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Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology**

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Subject: Mid-cycle/Final Review Memorandum

Product: Factor XIII Concentrate (Human), Corifact™
Approval Date Pending

Application Type/Number: BLA 125385

Applicant/sponsor: CSL Behring GmbH

Executive Summary

OBE/DE has completed an initial review of STN 125385 Biologics License Application (BLA) for Factor XIII Concentrate (Human), Corifact™, which will be manufactured and distributed by CSL Behring GmbH for routine treatment of congenital factor XIII deficiency. Factor XIII deficiency, also known as fibrin stabilizing factor deficiency, is perhaps the rarest of all factor deficiencies. The incidence of this bleeding disorder is estimated at one in five million births. Acquired factor XIII deficiency is much more common than congenital factor XIII deficiency. CSL Behring's Factor XIII Concentrate (Human) is indicated for routine prophylactic treatment of congenital factor XIII deficiency. The active ingredient of Factor XIII Concentrate (Human) is Human coagulation factor XIII, a fibrin stabilizing zymogen, obtained from pooled Human plasma.

The safety program of Factor XIII Concentrate (Human) consists of a total of 12 clinical studies. CSL Behring's Summary of Clinical Safety focuses on data from pivotal Study 2002, which was an uncontrolled, single-arm study. This study was conducted between March 2009 and February 2010 in subjects with congenital XIII deficiency. The other 11 supportive studies include 1 study of healthy volunteers (Study 1003), 8 studies on patients with congenital Factor XIII deficiency (Studies 3001, 3002, 7D-101PK, 7MN-101PK, 8J/201, 7MN-101PK [extension], 5001, 5986), and 2 studies on patients with -----(b)(4)----- (Studies 301CL and 302CL). From experience with these clinical studies and 17 years of postmarketing experience, CSL Behring concludes that adverse events (AEs) reported with the use of factor XIII are rare. Adverse drug reactions involving the following systems have been identified and reported during the post-marketing use of Factor XIII products: hypersensitivity reactions, viral transmission, thromboembolic events, and development of factor XIII inhibitors.

In addition to routine pharmacovigilance activities, CLS Behring intends to collect more detailed information about certain spontaneously reported cases with identified risks and then follow them up with a targeted questionnaire. To characterize AEs, CSL Behring will collect general information about the patient and risk factors. Given that the identified risks for Factor XIII Concentrate (Human) are as expected from foreign post-marketing experience, it appears that CSL Behring's plan for routine pharmacovigilance combined with additional activities, as outlined in their BLA application for Factor XIII Concentrate (Human), are sufficient. Therefore, a Postmarketing Requirement will not be necessary.

OBE agrees with CSL Behring's plan to further characterize the identified risks through additional pharmacovigilance activities. OBE advises CSL Behring to consider measures to expand the safety database to include certain populations, such as pregnant and lactating women, children younger than 2 years, and individuals older than 65 years.

I. Introduction

OBE/DE has completed an initial review of STN 125385 Biologics License Application (BLA) for Factor XIII Concentrate (Human), Corifact™, which will be manufactured and distributed by CSL Behring GmbH for routine treatment of congenital factor XIII deficiency. The purpose of the review is to identify potential safety issues that might need to be addressed in a pharmacovigilance plan (PVP). Note that text in italics is verbatim from the BLA.

Disease

Factor XIII deficiency, also known as fibrin stabilizing factor deficiency, is perhaps the rarest of all factor deficiencies. The incidence of this bleeding disorder is estimated at one in five million births. It is an autosomal recessive disorder and affects men and women equally. No ethnic or racial group is disproportionately affected. Factor XIII stabilizes the formation of blood clots, and when a deficiency of this protein exists, clots are tenuously formed and break down easily, causing recurrent bleeds. It is not a procoagulant. The prolonged bleeding that is associated with this deficiency usually involves trauma. Among severe cases, there is a high risk of intracranial bleeds with or without trauma. Pregnant women with factor XIII deficiency may risk spontaneous abortion, and men with this deficiency may show signs of infertility. Common characteristics include soft tissue bleeds, menorrhagia, joint bleeding, and persistent bleeding during circumcision or at the site of the umbilical cord. Diagnosis can be made by normal coagulation screening tests with a detailed family history, specific factor XIII assays, and clot solubility tests.¹

Acquired factor XIII deficiency is much more common than congenital factor XIII deficiency. In this setting, deficiency in the enzyme is caused by an inhibitor, usually an autoantibody binding to plasma factor XIII and interfering with normal function. Acquired factor XIII deficiencies can be associated with severe bleeding complications. Inhibitors to factor XIII can develop in association with use of medications such as isoniazid, penicillin and phenytoin. Acquired factor XIII deficiency has also been associated with systemic lupus erythematosus, leukemias, severe liver disease, disseminated intravascular coagulation, and inflammatory bowel disease.²

Product Background

CSL Behring's Factor XIII Concentrate (Human) is indicated for routine prophylactic treatment of congenital factor XIII deficiency. It is...*presently licensed in 13 countries and has been marketed since 1993. The general trade name outside the US is*

¹ <http://www.hemophilia.org/NHFWeb/MainPgs/MainNHF.aspx?menuid=71&contentid=58>.

