

Memo - Blood Products Advisory Committee, November 26, 2010 - Corifact

- **Date:** 26 November 2010

To: Jay Epstein, M.D.
Director, Office of Blood Research and Review

From: Basil Golding, M.D.
Director, Division of Hematology

Subject: Request to waive STN 125385 from referral to Blood Products Advisory Committee

CC: Robert Yetter, Ph.D., Associate Director for Review Management, CBER
Diane Maloney, J.D., Associate Director for Policy, CBER

Background

STN 125385 is an original biologics license application (BLA) submitted by CSL Behring (CSLB) for Factor XIII Concentrate (Human). The proposed indication is 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 product will be available in lyophilized form for reconstitution with Sterile Water for Injection for intravenous administration.

Reasons for Waiving Referral to BPAC

The Division of Hematology in the Office of Blood Research and Review reviewed the information from this application and determined that referral to the Blood Products Advisory Committee (BPAC) prior to approval was not needed for the following reasons (FDAAA [HR 3580-138 SEC. 918: REFERRAL TO ADVISORY COMMITTEE]):

1. Factor XIII Concentrate (Human) is manufactured using only plasma units collected in FDA approved plasma facilities. All donations comply with the requirements of 21 CFR 640.30 and 21 CFR 640.60. The protein is purified using conventional adsorption, precipitation and chromatographic methodologies that are commonly employed in the manufacture of other plasma-derived products.
2. Factor XIII Concentrate (Human), is licensed under the trade name Fibrogammin® P in 13 countries since 1993.

3. Human Albumin, glucose and sodium chloride are the major stabilizers and excipients of this product. Human Albumin (b)(4), manufactured by -----
----- (b)(4) -----.
4. The measures taken by CSLB to control adventitious agents in the manufacture of Factor XIII Concentrate (Human) are acceptable. The Factor XIII Concentrate (Human) manufacturing process includes one virus inactivation step – Pasteurization (60°C for 10 hours). In addition, CSLB has validated 2 purification steps for their capability to remove viruses as summarized in the following table:

Mean virus reduction factors of Factor XIII Concentrate (Human)

Manufacturing steps (Scale reduction in % of manufacturing scale)	Virus reduction factor [log10] (n) ^a					
	Enveloped viruses				Non-Enveloped viruses	
	HIV	BVDV	WNV	HSV-1	HAV	CPV
Adsorption to Al(OH)₃/Vitacel and defibrination (0.0094%)	≥ 5.8 (4)	2.8 ± 0.4 (2)	Not determined	≥ 7.6 (2)	1.3 ± 0.0 (2)	[0.4 ± 0.3] ^b (2)
Ion exchange chromatography (0.025%)	5.0 ± 0.7 (3)	3.4 ± 0.9 (6)	Not determined	Not determined	3.4 ± 0.5 (3)	3.7 ± 0.8 (5)
Pasteurization/Heat treatment (Not applicable)	≥ 5.8 (3)	≥ 5.8 (6)	≥ 5.8 (2)	≥ 5.8 (3)	4.3 ± 0.3 (6)	[1.0 ± 0.1] ^c (2)
Overall mean virus reduction factor	≥ 16.6	≥ 14.3	≥ 7.4	≥ 15.2	9.0	4.7

a: Number of experiments used for evaluation (production conditions)

b: Reduction factor below 1 log₁₀ was not considered in calculating the mean overall virus reduction

c: Reduction factor for B19V: ≥ 4.0 log₁₀ report: VER-B19-03

- The plasma pools for fractionation are tightly controlled. These pools are tested for -----
----- (b)(4) -----,
-----, and do not show high titers of B19V DNA (≤ 10⁴ IU/mL).
 - ----- (b)(4) -----.
5. The mechanism of action of Factor XIII Concentrate (Human) and its role in blood coagulation are well understood.
 6. The mechanism of action and safety profile of the product is fully understood, as it has been used widely outside the U.S. (as well as off-label inside the U.S.) since

1993. There are no safety questions/concerns regarding this product to be introduced to an advisory committee.

7. Review of information submitted in the BLA did not raise any controversial issues or pose unanswered scientific questions which would benefit from advisory committee discussion and recommendation.
8. The review of the clinical data does not raise any safety concerns with regards to thrombogenicity and immunogenicity.

Letter-ready comments that summarize this memo to be included in the approval letter:

We did not refer your application to the Blood Products Advisory Committee because the manufacture of Factor XIII Concentrate (Human) employs a process using conventional adsorption, precipitation and chromatographic methodologies that are common in the manufacture of other plasma-derived products. It has been on the market outside the U.S. since 1993. The mechanisms of action of Factor XIII Concentrate (Human) and its role in blood coagulation are well understood. Our review of information submitted in your BLA, including the clinical study design and trial results, did not raise concerns or controversial issues which would have benefited from an advisory committee discussion.