

REVIEW OF REQUEST FOR ORPHAN DRUG DESIGNATION

Date Submitted by Sponsor: February 23, 2012
Date Received by FDA: February 24, 2012
Date Review Completed: March 27, 2012

Designation Number: 12-3667

Trade name: TBD
Generic name (active ingredient): Recombinant Fusion Protein Linking Coagulation Factor IX with Albumin (rIX-FP)

Sponsor: CSL Behring LLC
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Contact name and address: Paula Hines, Ph.D.
Interim Director, Regulatory Affairs
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Manufacturer: Drug Product
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Proposed Orphan Designation: For the treatment of patients with congenital factor IX deficiency

Regulatory Status: This product is not approved anywhere in the world. BB - IND (No. 14978) for rIX-FP was submitted to the FDA on 18 January 2012 for patients with congenital factor IX deficiency:

Orphan Drug Designation History: Orphan Drug Designation of rIX-FP has been granted by the European Commission for treatment of hemophilia B. The Office of Orphan Products Development (OPD) has designated 6 products for treatment of hemophilia B. Three of those products have been approved. Each of the three is coagulation Factor IX. One of these approved products is a recombinant Coagulation Factor IX (BeneFIX®) that was approved and marketed in 1997. None of the three approved coagulation Factor IXs retain exclusivity.

Background of Disease or Condition

Factor IX (FIX) is a plasma glycoprotein that functions as a cofactor in the coagulation process. Hemophilia B is a severe bleeding disorder, which results from any of a variety of gene alterations all leading to reduced or defective synthesis of the FIX protein molecule (1). Normally diagnosed in early childhood, hemophilia B causes bleeding into the joints and muscles which occurs when the child begins to crawl or walk (1). The clinical manifestations of hemophilia B are categorized with respect to the severity of the FIX deficiency. Recurrent bleeding leads to progressive joint deformity, arthropathy, and debility. Hemorrhage into muscles can cause compression of arteries, veins, or nerves. Bleeding into the oropharynx, central nervous system, or retroperitoneal spaces can be life-threatening. Hemophilia B is inherited in an X-linked recessive pattern and is caused by mutations in the *F9* gene (1).

The official name of this gene is "coagulation factor IX." The gene (symbol F9) is located on the long (q) arm of the X chromosome between positions 27.1 and 27.2. Mutations in the *F9* gene lead to the production of an abnormal version of the protein called coagulation factor IX, or reduce the amount of this protein. The altered or missing protein cannot participate effectively in the blood clotting process. As a result, blood clots cannot form properly in response to injury (2). In males, one altered copy of the gene in each cell is sufficient to cause the condition. In females (who have two X chromosomes), a mutation would have to occur in both copies of the gene to cause the disorder. Because it is unlikely that females will have two altered copies of this gene, it is very rare for females to have hemophilia. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

Coagulation factor IX is made in the liver. This protein circulates in the bloodstream in an inactive form until an injury that damages blood vessels occurs. In response to injury, coagulation factor IX is activated by another coagulation factor called factor XIa. The active protein (coagulation factor IXa) interacts with coagulation factor VIII and other molecules. These interactions set off a chain of additional chemical reactions that form the blood clot (2).

The age of diagnosis and frequency of bleeding episodes are related to the level of factor IX clotting activity. In *severe hemophilia B*, spontaneous joint or deep-muscle bleeding is the most frequent symptom. Individuals with severe hemophilia B are usually diagnosed during the first two years of life; without prophylactic treatment, they may average up to two to five spontaneous bleeding episodes each month. Hemophilia B individuals with *moderate hemophilia B* seldom have spontaneous bleeding; however, they do have prolonged or delayed oozing after relatively minor trauma and are usually diagnosed before age five to six years; the frequency of bleeding episodes varies from once a month to once a year (3). Individuals with *mild hemophilia B* do not have spontaneous bleeding episodes; however, without pre- and post-operative treatment, abnormal bleeding occurs with surgery or tooth extractions; the frequency of bleeding may vary from once a year to once every ten years. Individuals with mild hemophilia B are often not diagnosed until later in life.

