Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology

MEMORANDUM

Date:	December 12, 2012
From:	Bethany Baer, MD Medical Officer, Division of Epidemiology
To:	Leigh Pracht Regulatory Project Manager Division of Blood Applications Office of Blood Research and Review
Through:	Christopher Jankosky, MD, MPH Chief, Therapeutics and Blood Safety Branch David Martin, MD, MPH Director, Division of Epidemiology
Subject:	Pharmacovigilance plan review for initial licensure
Applicant:	Inspiration Biopharmaceuticals
Product:	Recombinant Factor IX Concentrate, Ixinity (IB1001)
Proposed Indication:	Control and prevention of bleeding episodes in patients with hemophilia B. Peri-operative management in patients with hemophilia B.
Submission Type:	BLA 125426
PVP Submission Date:	August 29, 2012
Action Due Date:	February 4, 2013

1. INTRODUCTION

a. Product Description

Coagulation factor IX (Recombinant), IB1001 (also referred to as Ixinity) is a purified recombinant form of the human coagulation factor IX protein. It is produced in Chinese Hamster Ovary (CHO) cells and is a single chain glycoprotein with an amino acid sequence identical to the Thr148 allelic form of plasma-derived factor IX. It is used to treat patients with hemophilia B. It is functionally and structurally similar to BeneFIX (the recombinant factor IX currently marketed in the United States), and is not proposed to be superior to BeneFIX, but according to the sponsor would make recombinant factor IX more accessible to patients with hemophilia B.[1]

b. Regulatory History

The clinical study IB1001-01 under the IND 13551 was placed on clinical hold by the FDA on July 5, 2012 due to concerns regarding the development of anti-CHO antibodies in 21 of 68 subjects in the trial.[2] As of the writing of this Pharmacovigilance Plan (PVP) review memorandum, the IND remains on hold. IB1001 is not yet approved in any country.

c. Objectives

This memorandum is in response to a request from the Office of Blood Research and Review (OBRR) to the Office of Biostatistics and Epidemiology (OBE) to review the risk management plan submitted by Inspiration Biopharmaceuticals with the BLA 125426. The BLA is seeking initial licensing of the product coagulation factor IX (Recombinant) also referred to as IB1001 or Ixinity for the indications of:
1. control and prevention of bleeding episodes in patients with hemophilia B, and 2. peri-operative management in patients with hemophilia B.

Please note that text in italics is verbatim from the BLA.

2. MATERIALS REVIEWED

Source	Subtype	Document Reviewed
Inspiration	BLA 125426	Summary of Clinical Safety
Inspiration	BLA 125426	Pharmacovigilance Plan (United States) Version 0.1, dated 27 Aug 2012
Inspiration	BLA 125426/0.8	BLA Amendment
Wyeth	Package insert	BeneFIX Package Insert
FDA	Annual Surveillance Report	OBE Annual Surveillance Report for 2/12/11 to 2/11/12
Other	Publication	Monahan PE, Liesner R, Sullivan ST, Ramirez ME, Kelly P, Roth DA. Safety and efficacy of investigator-prescribed BeneFIX prophylaxis in children less than 6 years of age with severe

[1] BLA 125462, Summary of Clinical Safety, 2.7.4, p. 3.
[2] BLA 125462, Pharmacovigilance Plan, p. 20.

		haemophilia B. *Haemophilia*. 2010 May: 16:460-8..
Other	Publication	Uprichard J, Adamidou D, Goddard NJ, Mann HA, Yee TT. Factor IX replacement to cover total knee replacement surgery in haemophilia B: a single-centre experience, 2000-2010. *Haemophilia*. 2012 Jan;18(1):46-9
Other	Publication	Yang R, Zhao Y, Wang X, Sun J, Jin J, Wu D, Charnigo R, O'Brien A, Zhong Z, Rendo P. Evaluation of the safety and efficacy of recombinant factor IX (nonacog alfa) in minimally treated and previously treated Chinese patients with haemophilia B. *Haemophilia*. 2012 Sep;18(5):e374-8.

