further protecting the clot from degradation by plasmin. Cross-linked fibrin is the end product of the

coagulation cascade, and provides tensile strength to the primary hemostatic platelet plug.<sup>2</sup>

Corifact<sup>TM</sup> [Factor XIII Concentrate (Human)] is a sterile, preservative-free, heat-treated, lyophilized protein product made from pooled US-sourced human plasma. It is manufactured in the CSL Behring facility in Marburg, Germany. CSLB's Factor XIII Concentrate (Human) has been marketed in the EU since 1993. In recent years, various improvements have been made to the manufacturing process, -----  
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### 3. Clinical/Statistical

#### Overall Clinical:

The licensure of Corifact<sup>TM</sup> was granted on February 17, 2011, under the provisions of Accelerated Approval [21 CFR 314.510] using Factor (F) XIII activity trough levels as the surrogate endpoint. The clinical development program to support licensure of Corifact<sup>TM</sup> consisted of a PK study that evaluated plasma trough levels as a surrogate marker likely to predict clinical benefit. The clinical benefit and safety of Corifact was demonstrated in the post- marketing requirement study (Study BI71023\_3001), a one-year, 41-subject study that verified the clinical benefit by showing a correlation between trough levels of FXIII (5% to 20%) and clinical hemostatic efficacy. Under this program, observational long-term efficacy data of Corifact<sup>TM</sup> with regard to the frequency and severity of bleeding episodes in subjects with congenital Factor XIII deficiency was collected.

There were 5 subjects in the surgical sub-study; four subjects received FXIII in the peri-operative setting (0-7 days) for elective surgeries, two of them pre-operatively. One surgery was an emergency and the subject was treated with plasma prior to administration of Corifact<sup>TM</sup>. One subject, who received Corifact seven days prior to extraction of four wisdom teeth, experienced bleeding, which was successfully treated with an additional dose of Corifact (50% of the subject's routine dose). There were no adverse events related to the study product reported in the surgical sub-study.

The safety program of Corifact consisted of 12 clinical studies conducted in various populations. These included the PMR Study BI71023 3001, and eleven supportive studies (one in healthy volunteers, eight in congenital Factor XIII deficiency, and two in -----(b)(4)-----). Clinical experience in the EU since 1993 further supports the determination of safety.

#### Efficacy:

The effect of the Corifact<sup>TM</sup> on the surrogate end point of FXIII activity level and the latter's relationship to the treatment effect on the target clinical end point of effective prophylactic treatment has been confirmed in the phase 4 pivotal PMC study.

The primary endpoint was the total number of spontaneous bleeding events requiring treatment observed divided by the accrued exposure time (person-years). Doses were guided by the individual subject's Factor XIII activity levels, with the objective of dosing every 28 days to

maintain a trough Factor XIII activity level of 5 to 20% for approximately 12 months.

No subject experienced a spontaneous bleeding episode that was treated with a FXIII-containing product. Therefore annualized bleeding rate was 0 episodes per subject per year, which is statistically significant over the pre-defined annualized historical bleeding rate of 2.5 episodes per subject per year in patients receiving on-demand treatment for acute bleeding in patients with congenital FXIII deficiency.

Administration of Factor XIII Concentrate (Human) every 28 days proved to be a safe and effective, providing a clinically meaningful benefit to the subjects with congenital Factor XIII deficiency. The study proved that maintaining the trough FXIII activity level at Day 28 between 5% -20% prevents breakthrough bleeding in congenital FXIII deficient patient and thus demonstrated hemostatic efficacy of Corifact™ for routine prophylactic treatment of congenital FXIII deficiency.

In the surgical sub-study, there were 5 FXIII deficient subjects, who underwent surgery. One of the secondary objectives of the phase 4 study was to evaluate hemostatic efficacy for acute bleeding episodes, during and after surgical procedures. Five subjects underwent surgical procedures; 4 were elective and one was an emergency (appendectomy). Out of 4 elective surgeries, 3 subjects received Corifact prior to surgery (0 to 7 days prior to surgery) with no post-operative bleeding. One subject who received Corifact 7 days prior to surgery experienced bleeding post-extraction of all four wisdom teeth. The bleeding was stopped four hours after the oral surgery with an additional dose of Corifact (50% of the subject's routine dose). None of the subjects had treatment-related adverse reactions, one subject, who required emergency surgery, was pre-treated with plasma and developed a hypersensitivity reaction. The surgical sub-study showed that the Factor XIII Concentrate (Human) is safe and effective in the peri-operative management of FXIII deficient patients.

#### **4. Safety**

The safety program of Factor XIII Concentrate (Human) consisted of a total of 12 clinical studies and included 188, 108 subjects were < 16 years old.