² Hsieh L, Nugent D. Factor XIII deficiency. *Haemophilia*. 2008 Nov;14(6):1190-200. Review. PubMed PMID: 19141159.

Fibrogammin P.------(b)(4)-----

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The active ingredient of Factor XIII Concentrate (Human) is Human coagulation factor XIII, a fibrin stabilizing zymogen, obtained from pooled Human plasma. All plasma used in the manufacture of Factor XIII Concentrate (Human) is obtained from US plasma. Neither an International Nonproprietary Name for factor XIII nor a monograph in a pharmacopoeia is available.

Factor XIII Concentrate (Human) is presented as a white lyophilized powder and solvent for solution for injection/solution for infusion.

Factor XIII Concentrate is supplied as a purified and heat treated white lyophilized powder in a single-use vial. Each vial contains 1000-1600IU factor XIII, 120 to 200mg Human albumin, 80 to 120 mg glucose and 140 to 220 mg sodium chloride. The amount of total protein content is 120-320 mg/vial. Sodium hydroxide may have been used to adjust the pH. The product package consist of one carton containing the single use vial of Factor XIII Concentrate (Human) and 20mL Sterile Water for Injection (USP) for reconstitution, a filter transfer set (Mix2Vial) as well as one alcohol swab.

Factor XIII Concentrate does not contain any preservatives and is stable for 24 months when stored at +2 to +8°C. Within the expiration date Factor XIII Concentrate (Human) may be stored at room temperature (max. 25°C), not to exceed a cumulative storage period of 6 months. After reconstitution with 20 mL Sterile Water for Injection, the solution contains 50-80 IU/mL.

*The medicinal product is manufactured by CSL Behring GmbH in Marburg, Germany.*⁴

Clinical Studies of Factor XIII Concentrate (Human)

The only indication in the USA for this product will be for routine prophylactic treatment of congenital factor XIII deficiency. However, in its BLA application, CSL Behring mentions that it has conducted studies of Factor XIII Concentrate (Human) to treat conditions other than congenital factor XIII deficiency. Therefore, the safety data from these studies for other indications will be also considered in this mid-cycle review memo. All of the studies that contributed safety data to the evaluation of Factor XIII Concentrate (Human) are listed in Table 1.⁵

³ STN BL 125385, Clinical Overview, 2.5, p. 8.

⁴ STN BL 125385, Quality Overall Summary, 2.3, p. 4.

⁵ STN BL 125385, Clinical Summary of Safety, 2.7.4.1.1, pp. 12-20.