3. PHARMACOVIGILANCE PLAN REVIEW

Pharmacovigilance Plan (United States) Version 0.1 was received on August 29, 2012. A review of the pharmacovigilance plan with supporting background clinical trial information from the Summary of Clinical Safety is included below.

a. Clinical Safety Database

The single clinical trial, Protocol IB1001-01 Phase I/II/III is titled Pharmacokinetic and Outcome Study of Inspiration's Recombinant Factor IX Product, IB1001, in Subjects with Hemophilia B. *Briefly, subjects entered into either the pharmacokinetic (PK) or recovery phase of the Study IB1001-01 and progressed to 6 months of treatment with either an on-demand or prophylaxis schedule, and then if desired, to a continuation phase, where they could continue on IB1001 until product licensure or for up to one year, depending upon the approval by the applicable regulatory agency. The study also included a surgery sub-study phase in which subjects could participate separately, without a requirement for participation in the other study phases.*[3] There were 68 subjects in the safety and efficacy phase of the trial, including 52 subjects with >50 exposure days (ED). The surgery phase of the trial included a total of 16 major procedures in 14 subjects. Study IB1001-01 is not yet complete and is to include a long-term commitment to provide clinical efficacy, immunogenicity, and safety information on 50 previously treated patients for 100 ED.[4]

For Study IB1001-01, all of the 68 patients in the treatment phase were male. 79.4% were Caucasian, 10.3% were Asian, 4.4% were Black, 2.9% were Native Hawaiian and 2.9% were other race. The mean age was 36.3 years old, with a range from 7 to 64 years of age.[5]

Adverse Events in Clinical Study:

[3] BLA 125426, Summary of Clinical Safety, 2.7.4, p. 4.
[4] BLA 125426, Summary of Clinical Safety, 2.7.4, p. 5.
[5] BLA 125426, Summary of Clinical Safety, 2.7.4, p. 13.

Pharmacokinetic (PK) phase: The pharmacokinetic phase involved a crossover study with BeneFIX as a control. While the goal of this phase of the study was not a safety assessment, the cross-over design does provide a comparison between IB1001 and the only currently licensed recombinant factor IX product, BeneFIX. *There were 16 adverse events reported in 8 subjects during the PK study phase, including 8 events each in the BeneFIX and IXINITY PK study period [a single patient had a headache following both BeneFIX and IXINITY]. All events except for two were reported as mild or moderate. Assessment of severity was missing for one event (report of back pain during BeneFIX PK study period in one subject), and one case of grade 3 hemarthrosis. Joint bleeds are an expected occurrence in patients with severe hemophilia B, especially if their typical prophylaxis therapy is interrupted. . . . This event started two days following the 72 hour time point for the first PK study dose (BeneFIX) and prior to the PK dose of IXINITY. Two events were reported as possibly related to treatment, including one headache associated with comparator (BeneFIX) and one headache associated with IXINITY in the same subject.*[6] A list of the adverse events for IB1001 and BeneFIX are included in Table 1 below. The adverse events were comparable in number and characteristics between the two groups.

Table 1: Adverse Events in PK Phase (adapted from Summary of Clinical Safety, 2.7.4, p. 15)

Preferred Term	BeneFIX Phase n=32 n	IB1001 Phase n=32 n
Number of AE's	8 AE's in 6 subjects	8 AE's in 3 subjects
Headache	2	3
Migraine	1	0
Abdominal discomfort	1	0
Diarrhea	0	1
Vomiting	0	1
Back pain	1	1
Hemarthrosis	1	0
Pyrexia	1	1
Viral gastroenteritis	0	1
Nasopharyngitis	1	0

Treatment Phase:
For the treatment phase, 68 subjects were enrolled with 59 initially in the prophylaxis group and 9 in the on-demand group. Five subjects shifted between the two treatment groups and were considered in each treatment group for analysis of adverse events (AE's). There were 228 events reported in 46 subjects in the prophylaxis group and 30 events reported in 7 subjects in the on-demand group.[7] Approximately 70% of the subject treated in the prophylaxis regimen experienced an adverse event. Of the 228

[6] BLA 125426, Pharmacovigilance Plan, p. 22.
[7] BLA 125426, Pharmacovigilance Plan, p. 22.

events, at least 20 were associated with an accident, injury or procedure (including MVA, sports injuries, knee replacement surgery, falls).[8]

