



**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research**

Office of Biotechnology Products
Division of Therapeutic Proteins
Rockville, MD 20852
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Date: 9/25/2015

From: Joao Pedras-Vasconcelos

Through: Susan Kirshner, Review Chief

Subject: BLA 125582/0 CBER inter-center consult request for Idelvion [CXL654, Coagulation Factor IX (Recombinant), Albumin Fusion Protein (rIX-FP)]

PRODUCT: Idelvion (CSL654/Coagulation Factor IX (Recombinant), Albumin Fusion Protein (rIX-FP))

INDICATION: rIX-FP is being developed for the treatment of children and adults with hemophilia B (congenital Factor IX deficiency) for:

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

ROUTE OF ADMIN. Intravenous injection

DOSE REGIMEN: Calculated by body weight.
Available in 250, 500, 1000, 2000 IU single use glass vials.

SPONSOR: CSL Behring, Marburg Germany

CENTER/OFFICE/DIVISION: CBER/ OBRR/DHRR

CMC: Mikhail Ovanesov (committee chair)

RPM: Edward Thompson

BLA stamp date: 12/05/2015

Primary Review due date: (09/10/15)

PDUFA Action Date 10/05/2015

OBP Recommendations:

An OBP albumin-fusion product specialist reviewed the adequacy of the analytical methods and release specifications for control of albumin moiety (b) (4)

Drug Product of rIX-FP and has the following recommendations:

- 1. The sponsor should develop and validate an assay to monitor the functionality of the albumin moiety to be used for release and stability of (b) (4) drug product. The (b) (4) assay used in the characterization of (b) (4) may be a candidate for such an assay.**
 - a. During the validation effort the sponsor should test (b) (4) using this assay.**
- 2. For the inhibitor assay used to monitor treatment emergent neutralizing antibody responses to drug product, the sponsor should provide data examining the impact of anti-albumin antibodies on the detection of FIX inhibitors.**

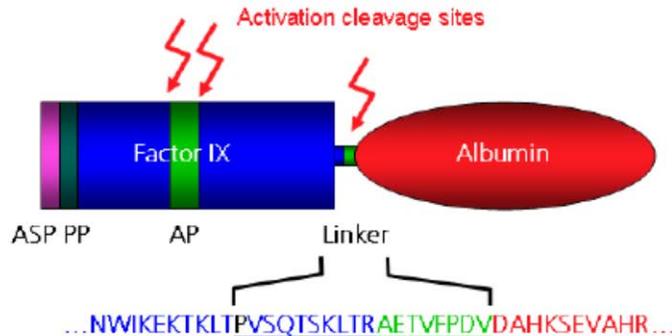
Introduction

Hemophilia B (HB, congenital Factor IX deficiency, Christmas disease) is a rare hereditary blood disorder caused by a deficiency or dysfunction of factor IX that leads to bleeding secondary to abnormal clot formation. The hemophilia B gene is located on the X chromosome with an X-linked recessive inheritance pattern, affecting 1 in 100,000 male births and rare females. Treatments for hemophilia B require replacement with a form of factor IX. Currently, there are two FDA-approved recombinant factor IX products (BeneFIX and Rixubis), and two approved plasma derived factor IX products (Alphanine and Mononine).

CSL Behring (CSLB, Marburg Germany) submitted to CBER on 05 December, 2014 BLA No. 125582 for Idelvion (CSL654, Coagulation Factor IX (Recombinant), Albumin Fusion Protein (rIX-FP)) for the treatment and prophylaxis of children and adults with hemophilia B including control and prevention of bleeding in surgical settings.

rIX-FP is a 125kDa single chain glycoprotein, 1018 amino acids in length, which encodes the most prevalent Thr148 allelic form of native factor IX genetically fused with human serum albumin (Figure 2.3.S-2). The human serum albumin (HSA) fusion results in an enhanced half-life for the drug product of 87-97hr compared to 18-24hr for other approved FIX therapeutics. This is due to the pH dependent interaction of the HSA moiety of the molecule with the neonatal Fc receptor (FcRn) and subsequent recirculation throughout the body. Endogenous HSA has a half-life of ~20 days. Typically, extracellular HSA is pinocytosed by cells in the vascular endothelium, and once in the acidic endosome, binds FcRN avoiding lysosomal digestion and is transported to the cell membrane where it dissociates from the receptor in the pH neutral extracellular environment and continues recirculating until it is degraded in the liver.