Since the late 1960s, the mainstay of treatment of bleeding episodes has been factor IX concentrates that initially were derived solely from donor plasma. By the late 1970s, more purified preparations became available, reducing a risk of thrombogenicity. Viral inactivation methods and donor screening of plasmas were introduced by 1990 and a recombinant factor IX concentrate became available shortly thereafter (4). HIV transmission from concentrates essentially occurred between 1979 and 1985. Approximately half of these individuals died of AIDS prior to the advent of effective HIV therapy.

Alloimmune inhibitors occur much less frequently in hemophilia B than in hemophilia A. Approximately 3% of individuals with severe hemophilia B develops alloimmune inhibitors to factor IX. These individuals usually have partial or complete gene deletions or certain nonsense mutations. At times, the onset of an alloimmune response has been associated with anaphylaxis to transfused factor IX or development of nephrotic syndrome (4).

Population Estimate

According to the sponsor, Hemophilia B has a prevalence of approximately 1 in 50,000 males (5). Based on the World Federation of Hemophilia Report on the Annual Global Survey, 2009, (6), and the sponsor's reported United States 2009 population of 310,232,863, the sponsor states that the U.S. prevalence of Hemophilia B is 4000 people.

Scientific Rationale

Description of Drug

Recombinant Fusion Protein Linking Coagulation Factor IX with Albumin (rIX-FP) is a purified recombinant protein comprised of recombinant coagulation factor IX linked to recombinant albumin by a short cleavable linker peptide. It consists of 1018 amino acids in a single chain glycopeptide and is intended for IV injection.

Description of Rationale

In order to generate rIX-FP, FIX cDNA was connected to human albumin cDNA via a FIX-derived linker sequence. The linker sequence between FIX and albumin is derived from an endogenous FIX sequence involved in normal FIX activation, enabling the cleavage of the fusion protein by the same enzymes (coagulation Factor XIa or Factor VIIa/Tissue Factor) which activate FIX during the normal process of blood coagulation. Thus, as a result of activation *in vivo*, in parallel active recombinant FIXa is cleaved from the albumin carrier moiety.

The advantage of this technology over other methods of extending protein half-life *in vivo* is that it allows an unchanged human recombinant FIX to be co-expressed as a fusion to recombinant human albumin. The effects of rIX-FP were evaluated in the animal studies described below.

Animal Studies

The pharmacodynamic efficacy of rIX-FP was examined *in vivo* using FIX knock out mice and hemophilia B dogs. These FIX deficient mice and dogs have demonstrated similar deficiencies in their coagulation systems compared to human hemophilia B patients and show an increased bleeding risk which is also present in hemophilia B patients.

Mouse Study 1

In this study the tail tip bleeding time was determined in hemophilia B mice (FIX knock out mice) after rIX-FP administration by quantifying time to hemostasis and total blood loss. A single intravenous bolus of rIX-FP and BeneFIX® (a marketed recombinant human factor IX product), respectively, at 50, 100 and 200 IU/kg was given to FIX deficient mice (15 mice/group). One group receiving isotonic saline (0.9 %) served as control. A tail tip bleeding assay with resection of about 3 mm of the tail tip was performed 15 minutes after drug substance administration to assess bleeding parameters. Both rIX-FP and BeneFIX® at all dose levels tested showed a clear hemostatic effect compared to the control group, i.e., a significant reduction in time to hemostasis and total blood loss. The efficacy did not differ from that of BeneFIX®.

Mouse Study 2

The purpose of this study was to investigate the effect of rIX-FP administration on the coagulation parameter "activated partial thromboplastin time" (aPTT), the period required for clot formation in the FIX knock out mice. A single intravenous bolus of rIX-FP and BeneFIX®, respectively, at 50, 100 and 200 IU/kg was given to FIX deficient mice, whereas one group receiving isotonic saline (0.9 %) served as control (14-17 mice/group). Measurement of aPTT was used to detect the effects on coagulation. Both rIX-FP and BeneFIX® showed a clear significant decrease in aPTT compared to the control group at all investigated dose levels. The rIX-FP efficacy did not differ from that of BeneFIX®.