The analysis of the frequency of adverse events on a per injection basis demonstrated a rate for any given event of less than 1%.....Musculoskeletal events associated with hemophilia (e.g. arthralgia), as well as one instance of sore throat, were excluded. Headache was an uncommon event (≥0. 1% to <1%). Rare events (≥0. 01% to <0.1%) include dizziness, palpitations, vomiting, diarrhea (with or without abdominal pain), nausea, fever, general discomfort, injection site reaction or altered taste. While there have been no events reported as hypersensitivity or allergic reactions, other rare events that have generally been mild but may be associated with allergic reaction include asthma, lethargy, rash, cough, and chest tightness or pain. Fever is the only event that would be in a more frequent category (uncommon rather than rare) based on analysis of the entire study population (n=77) versus the treatment phase population (n=68).[9]

On a per subject basis, adverse events that occurred in ≥5% of subjects, regardless of relatedness, included upper respiratory symptoms and infections, headache, dizziness, pyrexia, diarrhea, vomiting and insomnia…These events are generally consistent with the side effects that have been associated with the marketed recombinant factor IX.[10]

There were 21 study subjects that were found to be positive for anti-CHO antibodies during the study. One of the subjects was positive at initial screening and two other subjects had inconsistent or borderline results, so 18 patients were considered to have seroconverted.[11] The sponsor states that there were no adverse effects of these anti-CHO antibodies, but the FDA review team notes that there was limited follow-up on these patients. FDA concern over this issue is discussed further in section 3b, Safety Concerns.

Surgery Sub-Study:

In the surgery sub-study, IB1001 was safe and well-tolerated with few adverse events and those that occurred would be expected with major surgery. There were no serious adverse events. Five of fourteen subjects (16 procedures) experienced one or more adverse events during the peri-surgical timeframe, including pain, swelling, fever, nausea, and some bleeding or oozing at the surgical site. Transfusions were required in one subject in the postsurgical timeframe associated with a decreased hemoglobin level; no significant perioperative hemorrhages or other significant adverse events were reported in the other procedures.[12] The patient that required transfusions had a bilateral knee replacement that required extensive bone modeling. He had continued blood loss through post-surgical drains and required transfusions on post-operative days 3 and 4.

There were no deaths during the study IB1001-1.[13]

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[8] BLA 125426, Pharmacovigilance Plan, p. 21.
[9] BLA 125426, Summary of Clinical Safety, 2.7.4, p. 21.
[10] BLA 125426, Summary of Clinical Safety, 2.7.4, p. 25.
[11] BLA 125426, Pharmacovigilance Plan, p. 27.
[12] BLA 125426, Summary of Clinical Safety, 2.7.4, p. 25-26.
[13] BLA 125426, Summary of Clinical Safety, 2.7.4, p. 27.

Serious Adverse Events:
There were eleven serious adverse events (SAEs) reported in six subjects during all phases of study IB1001-01. These events, which all occurred during the treatment phase of the study, are summarized in Table 2 below. All of the events had other known causal factors except for subject (b)(6) abdominal pain. This patient had a normal abdominal and pelvic CT and normal labs, and the pain resolved within 2 weeks.[14]

Table 2: Serious Adverse Events in Study IB1001-01 (adapted from Summary of Clinical Safety, p., 28-29):

Subject	Preferred Term (associated cause)	Outcome	Intensity	Causality
(b)(6)	Hematoma (from fall)	Resolved	Moderate	Unrelated
(b)(6)	Acute diverticulitis	Resolved	Moderate	Unrelated
	Abdominal pain lower	Ongoing	Moderate	Unrelated
(b)(6)	Left foot laceration (from MVA)	Resolved	Mild	Unrelated
(b)(6)	Abdominal pain	Resolved	Moderate	Unrelated
(b)(6)	Spinal column stenosis	Resolved with sequelae	Severe	Unrelated – all were result of an MVA caused by a seizure in patient with a prior seizure disorder.
	Lumbar vertebral fracture (due to seizure while driving)	Resolved	Severe	
	Neuropathy peripheral	Resolved with sequelae	Severe	
	Back Pain	Resolved	Severe	
	Wound infection (at surgical site)	Resolved	Life-threatening	Unrelated
(b)(6)	Eye trauma (due to hockey puck)	Unknown	Unknown	Unrelated