Table 1: Factor XIII Concentrate (Human) clinical studies to be included in the market								
Protocol No.	Study Dates	Key Objective(s)	Study Design	N	M:F	Median Ag	Age Range	Primary Endpoints
BI71023_2002 Pivotal Study (Otherwise known as Study 2002)	3/2009 to 2/2010	To determine the steady-state PK of Factor XIII Concentrate (Human)	Prospective, open-label, single-arm, multicenter	14	7:7	26.5y	5-42y	Assessment of Factor XIII activity level for achievement of a trough level of ?5%; level at each time point; time with a level of ?5% and ?10%; and number of subject-days with a level <5% and <10%; Collection and evaluation of PK and safety (AEs, laboratory parameters, vital signs, virology testing, and physical examination)
BI71023_3001 (Otherwise known as Study 3001)	8/2009 to Ongoing	To evaluate observational long-term efficacy data with regard to the frequency and severity of bleeding episodes To evaluate the association between Factor XIII activity trough levels and clinical efficacy To evaluate long-term PK and safety data To evaluate hemostatic efficacy in treatment of acute bleeding events and for surgery prophylaxis	Prospective, open-label, single-arm, multicenter	27 (total upon completion: ~40)	13:14	17.8y	0-42y	The incidence density through Week 52 of spontaneous bleeding events requiring treatment (defined as administration of a Factor XIII-containing product to treat the bleeding event) and safety (AEs, laboratory parameters, activation of coagulation testing, potential viral testing, Factor XIII antibody testing, vital signs, and physical examination)
BI71023_3002 (Otherwise known as Study 3002)	9/2009 to Ongoing	To allow provision of Factor XIII Concentrate (Human) to US subjects until it becomes commercially available To collect additional long-term safety data	Prospective, open-enrollment, single-arm, multicenter	3 (total upon completion ~50)	2:1	7.0	1-27y	Collection and evaluation of long-term efficacy (frequency and severity of bleeding episodes), safety (AEs, laboratory parameters, vital signs, and physical examination), and PD (Factor XIII antibody and activity level) data
CE1232/0-5001 (Otherwise known as Study 5001)	3/1999 to 7/2001	To evaluate the tolerability and safety of Factor XIII Concentrate (Human) To evaluate bleeding events in subjects receiving prophylactic and on-demand treatment with Factor XIII Concentrate (Human)	Prospective, open-label, single-arm, multicenter	19 (12 on prophylaxis)	14:5	13.25y	0.05-46.89y	PK response to the first applied dose and safety (AEs and vital signs with optional laboratory parameters and viral testing)
Investigator IND (BB-IND (b)(4)) (Otherwise known as Study (b)(4))	1/2000 to 12/2008	To determine the safety, efficacy, and PK of Factor	Prospective, open-label, uncontrolled, multicenter study	72	48:24	12.0y	0-74y	Collection and evaluation of long-term efficacy (frequency and severity of bleeding episodes) and safety (AEs, laboratory parameters, viral testing, and physical examinations)
BI71.023/7D-101PK (Otherwise known as Study 7D-101PK)	8/1991 to 6/1992	To determine the PK of each Factor XIII concentrate (Human)	Prospective, randomized, double-blind, crossover, pilot	1	1:0	24y	24y	Evaluate and compare the main PK and safety (AEs, laboratory parameters, and vital signs) properties of both concentrates
BI71.023/7MN-101PK (Otherwise known as Study 7MN-101PK)	1/1992 to 4/1993	To determine the PK of each Factor XIII Concentrate (Human)	Prospective, randomized, double-blind, active-controlled, crossover	13	6:7	31y	11-54y	Evaluate and compare the main PK properties of plasma- and -----(b)(4)----- concentrates

Table 1 continued: Factor XIII Concentrate (Human) clinical studies to be included in the market								
BI71.023/ 8J/201 (Otherwise known as Study 8J/201)	10/1992 to 3/1993	To determine the recovery rate and PK of Factor	Open-label, uncontrolled	4	3:1	41.0y	26-43y	Evaluate the PK and safety (AEs, laboratory parameters, vital signs, and viral testing) properties
BI71.023/ 7MN-101PK (Otherwise known as Study 7MN-101PK [extension])	extension / 1/1993 to 10/1993	To evaluate the efficacy and safety of Factor XIII Concentrate (Human) for long-term therapy of congenital Factor XIII	Prospective, open-label, uncontrolled	2	0:2	41.5y	30-53y	Evaluate the PK and safety (AEs, laboratory parameters, viral testing, Factor XIII antibody testing, and vital signs) properties with long-term treatment
BI71.023/ 0-1003 (Otherwise known as Study 1003)	4/1997 to 10/1997	To determine the PK of Factor XIII Concentrate (Human) in healthy males	Prospective, open-label, uncontrolled	20	20:0	23.6y	18.9-34.9y	Evaluate the PK and safety (AEs, laboratory parameters, viral testing, vital signs, and physical examination) properties
BI71.023/ 7MN-301CL (Otherwise known as Study 301CL)	10/1994 to 1/1997	----- ----- ----- ---(b)(4)----- ----- ----- -----	Prospective, randomized, placebo-controlled, double-blind, multicenter	28	21:7	30.0y	18-47y	----- ----- ---(b)(4)----- -----
BI71.023/ 7MN-302CL (Otherwise known as Study 302CL)	7/1994 to 5/1996	----- ----- ----- ---(b)(4)----- ----- ----- -----	Prospective, randomized, placebo-controlled, double-blind, multicenter	33	14:19	30.0y	19-76y	----- ----- ---(b)(4)----- -----

II. Safety Assessment

The safety program of Factor XIII Concentrate (Human) consists of a total of 12 clinical studies. CSL Behring’s Summary of Clinical Safety focuses on data from pivotal Study 2002, which was an uncontrolled, single-arm study. This study was conducted between March 2009 and February 2010 in subjects with congenital XIII deficiency. The other 11 supportive studies include 1 study of healthy volunteers (Study 1003), 8 studies on patients with congenital Factor XIII deficiency (Studies 3001, 3002, 7D-101PK, 7MN-101PK, 8J/201, 7MN-101PK [extension], 5001, 5986), and 2 studies on patients with -----(b)(4)----- (Studies 301CL and 302CL).⁶

*In the 12 clinical trials included in this market application, a total of 3284 doses of Factor XIII Concentrate (Human) were administered. Of the doses administered, 2924 doses were given to subjects with rare congenital Factor XIII deficiency. As of the cut-off date (Dec 21, 2008 for Study 5986 and February 15, 2010 for the remaining clinical studies), a total of 176 unique subjects received at least one dose of Factor XIII Concentrate (Human)*⁷

⁶ BLA STN 125385, Clinical Overview, 2.5.5.1, p. 28.