Dog Study

The aim of this study was to assess the pharmacological efficacy, bioavailability and immunogenicity of rIX-FP in hemophilia B dogs and, in addition, to compare the acquired data with BeneFIX®. In this study three hemophilia B dogs were treated with rIX-FP and two with BeneFIX® using a single intravenous dose of 100 IU/kg. Blood samples were taken up to Day 36 for assessment of pharmacodynamic investigations (i.e., aPTT and whole blood clotting time (WBCT)). Both treatment groups demonstrated a clear hemostatic efficacy. WBCT and aPTT values were decreased after treatment and returned to pretreatment values after study drugs were cleared from the circulation. However, aPTT values stayed below 0.6 times the baseline value more than three

times longer in the rIX-FP group (5.4 days) than in the BeneFIX® group (1.6 days). It can be concluded that rIX-FP administration demonstrated a clear hemostatic efficacy in hemophilia B dogs.

Clinical Studies

No clinical trials evaluating the efficacy of rIX-FP have been performed. A Phase I/II study is currently ongoing in Israel and Bulgaria, but no data are available.

Clinical Superiority

The sponsor states that rIX-FP is being developed with the aim of providing a product with an extended half-life that could provide significant benefit to hemophilia B patients by decreasing the frequency of prophylactic treatments compared to currently available products. The sponsor states that the nonclinical program demonstrated hemostatic efficacy in two relevant animal models of FIX deficiency mimicking the disease state of hemophilia B patients and superior pharmacokinetic properties in several animal models. Thus, rIX-FP is expected to provide a major contribution to patient care based on its longer half-life which would allow for less frequent dosing.

DISCUSSION AND CONCLUSIONS

In this application, CSL Behring LLC. requests orphan-drug designation for their Recombinant Fusion Protein Linking Coagulation Factor IX with Albumin (rIX-FP) for the treatment of patients with congenital factor IX deficiency (hemophilia B).

Prevalence Estimate

The sponsor reported the birth rate of hemophilia B in males and the population of the U.S. in 2009. Although the calculations were not provided, the sponsor estimated the prevalence of hemophilia B to be 4000.

This reviewer found several estimations of the prevalence of hemophilia B. According to the World Federation of Hemophilia (2009) (6) hemophiliacs make up 0.005% of the US. population. The prevalence for both hemophilia A and B based on this percentage and the present US population of 313,233,883 is 15,661. The ratio of hemophilia A to B is 4 to 1 (2) leaving a prevalence estimate of hemophilia B of 3,132.

Another recent estimate from the CDC UDC of the number of patients with Hemophilia A or B in the U.S. is 23,101 patients (7). Using the 4 to 1 ratio of A to B leaves a prevalence estimate for hemophilia B of 4,620.

According to the World Federation of Hemophilia website on March 25, 2012, about 1 in 10,000 people are born with hemophilia (8). This includes both hemophilia A and B. Considering the present US population of 313,233,883, results in a total estimated prevalence of 31,320. Using the ratio of A to B (4:1), the prevalence estimate for hemophilia B would be 6260.

Finally, the most recent prevalence estimate for the latest OOPD designation of hemophilia B (#3575) in 2011 was 8,141. Thus, each of these prevalence estimates for hemophilia B (the highest being 8,141) is far less than the 200,000 regulatory limit for orphan drug designation.

Scientific Rationale

The sponsor has provided an adequate scientific rationale to support orphan designation. The sponsor presented two studies in FIX knock out mice and one study in a dog model of hemophilia B. All three studies compared the effects of rIX-FP to the approved coagulant factor IX, BeneFIX®. The sponsor contends that these animal studies demonstrated that rIX-FP displays an extended half-life as compared to BeneFIX®, and thereby clinical superiority to the presently available therapy. The sponsor stated that the clinical superiority would be based on fewer dosing administrations that the patients would have to undergo.