The lack of significant safety findings, specifically lack of any detected inhibitors in subjects followed for up to 24+ months, and lack of detection of all other serious class specific adverse events [thromboembolic events, hypersensitivity (including anaphylaxis) and nephrotic syndrome] provide strong support that the safety profile of IB1001 is

[14] BLA 125426, Summary of Clinical Safety, 2.7.4, p. 31.

acceptable and desirable for use in the treatment of subjects with hemophilia B.[15] There will be additional safety information provided through the long-term follow-up of study IB1001-01. There are no new safety concerns raised by the reported adverse events, and as pointed out by the sponsor, many specific potential risks associated with this type of factor product were not seen in the clinical trials (thromboembolic events, hypersensitivity, and nephritic syndrome).

b. Safety Concerns

Thrombogenicity: *In the PK phase of Study IB1001-01, laboratory parameters monitored included thrombogenic markers (prothrombin fragment 1+2 (F1+2), d-dimer and thrombin-antithrombin complex (TAT)), high sensitivity C-reactive protein (hsCRP), and factor IX. There was significant variability in the results of the thrombogenic marker assays, however there were no cases of or a pattern indicative of clinically relevant thrombogenicity in subjects treated with either IB1001 or BeneFIX, and none were associated with AEs…. In the treatment study phase, laboratory parameters for blood chemistry, hematology, and urinalysis have been observed over the course of study participation for all subjects. There were no clinically meaningful trends in individual lab values over time, although there were a few time points where individual abnormal values were considered clinically significant*[16]. Thrombosis is a theoretical concern with any substance that affects the clotting cascade. There were no clinical adverse events or thrombosis in the clinical trials for IB1001, but the trials are limited in number of patients. As is common for this category of product, this type of rare adverse event would need to be monitored in a larger population, potentially post-licensure.

Lack of Effect: Due to the nature of hemophilia, patients receiving treatment and having less than expected therapeutic effect are at risk of serious bleeding episodes. Decreased efficacy of any factor replacement can potentially be due to inhibitor development or lack of compliance with dosing. It is difficult to fully account for the effect of lack of compliance with dosing, but instructions are given in the package insert to adjust the dose if bleeding is seen on the current dose. Inhibitor formation is addressed in the immunogenicity section below.

Immunogenicity – Anti-Factor IX Antibodies: *As of the cut-off date of the last study report (December 2011), no inhibitors have been detected in any of the subjects participating in study IB1001-01, including 52 subjects with more than 50 exposure days to IB1001 and several subjects who have been on prophylaxis for long periods (27 for more than a year and 10 for more than 2 years)*[17]. Inhibitor development is an unfortunate but expected event with use of all factor replacement products. It is included on the label for IB1001 and other factor IX products. Because study IB1001-01 did not show inhibitor development, IB1001 does not appear to cause a greater level of inhibitor development than other comparable products.

[15] BLA 125426, Summary of Clinical Safety, 2.7.4, p. 30.
[16] BLA 125426, Summary of Clinical Safety, 2.7.4, p. 33-34.
[17] BLA 125426, Summary of Clinical Safety, 2.7.4, p. 34.

Immunogenicity – Anti-CHO Antibodies: The sponsor states that *as a consequence of the manufacturing process, trace quantities of CHO cell protein are present in IB1001. While studies of marketed recombinant factor products produced in CHO cells suggest that antibodies against such proteins can sporadically be detected in patients as well as non-hemophilic subjects (Ingerslev J et al, 2002), there has been no clinical evidence that this is typical or is associated with any clinical consequences.*[18] Of note, the Ingerslev article referenced describes a study on Recombinate, a recombinant human factor VIII synthesized in Chinese Hamster Ovary cells and first introduced in 1992 and the conclusions on safety may not fully apply to IB1001. Different processing can lead to varying levels of CHO protein between products. With 18 patients of the 68 tested (26%) in the IB1001-01 study seroconverting for anti-CHO antibodies, the FDA clinical review and Chemistry, Manufacturing and Controls (CMC) teams have expressed great concern that the level of CHO protein in IB1001 is greater than in other similar products. There has also been limited follow-up on these patients with anti-CHO antibodies in study IB1001-01. The sponsor reports that there were no clinical characteristics or patient medical histories that appeared to be related with seroconversion. The data suggest that higher doses may be a risk factor. The significance of these antibodies is unclear as there has been no evidence of allergic reactions or other adverse events related to the antibody formation.[19] Concerns regarding these antibodies led to the FDA placing the IND for IB1001 on clinical hold on July 5, 2012.[20] On October 11, 2012, the sponsor submitted an updated follow-up on these patients. The results, similar to previous data provided by the sponsor, stated that 17 of 66 (26%) subjects showed clear seroconversion to anti-CHO antibodies.[21] The review team is currently communicating with the sponsor to discuss additional follow-up on patients who developed anti-CHO antibodies during the clinical trial as well as manufacturing changes to address the level of CHO protein in this product.