⁷ BLA STN 125385, Clinical Overview, 2.5.5.2, p. 29.

With regard to demographics, in pivotal study 2002, among the 14 subjects who received at least one dose of Factor XIII Concentrate (Human), one-half (50.0%) of the subjects were female, and the mean age was 24.0 years. All of the subjects had a documented congenital Factor XIII deficiency. In contrast, across the 11 supportive studies, the majority (64.0%) were male. Among the seven studies in which race was documented, the distribution consisted of the following: 72.3% Caucasian, 6.9% African American, 4.0% Asian, 7.9% Hispanic, 8.4% other, and 0.05% missing data. The mean age ranged from 11.67 to 37.75 years. Limited demographic data were available for the 3 subjects in study 3002 and the 4 subjects in Study 8J/201.^{8,9} Based on available data, CSL Behring observes no apparent safety differences between pediatric and adult subjects, male and female, or among race groups in the Factor XIII Concentrate (Human) clinical Program.^{10, 11} In addition, there were no unexpected safety findings in the factor XIII Concentrate (Human) clinical program.¹²

The incidence of treatment-emergent AEs in pivotal study 2002 was 57.1%. No deaths or other serious adverse events (SAEs) were reported and no subject prematurely discontinued due to AEs. The incidence of AEs among supportive studies looking at subjects with congenital factor XIII deficiency varied. *The incidence of related treatment-emergent AEs was 20.0% in Study 1003. No deaths or other SAEs were reported and no subject prematurely discontinued due to treatment-emergent AEs. As of the cut-off date (31 December 2008), the incidence of treatment-emergent AEs in 9 year Study 5986 was 55.6%; the incidence of related treatment-emergent AEs was 4.2%. Three subjects prematurely discontinued due to treatment-emergent AEs resulting in death. In addition to the three treatment-emergent AEs resulting in death, 5 subjects (6.9%) experienced six treatment-emergent SAEs. Among the remaining supportive studies, the incidence of related treatment-emergent AEs was \leq 5.3%, with the exception of Study 7MN-101PK (30.8%). No deaths were reported and one other treatment-emergent SAE was reported in Study 5001. No subjects prematurely discontinued from the studies due to treatment-emergent AEs.*

In study 1003 of healthy volunteers, the incidence of related treatment-emergent AEs was 20.0%. No deaths or other SAEs were reported and no subject prematurely discontinued due to treatment-emergent AEs. In -----(b)(4)----- Study 301CL, the incidence of treatment-emergent AEs was 10.7%; the incidence of related treatment-emergent AEs was 7.1%. In -----(b)(4)----- Study 302CL, the incidence of treatment-emergent AEs was 24.2%; the incidence of related treatment-emergent AEs was 6.1%. No deaths were reported and no subjects prematurely discontinued from the -----(b)(4)----- studies due to treatment-emergent AEs. One other treatment-emergent SAE was reported in Study 302CL.¹³

⁸ BLA STN 125385, Clinical Overview, 2.5.5.4, p. 30.

⁹ BLA STN 125385, Clinical Summary, 2.7.4.1.4, p. 32.

¹⁰ BLA STN 125385, Clinical Overview, 2.5.5.8.1.1, p. 45.

¹¹ BLA STN 125385, Clinical Overview, 2.5.5.8.1.2, p. 45.

¹² BLA STN 125385, Clinical Summary, 2.7.4.2.1, p. 34.

¹³ BLA STN 125385, Clinical Overview, 2.5.5.5.1, p. 30-31.

The most common treatment-emergent AEs occurring in over one subject reported in the 176 unique subject Factor XIII Concentrate (Human) clinical program were contusion (7.4%), joint injury (4.0%), arthralgia (3.4%), rash and “uncoded” (2.8% each). Treatment-related AEs occurring in only one subject, including AEs with a missing relationship, reported in Factor XIII Concentrate (Human) clinical program were arthralgia, blood lactate dehydrogenase increased, headache, and rash (1.1% each).¹⁴

*The only deaths that were reported occurred in 9-year congenital Factor XIII deficiency Study 5986. As of the cut-off date (31 December 2008), 3 subjects (4.2%) in Study 5986 had treatment-emergent AEs that led to withdrawal from the study and resulted in deaths. The events included (self-inflicted) gun shot wound, road traffic accident, and hypertension. In the opinion of the investigator, none of the events were related to treatment with Factor XIII Concentrate (Human).*¹⁵