However, clinical superiority is only necessary and applicable if rIX-FP is indeed the "same drug" as the already approved recombinant factor IX. That is, according to CFR316.20(b)(5), "where the sponsor of a drug that is otherwise the same drug as an already-approved orphan drug seeks orphan designation for the subsequent drug for the same rare disease or condition, an explanation of why the proposed variation may be clinically superior to the first drug" should be included in the request for designation. FDA regulations also state that "Two protein drugs would be considered the same if the only differences in structure between them were due to posttranslational events or infidelity of translation or transcription or were minor differences in amino acid sequence; other potentially important differences, such as different glycosylation patterns or different tertiary structures, would not cause the drugs to be considered different unless the differences were shown to be clinically superior." It is known from the sponsor's references that recombinant fusion protein linking coagulation factor IX with albumin with a linker peptide sequence is formed via a process in which Factor IX wild-type cDNA is cloned into an expression vector and prepared for genetic fusion with the linker and albumin cDNA. The fused genetic material is then used to produce recombinant factor IX fused with albumin. FDA regulations state that two protein drugs would be considered the same if the only differences in structure between them were due to post-translational events (these are not post-translational events) or infidelity of translation or transcription or were minor differences in amino acid sequence. The DNA is not equivalent because the DNA of the FIX-albumin molecule contains the DNA of albumin (and the linker, too). Thus, the sponsor is exempt from the clinical superiority explanation requirement for orphan drug designation of rIX-FP.

RECOMMENDATION

CSL Behring LLC has requested orphan designation for Recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) for treatment of patients with congenital factor IX deficiency. The estimated US prevalence of hemophilia B is 8,141. It is recommended that the sponsor's request for an orphan designation for Recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) for the treatment of patients with congenital factor IX deficiency (hemophilia B) be granted. This designation includes Routine prophylaxis treatment, Control and prevention of bleeding episodes, and Prevention and control of bleeding in perioperative settings.

James H. Reese 3/28/12

James H. Reese, Ph.D., RAC
Health Science Administrator
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Henry H. Startzman III 3/30/2012

Henry Startzman III, MD
Associate Director, Designations Program

Concurrence:

Henry H. Startzman III for Gayatri R. Rao Date: *3/30/2012*

Gayatri R. Rao, MD, JD
Acting Director
Office of Orphan Products Development

cc:

HF-35/Designation file # 11-3667)

HF-35/Chron File

HF-35/JReese

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APR 27 2012

CSL Behring LLC
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Attention: Paula Hines, Ph.D.
Interim Director, Regulatory Affairs

Re: Designation request # 12-3667

Dear Dr. Hines:

Reference is made to your request for orphan-drug designation submitted on February 23, 2012, of recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) for "treatment of patients with congenital factor IX deficiency." Please also refer to our letter dated February 24, 2012.

Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), your orphan-drug designation request of recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) is granted for *treatment of patients with congenital factor IX deficiency (hemophilia B)*. *This designation includes routine prophylaxis treatment, control and prevention of bleeding episodes, and prevention and control of bleeding in perioperative settings.* Please be advised that it is the active moiety of the drug and not the formulation of the drug that is designated.

Please note that if the above drug receives marketing approval for an indication broader than what is designated, it may not be entitled to exclusive marketing rights under section 527 (21 U.S.C. 360cc). Therefore, prior to final marketing approval, we request that you compare the drug's designated orphan indication with the proposed marketing indication, and submit additional information to amend the orphan-drug designation if warranted.

Please submit to the Office of Orphan Products Development a brief progress report of drug development within 14 months after this date and annually thereafter until

marketing approval (*see* 21 C.F.R. 316.30). Finally, please notify this Office within 30 days of a marketing application submission for the drug's designated use.

If you have questions regarding the development of your designated product, please feel free to contact James H. Reese, Ph.D., RAC, at (301) 796-8660. Please refer to this letter as official notification. Congratulations on obtaining your orphan-drug designation.

Sincerely yours,

A handwritten signature in cursive script that reads "Gayatri Rao".

Gayatri R. Rao, M.D., J.D.
Acting Director
Office of Orphan Products Development

CSL Behring LLC

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cc:

OP File # 12-3667

Chron

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jb 4/4/12

DESIGNATION GRANTED