Hypersensitivity: *Additionally, there have been no reports of anaphylaxis or other serious allergic type reaction, nor has nephrosis been documented in any treated patient.*[22] As noted in the 3a. Clinical Safety Database, Treatment phase, there were cases of asthma, lethargy, rash, cough, and chest tightness or pain that could have been signs of hypersensitivity. Allergic reactions are a common concern for this type of factor replacement. There was no sign of increased risk for this product during the clinical trials, but the full significance of the anti-CHO antibody development is not known. This antibody formation could theoretically increase risk of hypersensitivity events.

Nephrotic Syndrome: There have been reports in the literature of nephrotic syndrome following high doses of a plasma-derived factor IX being used in immune tolerance therapy (ITT) in hemophilia B patients with factor IX inhibitors and a history of allergic reactions. IB1001 has not been studied for use in immune tolerance therapy. As stated under the hypersensitivity section above, there were no cases of nephrosis in the clinical

[18] BLA 125426, Summary of Clinical Safety, 2.7.4, p. 34-35.
[19] BLA 125426, Pharmacovigilance Plan, p. 32.
[20] IND 13551, Clinical Hold Letter from FDA dated July 5, 2012.
[21] BLA 125426/0.8, Amendment to BLA Application, p. 2.
[22] BLA 125426, Summary of Clinical Safety, 2.7.4, p. 34.

studies. Of note, the sponsor is not currently applying for the indication for IB1001 to include use for ITT. The proposed label specifically addresses the lack of safety information with ITT.

Pregnancy: IB1001 has not been studied in pregnant or lactating subjects. Due to the X-linked recessive inheritance pattern of this disease, there are extremely few affected females.

Viral Transmission: As IB1001 is a recombinant product, there is less risk of transmission of blood-borne viral pathogens compared to products produced from pooled human plasma. In addition, the manufacturing process of IB1001 contains three well-documented, effective steps for virus removal and inactivation. These steps are S/D treatment, the (b)(4) chromatography and the (b)(4) filtration.[23]

c. Sponsor's Proposed Actions

During the clinical trials, the sponsor did not find any known identified risks. The sponsor has identified the following important potential risks: immunogenicity, lack of effect, thrombogenicity, hypersensitivity (including anaphylaxis), and nephrotic syndrome. These adverse events were not seen during the clinical trials for IB1001, but they have been reported following the administration of other marketed factor IX products.[24] Areas of important missing information are: pregnant or lactating women, elderly patients (>65 years old), patients with hepatic insufficiency, patients with renal insufficiency, children (<12 years old) previously treated with factor IX products, children previously untreated with factor IX products, and patients administered IB1001 for use as immune tolerance therapy in patients who have developed inhibitors to factor IX. The table 3 below outlines the sponsor's pharmacovigilance plan for the important risks and missing information for IB1001. The sponsor is planning to continue the study IB1001-01 for long-term monitoring of adults and adolescents. This continuation phase includes the assessment of antibodies to CHO cells and inhibitor testing. The sponsor also has ongoing and planned studies in previously untreated children (IB1001-02) and previously treated children (IB1001-03).[25]

Table 3: Summary of Safety Concerns and Planned Pharmacovigilance Actions (adapted from Tables 17 and 18 Pharmacovigilance Plan, p. 46-48):

Important Potential Risks	
Immunogenicity Lack of Effect Thrombogenicity	-Routine pharmacovigilance -Long-term safety study IB1001-01 Continuation Phase -Clinical studies IB1001-02 and -03 -Cumulative review in all PDERs
Hypersensitivity (including anaphylaxis)	-Routine pharmacovigilance -Long-term safety study IB1001-01 Continuation Phase

[23] BLA 125426, Pharmacovigilance Plan, p. 46.
[24] BLA 125426, Pharmacovigilance Plan, p. 32.
[25] BLA 125426, Summary of Clinical Safety, 2.7.4, p. 30.