A summary of all SAEs in the Factor XIII Concentrate (Human) clinical program is presented in Table 2.¹⁶

Table 2: Summary of treatment-emergent serious adverse events			
Subject Number Age/Gender/Race	Preferred Term	Relationship to Study Drug	Severity
Study 5986			
(b)(6) 17/Female/Hispanic	Syncope Suicidal behavior	No Not available	Mild Not Available
(b)(6) 0/Male/Asian	Catheter related infection (indwelling catheter infection)	Not available	Not available
(b)(6) 32/Male/Caucasian	Vasculitis	No	Moderate
(b)(6) 13/Male/Caucasian	Road traffic accident*	No	Severe
(b)(6) 19/Male/Caucasian	Gun shot wound*	No	Severe
(b)(6) 49/Female/Caucasian	Wound infection	Not available	Not available
(b)(6) 0/Female/Asian	Brain mass	Not available	Not available
(b)(6) 74/Male/Caucasian	Hypertension*	No	Severe
(b)(6) 5/Female/not available	Splenic laceration Possible hypersensitivity reaction	Not available Yes	Severe Not available
(b)(6) <1/Male/ not available	Bacterial pharyngitis/viral URI	No	Moderate
Study 302CL			
(b)(6) 74/Male/not available	Acute ischemia	Yes	Not available
Study 5001			
(b)(6) 11/Female/Caucasian	Migraine	No	Moderate

*Resulted in death.

¹⁴ BLA STN 125385, Clinical Overview, 2.5.5.5.1.1, p. 33.

¹⁵ BLA STN 125385, Clinical Overview, 2.5.5.5.1.2, p. 34.

¹⁶ BLA STN 125385, Clinical Overview, 2.5.5.5.1.3, p. 36.

No episodes of thromboembolism were identified in pivotal study 2002. However, 1 subject experienced possibly related thrombin-antithrombin III complex increased and prothrombin increased (verbatim term: elevated prothrombin fragment). These elevations were not associated with AEs consistent with thrombosis and in both cases, the elevations resolved on repeat testing despite continued treatment with Factor XIII Concentrate (Human). No episodes of thromboembolism were identified in healthy volunteer Study 1003, the supportive congenital Factor XIII deficiency studies, and -----(b)(4)----- Study 301CL. One subject who received Factor XIII Concentrate (Human) in -----(b)(4)----- Study 302CL experienced acute ischemia and a subsequent myocardial infarction following a PTCA procedure. Of note, this subject did not have congenital Factor XIII deficiency and received a total dose of Factor XIII Concentrate (Human) that was over five times the normal dose for congenital deficiency. This subject received a total dose of 15,000 U over a 10-day period vs. in congenital deficiency a single dose of 2,800 U every 28 days [based on 70 kg weight] is the normal dose. In summary, among all the clinical studies, only one thromboembolic event was reported in a subject who did not have congenital factor XIII deficiency.¹⁷

Among all the clinical studies, the incidence of hypersensitivity was low. In pivotal study 2002, 1 subject experienced a mild rash (verbatim term: rash noted on dorsum had bullous formation and also noted to be scaly around the bullae) on Day 65 that was considered unrelated to study product and was ongoing. As of the cut-off date (15 February 2010), no possible hypersensitivity reactions were reported in ongoing congenital Factor XIII deficiency Studies 3001 and 3002. No possible hypersensitivity reactions were reported in completed healthy volunteer Study 1003, congenital Factor XIII deficiency Studies, 7D-101PK, 7MN-101PK ext., and 8J/201, and -----(b)(4)----- Studies 301CL or 302CL. As of the cut-off date (31 December 2008) for 9-year Study 5986, 9 subjects reported treatment-emergent AEs that may have been associated with hypersensitivity reactions and 1 subject received oral diphenhydramine between infusions for symptoms of pruritus on the face, neck, hands, or arms. After the cut-off date for Study 5986, a 5-year-old female subject (Subject (b)(6)) experienced an acute episode of respiratory compromise and gastrointestinal symptoms following a dose of Factor XIII Concentrate (Human). The subject improved after a dose of diphenhydramine. This event was assessed as being related to study product and potentially life-threatening by the Investigator. CSLB and the coordinating investigator consider this case to be consistent with a hypersensitivity reaction. One subject in Study 5001 reported a treatment-emergent AE associated with hypersensitivity reaction. The subject reported an allergic reaction (described as urticaria [wrists and buttock]) at Visit 4. The event was mild in severity, related to study drug, and resolved within 1 day.¹⁸

With regard to viral safety, eight studies (pivotal study 2002, healthy volunteer study 1003, and congenital Factor XIII deficiency studies 3001, 3002, 8J/201, 7MN-101PK [extension], 5001, and 5986) addressed the viral safety of treatment with Factor XIII

¹⁷ BLA STN 125385, Clinical Overview, 2.5.5.5.1.5.1, p. 36.

