

Midcycle Pharmacology / Toxicology Review - Corifact

To: File (STN 125385)

From: La’Nissa A. Brown-Baker, Ph.D., Pharmacologist, Division of Hematology
(DH)/OBRR

Through: Iftexhar Mahmood, Team Lead, Pharm/Tox Group, Division of Hematology/OBRR

Subject: Filing of Midcycle STN 125385/0 - CSL Behring’s BLA Factor XIII Concentrate
(Human), Pasteurized Corifact TM

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I. Background

Congenital Factor XIII deficiency is a rare autosomal recessive disease usually associated with a severe bleeding diathesis. Factor XIII (FXIII) after activated by thrombin is an enzyme of the coagulation system that cross-links fibrin. Factor XIII deficiency is the rarest of all factor deficiencies and is also known as Fibrin Stabilizing Factor deficiency diagnosed by coagulation screening tests and detailed family history. The incidence of FXIII deficiency is about 1 in 2-5 million people. Historical data demonstrate that FXIII replacement therapy is the most widely utilized and effective therapy with fresh frozen plasma, cryoprecipitate or crude factor XIII concentrate from placenta.

CSL Behring has manufactured a novel plasma derived FXIII called Corifact™ approved for orphan designation for congenital FXIII deficiency. CSL Behring is proposing an indication for the use of its product human FXIII concentrate, pasteurized, also known as Fibrogammin P or P/N, as prophylaxis treatment of FXIII deficiency as a longer acting version than currently marketed FXIII products. Fibrogammin P has a long standing history for clinical use in the EU over a decade. Common side effects following FXIII therapy include anaphylactic reactions, inhibitor development, thromboembolic events, and rarely transmission of disease. Nevertheless, the benefits of replacement FXIII therapy far outweigh the risks.

II. Proposed Use and Doses

CSL Behring's Factor XIII concentrate will be administered intravenously as prophylactic therapy at 10-40 U/kg every 4-6 weeks. The dose and frequency will be determined by treating physician tailored to plasma levels of each patient. The proposed indication is for prophylactic treatment of FXIII deficiency as the half-life is longer than other coagulation factors.

III. Recommendations

Based on the review of pharmacological and toxicological data presented, I recommend filing of this Biological License Application (BLA) STN 125385 for Factor XIII Concentrate (Human), Pasteurized [Corifact™].

Recommendation for non-clinical studies:

Due to the potential of immunogenicity as associated with all biologics (replacement therapies), I recommend that the sponsor consider continued post-marketing monitoring to address immunogenic concerns as this biological product will be administered as a prophylaxis in clinical setting. I also recommend that the sponsor integrates the existing clinical experience and knowledge to address this major safety concern.

IV. Comments

- No teratogenic, reproductive & developmental toxicity, mutagenic, secondary pharmacodynamics, genotoxicity or carcinogenic studies were performed using Corifact™ or its predecessors.
- The immunogenicity of treatment with FXIII is a major concern as with all biologics, especially with a prophylactic indication. The sponsor has drafted a plan to monitor immunogenicity following FXIII administration such as inhibitor and antibody development in clinical trials and a post-marketing commitment.
- There were no substantial or unexpected adverse events in pre-clinical testing following FXIII administration.

V. List and Summary of Non-clinical Studies in STN 125385

Study No. (b)(4) 01-00 The Influence of Factor XIII Substitution on bleeding time and clot strength in a FXIII knockout mouse model

Study No. V-692.1 - Factor FXIII from Human Plasma as component of Fibrin Adhesive Effect on Bursting Strength of Rat Skin Wound

Study No. 154-12 - Acute Toxicity Studies with plasma factor FXIII

Study No. B71368 - Fibrogammin P: 14-day intravenous (Bolus) Toxicity Study in the - (b)(4)-- Rat with an Interim Sacrifice after 5 treatments

Study No. 154.24: Local Toxicity study in rabbits after intravenous, intra-arterial and paravenous injection of BI 71.0123 (plasma factor XIII)

Study No. 154-35 - Safety Pharmacological Investigations with Plasma Factor XIII in --(b)(4)-- Dogs

Study No. 154-11 - Acute Toxicity studies with plasma Factor XIII

Study No. 154-12 - Acute Toxicity studies with plasma factor XIII

Study No. V-211e - Testing for possible formation of antigenic components through modification of production Procedure

Study No. S10844 – In vivo thrombogenicity test

VI. Summary of Preclinical Studies

Study No.	Purpose	Species	Study observations
V-692.1	Efficacy	Rat	Wound healing (tear off assay w/ adhesives)
(b)(4) 01/00	Efficacy	K.O. mice vs. WT (----- (b)(4)--)	1.25-200 U/kg; i.v. TEG & bleed time 200 U/kg
154-35	Safety Pharmacology	Hemophilia A - (b)(4)--	1F/1M; 10, 35, 70 U/kg
154-11	Acute (single) dose toxicity	Mouse	N=10 (5M/5F); i.v. saline, 710, 1775, 3550 IU/kg
154-12	Acute (single) dose toxicity	Rat	N=10/gr. (5M/5F) i.v. saline, 71,710, 1420 IU/kg
154-24	Local tolerance	Rabbit	i.v., i.a., p.v. n=3/gr., 250, 71 and 71 IU/kg BW

Study No.	Purpose	Species	Study observations
			vs. saline
V-211e	Antigenicity	Rabbit/Guinea pig	----- (b)(4) ---- test; passive cutaneous anaphylaxis
S10844	Thrombogenicity	Rabbit	Saline, 35, 100, 350 U/kg i.v.
B71368	Repeat-dose toxicity	rat	N=26 (13M/13F); Saline, 35, 100, 350 U/kg i.v.

----- (b)(4) ----- mouse
arterial p.v. = paravenous
----- (b)(4) ----- mouse
weight

i.v. = intravenous i.a. = intra-
WT = wildtype gr. = group
TEG = thromboelastography BW = body

General Comments: Based on the repeat dose and acute dose toxicity, local tolerance, pharmacodynamics, toxicokinetics, antigenicity, thrombogenicity, and efficacy studies in the pre-clinical program submitted for CSL Behring's FXIII, pasteurized (Corifact) appear adequate to address the safety concerns. The findings presented indicate FXIII (Corifact) is well tolerated with an appropriate safety margin based on proposed dosage. Immunogenicity has been monitored in clinical trials, but continues to be a major concern for prophylaxis indication. Studies have monitored TEG and bleeding time which improved following FXIII administration. Previous clinical experience that has been compiled on FXIII negates necessity for additional toxicity studies in additional higher order animals as component of preclinical program.

There were additional literature submissions to support Factor XIII concentrate administration compared to recombinant FXIII; factor XIII administration in sheep a review article on factor XIII deficiency; and a clinical review on FXIII function.