	-Clinical studies IB1001-02 and -03 -Cumulative review in all PDERs -Monitoring for anti-CHO in clinical studies and in patients who report allergy or hypersensitivity reactions
Nephrotic Syndrome	-Routine pharmacovigilance -Cumulative review in all PDERs
Important Missing Information	
Elderly patients (>65 years old) Patients with hepatic insufficiency Patients with renal insufficiency	-Routine pharmacovigilance -Cumulative review in all PDERs
Children (<12 years old) previously treated with factor IX products	-Routine pharmacovigilance -Clinical study IB1001-02 – Phase III/IV Pediatric Study in pediatric subjects with hemophilia B previously treated with Factor IX products -Cumulative review in all PDERs
Children previously untreated with factor IX products	-Routine pharmacovigilance -Clinical study IB1001-03 – Phase III/IV Pediatric Study in children with hemophilia B previously untreated with Factor IX products -Cumulative review in all PDERs
Administration of IB1001 for use as immune tolerance therapy (ITT) in patients who have developed inhibitors to factor IX	-Routine pharmacovigilance -Clinical study IB1001-03–Phase III/IV Pediatric Study in children with hemophilia B previously treated with Factor IX products-to identify inhibitor incidence & determine need to evaluate ITT; Need for further evaluation to be determined based upon outcome of IB1001-03 -Cumulative review in all PDERs

4. OTHER INFORMATION FROM MANAGED REVIEW PROCESS

The clinical team is concerned regarding the formation of anti-CHO antibodies as discussed in section 3b above. This concern has led to the associated IND being put on clinical hold in July 2012. There are ongoing discussions with the sponsor regarding a manufacturing change to add a step to decrease the amount of CHO proteins in the product. Comparability study protocols submitted by the sponsor are currently being reviewed. The patients with anti-CHO antibodies developing in the clinical trial are also being monitored to determine if there are clinical effects from these antibodies.

5. POST-LICENSURE SAFETY REVIEW

BeneFIX is the only currently approved factor IX (recombinant) product. BeneFIX is also made in Chinese Hamster Ovary cells and contains trace amounts of CHO proteins. The BeneFIX package insert states that patients receiving BeneFIX may develop

hypersensitivity to these non-human mammalian proteins.[26] Post-marketing adverse reactions reported in the package insert for BeneFIX are inadequate factor IX recovery, inadequate therapeutic response, inhibitor development, anaphylaxis, angioedema, dyspnea, hypotension and thrombosis. BeneFIX's package insert warns that the safety of BeneFIX administered by continuous infusion has not been established. Some of the post-marketing reports of thromboembolic events described the AE occurring during BeneFIX continuous infusion.[27] Also, cases of anaphylaxis could theoretically have been caused by antibodies to CHO or to other substances.

The FDA internal annual surveillance report for BeneFIX covering the time period of 2/12/11 – 2/11/12 included an annual AERS search which found 49 worldwide adverse events with 42 of those being serious. There were 5 deaths reported: 2 were unrelated to the drug use (gun shot wound, motor vehicle accident), 2 had very limited information but one of these may have involved a hemorrhage, and the fifth case was a patient who had an acute hemorrhage during a lithotripsy operation. A nephrectomy was performed and after a prolonged period the hemorrhage resolved. The patient developed renal failure and respiratory failure and died within 3 months of the initial procedure. For the serious cases, the most common preferred terms were factor IX inhibition, hypersensitivity, drug ineffective, hemorrhage, urticaria, anaphylactic reaction, anaphylactoid reaction, convulsion, death, and dizziness.