¹⁸ BLA STN 125385, Clinical Overview, 2.5.5.5.1.5.2, p. 37-38.

Concentrate (Human). Viral safety was not assessed in four supportive studies (congenital deficiency studies 7D-101PK and 7MN-101PK and -----(b)(4)----- studies 301CL and 302CL). The status of all virus safety parameters remained unchanged throughout pivotal Study 2002, indicating that no transmission of virus occurred. Viral serology data for ongoing Studies 3001 and 3002 are not included in this submission, but will be included in the safety update (CRMTS #7345). The available data from the completed supportive clinical trials support the viral safety of Factor XIII Concentrate (Human). No seroconversion for viral markers was proven to be attributed to the administration of Factor XIII Concentrate (Human) in following studies: Study 1003, Study 5986, Study 8J/201, Study 7MN-101PK (extension). Four of the 19 enrolled subjects in congenital Factor XIII deficiency Study 5001 had a missing baseline assessment and had a potential infection by blood-borne viruses. Each of the 4 subjects were anti-HAV positive after Visit 1. Through an evaluation of the data CSL Behring concluded that in 3 of the 4 subjects with anti-HAV positive results, the seroconversions were due to vaccination. The fourth had transient antibody titers that were not consistent with an infection by the respective virus. In summary, among all the clinical studies, there were no proven cases of viral transmission of infectious diseases ¹⁹

No factor XIII inhibitors have developed among subjects in the following studies: pivotal study 2002, study 3001, Study 5001, Study 5986, and Study 7MN-101PK. Measurements for Factor XIII inhibitors were not performed in healthy volunteer Study 1003, congenital Factor XIII deficiency Studies 3002, 7D-101PK, 7MN-101PK, 8J/201, and -----(b)(4)----- Studies 301CL and 302CL.²⁰

Post-marketing Data

Since 1993, Factor XIII Concentrate (Human) has been available outside the US as “Fibrogammin P.”²¹

Between June 1993 and 31 March 2010, a total of 50 spontaneous reports of suspected adverse drug reactions (ADRs), including 2 cases received from unsponsored (non interventional) studies, were collected from the worldwide market. During this period -----(b)(4)---- IU of Factor XIII concentrate were distributed, corresponding to ---(b)(4)--- estimated single standard doses of 750 IU. This reflected an overall reporting rate of 1 report per -(b)(4)- estimated single standard doses

The “expected” adverse reaction safety profile of Factor XIII concentrate as described Company Core Safety Information (CCSI) includes allergoid/anaphylactoid reactions, suspected viral transmission, thromboembolic events, and development of inhibitors to Factor XIII. It should be noted that despite the rarity of these events in both clinical

¹⁹ BLA STN 125385, Clinical Overview, 2.5.5.5.1.5.3, p. 39-40.

²⁰ BLA STN 125385, Clinical Overview, 2.5.5.5.1.5.4, p. 41.

²¹ STN BL 125385, Pharmacovigilance Plan, 1.5.1, p. 24.

studies and in post-marketing experience, they are considered relevant because of ‘biologic plausibility’ and not frequency nor severity of observed events.²²

Literature Review

A literature search on PubMed for non-industry funded studies or reviews on safety of plasma-derived Factor XIII replacement in patients with congenital factor XIII deficiency produced one review written within the last 10 years. This review, written in 2008, states that, “Plasma-derived factor XIII concentrates have also been available to treat the extremely rare but severe bleeding associated with homozygous factor XIII deficiency. No adverse events (AEs) associated with the clinical use of congenital factor XIII deficiency have been reported.²³” This illustrates that few data exist for this product with its indicated use.

Experience with Similar Products

As of the date of this review, no Factor XIII product has been licensed in the USA.

III. Pharmacovigilance Planning Assessment

The PVP submitted by CSL Behring addresses important identified risks and important missing information. Important potential risks were not identified. ADRs involving the following systems have been identified and reported during the post-marketing use of Factor XIII products: hypersensitivity reactions, viral transmission, thromboembolic events, and development of factor XIII inhibitors.

Possible Safety Concerns

From experience with clinical studies and 17 years of postmarketing experience, CSL Behring concludes that AEs reported with the use of factor XIII are rare. The collection of data has been limited by the rarity of the disease and infrequent AE reports. In addition to routine pharmacovigilance activities, CLS Behring intends to collect more detailed information about certain spontaneously reported cases with identified risks and then follow them up with a targeted questionnaire. To characterize AEs, CSL Behring will collect general information about the patient and risk factors. Specific questions to elicit more information will further characterize the identified risks. CSL Behring believes this will contribute significantly to the understanding of risk factors for the occurrence of rare or very rare AEs.