Study BI71023\_2002 was a pivotal PK study with a surrogate efficacy endpoint. Study BI71023\_3001 was a PMR phase 4 study, which was the study submitted in support of this efficacy supplement. Study BI71023\_3002 was a postmarketing long-term safety study to provide study product to subjects until Corifact became commercially available. The other supportive studies included one study in healthy volunteers (Study 1003), 8 studies in patients with congenital Factor XIII deficiency (Studies, 7D-101PK, 7MN-101PK, 8J/201, 7MN-101PK [extension], 5001, 5986), and 2 studies in patients with -----(b)(4)----- (Studies 301CL and 302CL).

A total of 4314 infusions of Corifact were administered in these subjects.

The most common adverse reactions reported in the clinical trials in greater than 1% were joint inflammation, hypersensitivity, rash, pruritus, erythema, hematoma, arthralgia, headache, elevated thrombin-antithrombin levels, and increased blood lactate dehydrogenase. There were no deaths, premature discontinuation, episodes of thromboembolism and cases of viral transmission in the clinical studies.

PMR Phase 4 Study I71023 3001:

There were three adverse reactions in the phase 4 study, which were assessed to be drug-related; knee pain, swelling of right knee, and swelling of left knee was reported in one subject, swelling of elbows and fingers, pruritus of both hands, and redness in the second subject and 3 episodes of thrombin-antithrombin III complex increased in the third subject, without any clinical signs and symptoms of thrombo-embolism. One subject had a reaction of hives from the FFP administration despite being given diphenhydramine 25 mg IV prophylaxis.

Safety Observational Study 3002:

A case of neutralizing antibodies against FXIII was reported in the postmarketing clinical study in a 26-year old subject with congenital FXIII deficiency. The patient received prophylactic treatment with Corifact for ten years. Concomitant medications included interferon for hepatitis C infection. This patient presented with bruising, and post-infusion FXIII levels were found to be lower than expected. Over several weeks, FXIII recovery values decreased, so the dose and frequency of treatments were increased. Neutralizing antibodies to FXIII were detected, interferon treatment was discontinued, and the subject underwent plasmapheresis. Within a month, neutralizing antibodies were no longer detectable, FXIII recovery levels improved, and the previous prophylactic regimen was resumed without further breakthrough bleeding or reappearance of FXIII inhibitory antibodies.

**5. CMC/Clinical Pharmacology/Non-clinical Pharmacology/Toxicology**

There was no new information submitted in the current supplement.

**6. Bioresearch Monitoring (BIMO)**

The Bioresearch Monitoring inspections of three clinical sites did not reveal problems that impact the data submitted in the application. Following are the three sites where Bioresearch Monitoring inspections were conducted:

<b>Site Number</b>	<b>Study Site</b>	<b>Location</b>	<b>Form FDA 483 Issued</b>	<b>Inspection Final Classification</b>
<b>2</b>	Children’s Hospital of Orange County	Orange, California	Yes	VAI
<b>5</b>	Vanderbilt University	Nashville, Tennessee	No	NAI
<b>17</b>	University of Michigan	Ann Arbor, Michigan	Yes	VAI

**7. Pediatric Research Equity Act (PREA)**

This submission did not trigger PREA because of Orphan Drug status.

## **8. Advisory Committee Meeting**

N/A

## **9. Pharmacovigilance**

In addition to routine pharmacovigilance activities, OBE recommends that CSL Behring amend its pharmacovigilance plan with the following additions:

- Report cases of thrombosis and Factor XIII inhibitor development as 15-day expedited reports.
- Add patients over 55 years old as a population for which there is missing information. This population can be followed by routine pharmacovigilance.

## **10. Labeling**

The proposed prescribing information and the PPI submitted on January 15, 2013 are acceptable. Carton and immediate container labels were reviewed by APLB and found them to be acceptable.

## **11. Recommendation/Risk Benefit Assessment**

The approval of this efficacy supplement is recommended. There have been no concerns identified regarding the risk/benefit ratio.

## **12. Post Marketing Requirement:**

N/A

## **13. Post Marketing Commitments**

N/A

## **15. References**

1. Lauer P, Metzner HJ, Zettlmeißl G, Li M, *et al.*, Targeted Inactivation of the Mouse Locus Encoding Coagulation Factor XIII-A: Hemostatic Abnormalities in Mutant Mice and Characterization of the Coagulation Deficit. *Thromb Haemost.* 2002;88:967-74
2. Dardik R, Loscalzo J, and Inbal A., Factor XIII (FXIII) and Angiogenesis. *J Thromb Haemost.* 2006;4:19-25