A literature search on BeneFIX and recombinant factor IX on Dec. 3, 2012 revealed three relatively recent articles related to safety (PubMed search for "BeneFIX" and "safety" and "recombinant factor IX" and "safety" covering the past 5 years). The first article[28] describes a study of safety and efficacy of BeneFIX prophylaxis in children with severe hemophilia. The article states that approximately 7000 patients worldwide have used BeneFIX. A prospective, open-label clinical study included 25 subjects, with 10 of these subjects accruing more than 50 exposure days. Only two of the subject had adverse events felt to be related to BeneFIX. One had a mild rash and the other patient had an allergic reaction that was associated with a low-titer FIX inhibitor. The inhibitor titers spontaneously decreased and were undetectable 2 and 3 months later. The patient received premedication and did not have allergic reactions with subsequent doses. There were no reports of thrombosis in the study. Two subjects had elevated thrombogenic markers, but they had no associated clinical symptoms. In the study, factor IX inhibitor and anti-FIX antibody assessments were conducted at baseline and every 1-3 months thereafter. The one inhibitor subject was the only patient found to be anti-FIX ELISA positive. The article did not mention the potential development of anti-CHO antibodies. The authors concluded that safety was established for BeneFIX due to the low incidence of treatment-related adverse events.

[26] BeneFIX package insert, section 5.2
[27] BeneFIX package insert, section 6.2
[28] Monahan PE, Liesner R, Sullivan ST, Ramirez ME, Kelly P, Roth DA. Safety and efficacy of investigator-prescribed BeneFIX prophylaxis in children less than 6 years of age with severe haemophilia B. *Haemophilia*. 2010 May: 16:460-8.

A second article was a manufacturer-sponsored study assessing the efficacy and safety of BeneFIX in China.[29] Thirty-five patients were treated with BeneFIX. Thirteen of the patients reported 21 AEs and none were felt to be related to the study drug by the investigators. One patient was found to be positive for FIX inhibitors at study entry and was subsequently withdrawn from the study. There were no cases of new FIX inhibitor development during the study. There were no new safety concerns identified in the study.

A third article[30] described a retrospective study that reviewed 13 knee replacement surgeries in 11 patients with hemophilia B performed by the same surgeon over a ten-year period. Ten patients received plasma-derived Factor IX and the remaining one received BeneFIX. Seven of the patients received continuous infusions of Factor IX. Across all the cases, there was no excess hemorrhage, no thrombosis and no infections.

6. INTEGRATED RISK ASSESSMENT

The primary concern regarding IB1001's safety is the unknown significance of 26% of clinical study patients developing anti-CHO antibodies. CMC is evaluating a manufacturing change to decrease the residual CHO protein in the product and comparability protocols are being reviewed. It is possible that manufacturing changes may affect the final product in such a way that the safety profile is altered. The final risk assessment cannot be determined until further information is gathered regarding follow-up of the patients in the original clinical study, as well as the sponsor's plan to address the levels of CHO protein in the product.

7. RECOMMENDATION

OBE has reviewed the sponsor's pharmacovigilance plan for IB1001 as outlined above. There is critical follow-up information still outstanding from the clinical trial and ongoing manufacturing changes, specifically regarding the development of anti-CHO antibodies in a significant number of study subjects. As a result, it has not yet been determined by the clinical and CMC review members which additional studies will be required prior to possible approval. The review team has decided to issue a Complete Response letter outlining the current issues that need to be resolved for further consideration. OBE's recommendation regarding the PVP and any possible postmarketing requirements will need to be delayed until further information is available and the response to the CR letter is received.

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[29] Yang R, Zhao Y, Wang X, Sun J, Jin J, Wu D, Charnigo R, O'Brien A, Zhong Z, Rendo P. Evaluation of the safety and efficacy of recombinant factor IX (nonacog alfa) in minimally treated and previously treated Chinese patients with haemophilia B. *Haemophilia*. 2012 Sep;18(5):e374-8.

[30] Uprichard J, Adamidou D, Goddard NJ, Mann HA, Yee TT. Factor IX replacement to cover total knee replacement surgery in haemophilia B: a single-centre experience, 2000-2010. *Haemophilia*. 2012 Jan;18(1):46-9.