²² STN BL 125385, Pharmacovigilance Plan, 1.5, p. 24.

²³ Ofosu FA, Freedman J, Semple JW. Plasma-derived biological medicines used to promote haemostasis. *Thromb Haemost.* 2008 May;99(5):851-62. Review. PubMed PMID: 18449414.

Table 3 below provides details of additional pharmacovigilance activities beyond those considered routine for each important identified risk.²⁴

Table 3: Detailed action plan for safety observations/signals	
Hypersensitivity Reactions	
Item	Pharmacovigilance Activity
Action proposed	Clinical study: Study BI71023_3001 Clinical study: Study BI71023_3002
Objective of proposed action	Monitor frequency, severity, and outcome of allergic reactions
Rationale for proposed action	The administration of all plasma derived products conveys a risk of hypersensitivity reactions. Further data on Factor XIII will allow additional risk quantification.
Monitoring by the sponsor for safety issue and proposed action	Collection of hypersensitivity AEs Clinical study report
Milestones for evaluating and reporting	Periodic safety reports to the BLA
Viral Transmission	
Item	Pharmacovigilance Activity
Action proposed	Additional follow-up and target questionnaire Clinical study: Study BI71023_3001 Clinical study: Study BI71023_3002
Objective of proposed action	Evaluation of product safety and risk of transmission with current manufacturing techniques
Rationale for proposed action	Factor XIII Concentrate (Human) is made from human plasma, and theoretically, despite donor screening and virus inactivating processes, may contain infectious agents. Additional data from clinical studies will provide information on current manufacturing processes and risk of transmission.
Monitoring by the sponsor for safety issue and proposed action	Target questionnaire for follow up of postmarketing cases Study 3001: Virology testing is performed at the Screening Visit, Week 24 (during a treatment visit), and the End-of-Study Visit and includes a complete hepatitis panel (anti-hepatitis A antibody, hepatitis B surface antigen, anti-hepatitis B surface antigen antibody, anti-hepatitis B core antigen antibody, and anti-hepatitis C antibody), anti-parvovirus B19 IgG, and anti-HIV antibody. Study 3002: collection of viral transmission AEs Clinical study reports Annual updates as per IND
Milestones for evaluating and reporting	CSL Behring will provide a safety update 3 months after the BLA is submitted for Study BI71023_3001 and Study BI71023_3002.

²⁴ STN BL 125385, Pharmacovigilance Plan, 2.2, p. 37.

Table 3 continued: Detailed action plan for safety observations/signals	
Thrombosis	
Item	Pharmacovigilance Activity
Action proposed	Additional follow-up and target questionnaire Clinical study: Study BI71023_3001 Clinical study: Study BI71023_3002
Objective of proposed action	Assessment of thrombogenicity parameters Evaluation of thromboembolic adverse events
Rationale for proposed action	Thromboembolic events are rare, and due to high background incidence in general population, the collection of thrombogenicity parameters is necessary to assess risk due to the product vs background.
Monitoring by the sponsor for safety issue and proposed action	Target questionnaire for follow up of postmarketing cases Study 3001: A blood sample is obtained at Baseline and at the Weeks 12, 24, 36, 48, and End-of-Study Visits (or at early withdrawal) for the determination of prothrombin fragment 1+2, thrombin-antithrombin, and D-dimer. Study 3002: evaluation of thromboembolic AEs Clinical study reports Annual updates as per IND
Milestones for evaluating and reporting	CSL Behring will provide a safety update 3 months after the BLA is submitted for Study BI71023_3001 and Study BI71023_3002.
Development of Inhibitors	
Item	Pharmacovigilance Activity
Action proposed	Clinical study: Study BI71023_3001 Clinical study: Study BI71023_3002
Objective of proposed action	Collection of additional data
Rationale for proposed action	The development of inhibitors is rare, but periodic sampling and sampling after bleeding may increase detection.
Monitoring by the sponsor for safety issue and proposed action	Study 3001: Samples are collected for determination of Factor XIII antibody at Weeks 12, 24, 36, 48, at the End-of-Study Visit (or at early withdrawal), and also as soon as possible after any bleeding episode of \geq Grade 2 CTCAE intensity. Study 3002: Samples will be collected for Factor XIII antibody testing at baseline, every 48 weeks, and at end of study. Clinical study reports Annual updates as per IND
Milestones for evaluating and reporting	CSL Behring will provide a safety update 3 months after the BLA is submitted for Study BI71023_3001 and Study BI71023_3002.
Safety in Pregnancy	
Item	Pharmacovigilance Activity
Action proposed	Routine PV with additional follow up and specialized questionnaire
Objective of proposed action	Collection of additional data
Rationale for proposed action	Published literature supports use in pregnancy, labor and delivery. Additional data in real- life situations is needed.
Monitoring by the sponsor for safety issue and proposed action	Continuous review of reported cases
Milestones for evaluating and reporting	Periodic safety reports to the BLA