Figure 2.3.S-2 Structure and Elements of rIX-FP*



*ASP = albumin signal peptide. PP = FIX propeptide. AP = activation peptide.

rIX-FP is produced in CHO cells, and purified to Drug Substance (DS) via a series of (b) (4) virus inactivation/filtration, (b) (4). The DS is subsequently formulated into Drug Product (DP), and filled, and lyophilized in glass vials. rIX-FP DP is available as lyophilized powder in four fill sizes of 250, 500, 1000 and 2000 IU, and three dosage strengths (100, 200 and 400 IU/mL).

As rIX-FP is an HSA-fusion protein, the first product of its kind being approved by CBER, the Division of Hematology Research and Review (DHRR), in the Office of Blood Research and Review (OBRR) requested an inter-center consultative review from OBP due to our prior experience with this class of biologics. The following question was submitted in the request:

- **Please comment on the adequacy of the analytical methods and release specifications for control of Albumin moiety in (b) (4) Drug Product of the albumin-fusion product.**

Drug Substance and DP Specifications

The critical quality attributes for FIX-FP DS (Table 2) and DP (Table 3) are monitored using a series of physical-chemical methods. Highlighted in yellow are the assays used to monitor HSA content. *(b) (4)

Table 2: Present and proposed Specifications for the rIX-FP Drug substance

Test	Present Specification	Proposed Specification (including alert limits as specified)
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(b)	(b)	(4)
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Table 3: Present and proposed Specification for the rIX-FP Drug product

Test	Present Specification	Proposed Specification
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(b)	(b)	(4)
FIX coagulation Assay	(b)	(4)
Albumin by	(b)	(4)

(b) (4)

FIXa Assay		
(b) (4)		(b) (4)
(b) (4) FIX activity		(b) (4)
(b) (4)		(b) (4)
(b) (4) visible particles by (b) (4)		
Endotoxin		
Sterility	Pass if no contamination detected	
Appearance by visual inspection (Lyophilized cake)	Pass if pale yellow to (b) (4) (b) (4) cake	(b) (4)
Residual water (b) (4) (b) (4)		(b) (4)
Appearance by visual inspection (Dissolution time)		
Appearance by visual inspection (Appearance after reconstitution)	Pass if yellow to colorless clear liquid and free of visible particles	

Albumin by (b) (4)
(b) (4)

[Redacted content]

2 Pages determined to be not releasable: (b)(4)

HB is a genetic deficiency that leads to impaired expression of factor IX, the extent of which depending on the nature and number of mutations in the *F9* gene of individual patients. The standard of care for patients with HB involves infusions of plasma-derived or recombinant FIX (rFIX) as prophylaxis or on demand. This treatment approach is sometimes complicated by the development of an immunogenic response against the drug product, resulting in the formation of neutralizing anti-drug antibodies known as “inhibitors” in hematology. Published literature suggests that 1–3% of patients with HB develop inhibitors, which in addition to rendering treatments ineffective are occasionally associated with anaphylaxis and development of nephrotic syndrome. The most common type of mutations in HB are missense mutations (67%) whereas nonsense mutations and deletions occurred at considerably lower frequencies (13% and 8% respectively). Not surprisingly the prevalence of inhibitors is significantly higher in patients with nonsense mutations, deletions and frameshift mutations compared to patients with missense mutations, since the patients will be less tolerant to the replacement FIX therapeutic. The rIX-FP clinical program supporting BLA 125582 includes 5 open-label, prospective clinical studies involving 111 pediatric, adolescent and adult patients. Four studies are completed and one is ongoing. To monitor product immunogenicity in these studies, the sponsor developed anti-drug antibody screening and confirmatory assays, and an inhibitor (neutralizing antibody) assay. The sponsor tested specificity to rFIX-FP, to rFIX, plasma-derived FIX, albumin, and CHO cell proteins in accordance with Agency advice. The results of their studies are summarized in the table below.

Table 14.3.6 Treatment-Emergent Non-inhibitory Antibodies and CHO Cell Antibodies (Safety Population)

Parameter	Total (N=107) n (%)
Antibodies Against rIX-FP	
Yes	0
No	107 (100.0)
Antibodies Against pdFIX	
Yes	0
No	2 (100.0)
Antibodies Against rFIX	
Yes	0
No	2 (100.0)
Antibodies Against Albumin	
Yes	0
No	2 (100.0)
Antibodies Against CHO Cell Proteins	
Yes	0
No	90 (100.0)

Reviewer comment:

According to the CBER BLA committee chair, Mikhail Ovanesov, the screening assay does not have 5% false positive recommended by the Agency. So the above results may be due to an assay with a poorly determined cut point, and not valid.

In addition, the inhibitor assay validation did not test for the impact of (b) (4) on the FIX activity assay used to detect inhibitors in patient samples, and the sponsor should provide data examining this. Although the validation of the immunogenicity assays are under CBER purview, a recommendation to request this data will be made to DHRR (see OBP Recommendations at the top of the review).