CSL and CSL Behring (CSLB) have established a global pharmacovigilance (PhV) organization (CSL Global PhV Organization, which maintains a system to ensure that information about all individual case safety report (ICSR) [including cases of suspected adverse (drug) reactions (ADR) and product exposure during pregnancy] reported to the company from any source, including company medical/sales representatives and 3rd Party Distributors, is collected and collated at the designated pharmacovigilance sites of the CSL Group. The CSL PhV Sites operate in accordance with the applicable regulatory requirements, ICH guidelines, and global company internal standards. In accordance with the applicable local regulatory requirements, each of the PhV Sites has nominated a Qualified Person (or Authorized Official, respectively) being responsible for pharmacovigilance.²⁵

In terms of pharmacovigilance for marketed products, the CSL PhV Sites are responsible for the ICSR processing, medical review and assessment, and expedited reporting in accordance with the applicable regulatory requirements to regulatory authorities of ICSRs received from the following sources:

- *Spontaneous reports from Healthcare Professionals (and lay persons, as applicable);*
- *Company initiated non-interventional post-authorization studies;*
- *Worldwide scientific literature;*
- *Post-authorization studies not sponsored by CSLB;*
- *From partner companies in accordance with the applicable Supply and Distribution Agreements, and the related Quality Agreements and/or Pharmacovigilance Agreements.*

*In the role of a **Responsible PhV Site/PhV Center of Excellence (PhV CoE)** the sites have ultimate responsibility for (but not limited to) ICSR follow-up activities, decision on additional investigations as appropriate, final regulatory and medical causality assessment, ongoing pharmacovigilance evaluation, preparation of periodic safety update reports (PSURs) and prompt responses to pharmacovigilance related inquiries from regulatory authorities.*

*The CSL PhV Sites work as Data Entry, Data Owner and Reporting Sites on one global PhV database “**WAVES (Worldwide Adverse Experience System) Global**”, which contains all ICSRs for any CSL/CSLB marketed product (and SAE [serious adverse event]/SAR [serious adverse reaction]/SUSAR [suspected unexpected serious adverse reaction] for CSL products investigated in company sponsored interventional clinical trials) including all legacy ICSRs from the predecessor systems.²⁶*

Given that the identified risks for Factor XIII Concentrate (Human) are as expected from foreign post-marketing experience, it appears that CSL Behring’s plan for routine

²⁵ BLA STN 125385, CSL/CSLB Global Pharmacovigilance System, 1.1, p. 2.

²⁶ BLA STN 125385, CSL/CSLB Global Pharmacovigilance System, 1.2.3, p. 3.

pharmacovigilance combined with additional activities, as outlined in Table 3 above are sufficient. Therefore, a Postmarketing Requirement will not be necessary.

Recommendations

CSL Behring should proceed with their proposed pharmacovigilance activities for Factor XIII Concentrate (Human) as previously submitted to the FDA on June 30, 2010. As noted in the PVP, CSL Behring should conduct routine monitoring and reporting of adverse events, including submitting 15-day expedited reports for serious, unlabeled adverse events and Periodic Safety Update Reports (PSURs), quarterly for the first three years after licensure and yearly thereafter, as required under 21 CFR 600.80. In addition, OBE agrees with CSL Behring's plan to further characterize the identified risks through additional pharmacovigilance activities, such as collecting more detailed information about certain spontaneously reported cases with identified risks, following them up with a targeted questionnaire, and collecting general information about the patient and risk factors.

CSL Behring should consider measures to expand the safety database, given the short study duration, the small number of subjects systematically evaluated, and the limited numbers in certain groups (pregnant and lactating women, children younger than 2 years, and individuals older than 65 years).

Letter-ready Comments

1. Proceed with the proposed pharmacovigilance activities for Factor XIII Concentrate (Human) as you have previously submitted to the FDA on June 30, 2010. Routine monitoring and reporting of adverse events should be conducted, including submitting 15-day expedited reports for serious, unlabeled adverse events and Periodic Safety Update Reports (PSURs), quarterly for the first three years after licensure and yearly thereafter, as required under 21 CFR 600.80.
2. Measures should be considered to expand the safety database, given the short study duration, the small number of subjects systematically evaluated, and the limited numbers in certain groups (pregnant and lactating women, children younger than 2 years, and individuals older than 65 years).