CLINICAL PHARMACOLOGY REVIEW

Division of Hematology Product Review Branch

Office of Blood Review & Research

STN 125426/0
Sponsor: Cangene Corporation
Product: Coagulation Factor IX (recombinant)
Indication: Control and prevention of bleeding episodes and peri-operative management in patients with hemophilia B
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Submission Date: April 6, 2012
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INTRODUCTION

Treatment for hemophilia B involves administering factor replacement therapy on either as-need basis or to prevent bleeds, as prophylaxis. Prophylaxis has been found to be an important means of reducing joint damage in children with severe hemophilia. Several factors affect the choice of concentrate used, including safety, efficacy, ease of reconstitution and administration, cost, affordability, and availability.

With advancements in technology, recombinant factor IX could be manufactured with a higher purity and containing fewer plasma proteins than plasma factor IX. Recombinant factor IX is produced in Chinese hamster ovary cells and has been available in the United States since 1997 (BeneFIX). Cangene Corporation (Emergent BioSolutions) has developed an intravenous recombinant factor IX, IB1001.

IB1001 (trenonacog alfa) is a recombinant coagulation factor IX under development by Inspiration Biopharmaceuticals, Inc. IB1001 contains trenonacog alfa as active substance (500 IU, 1000 IU or 1500 IU of recombinant factor IX) and is supplied as a sterile, non-pyrogenic, lyophilized powder for reconstitution with Sterile Water for Injection (SWFI), presented in glass vials with rubber stoppers.

IB1001 is a 415 amino acid, single chain glycoprotein with a molecular weight of approximately 55,000 Daltons. The primary amino acid sequence of IB100l is identical to the Thr148 allelic form of plasma-derived factor IX that is found in 80% of the normal population. The recombinant glycoprotein contains (b)(4)

IB1001 is a purified recombinant form of the human coagulation factor IX protein produced in Chinese Hamster Ovary (CHO) cells. No animal or human proteins are added during the manufacture of IB1001. The intended therapeutic indication for IB1001 is the intravenous treatment and prophylaxis of bleeding, and peri-operative management in patients with hemophilia B (congenital factor IX deficiency). The dosage and duration of the treatment depends on the severity of the factor IX deficiency, on the location and extent of the bleeding episode, clinical condition of the patient and on factor IX recovery.

The following review provides the pharmacokinetics (PK) characteristics of recombinant Factor IX product IB1001. This study also compares the PK of IB1001 with BeneFIX.

FINAL CLINICAL PHARMACOLOGY LABELING

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Hemophilia B is a sex-linked hereditary disorder of blood coagulation caused by a deficiency in factor IX and results in bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. Treatment with IXINITY replaces factor IX, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

12.2 Pharmacodynamics

The administration of IXINITY increases plasma levels of factor IX and can temporarily correct the coagulation defect in these patients, as reflected by decrease in the aPTT..

12.3 Pharmacokinetics

Pharmacokinetic studies with IXINITY were conducted in 32 previously treated patients (PTPs) ≥ 12 years of age with severe to moderately severe hemophilia B (factor IX ≤ 2 IU/dL). Intravenous administration of 75 ± 5 IU of IXINITY to 32 PTPs showed an initial recovery ranging from 51 to 113% (median 70%). The results of pharmacokinetic studies are summarized below in Table 4.

Table 1 Pharmacokinetic Parameters for IXINITY (n = 32)

Parameters	**Mean (± SD)** **(Range)**
$AUC_{0-\infty}$ (IU/dL/hr)	1573 (± 451) (862-2643)
Incremental Recovery (IU/dL per IU/kg)	0.98 (± 0.21) (0.67–1.50)
Terminal Half-life (hours)	24 (± 7) (13-43)
C_{max} (IU/dL)	74 (±17) (51-113)
Mean Residence Time (hours)	32(± 6) (19-47)
VD_{ss} (mL/kg)	175 (± 57) (102–314)
Clearance [mL/(kg·hr)]	5.1 (1.3) (2.8–7.7)

Pharmacokinetic parameters were re-assessed in a subset of 14 subjects after prophylaxis treatment with IXINITY for a median of 5.8 months (range 3.1 to 18.6 months) as summarized in Table 5 below.

Table 2 Pharmacokinetic Parameters of IXINITY following Repeat Dosing (n = 14)

Parameters	**Initial Mean (± SD)**	**Follow-up PK Mean (± SD)**
$AUC_{0-\infty}$ (IU/dL/hr)	1438 (± 409)	1530 (± 435)
Incremental Recovery (IU/dL per IU/kg)	0.96 (± 0.22)	0.95 (± 0.18)
Terminal Half-life (hours)	24 (± 7)	24(± 7)
C_{max} (IU/dL)	73 (± 16)	73 (± 15)
Mean Residence Time (hours)	30 (± 6)	31 (± 5)
VD_{ss} (mL/kg)	193 (± 62)	185 (± 70)
Clearance [mL/(kg·hr)]	5.6 (± 1.3)	5.3 (± 1.5)

Repeat dosing did not impact the pharmacokinetics of IXINITY.
The PK data were divided into two subgroups of subjects with a BMI ≤ 30 (n = 26) or BMI > 30 (n = 6). The AUC(0-∞) and Cmax values of IXINITY were 40% and 34% higher, respectively, in subjects with BMI > 30.

RECOMMENDATION

The study design, results, and the conclusions of the pharmacokinetic study of IB1001 are acceptable. The applicant has also incorporated the clinical pharmacology labeling as suggested by the FDA.

Study Title: Pharmacokinetic Study of Inspiration's Recombinant Factor IX Product, IB1001, in Subjects with Hemophilia B.

The objective of this PK study is to evaluate the PK of Factor IX (IB1001) in subjects with hemophilia B and compare the product (IB1001) with the marketed recombinant factor IX (BeneFIX).

Subjects with a minimum of 150 exposure days to a factor IX preparation were screened based on medical history, laboratory testing, age, and willingness to complete the trial. Up to 34 subjects who satisfied all inclusion/exclusion criteria were enrolled into the BeneFIX/IB1001 PK study to ensure that data for 28 subjects would be available for evaluation. The PK study was finally conducted in 32 subjects (age range 15-64 years).

Following a washout period of a minimum of 5 days from any factor IX product, subjects were to receive treatment according to a randomized, double-blind, cross-over design with either BeneFIX or IB1001. Depending upon randomization, sites administered either a single intravenous 75 ± 5 IU/kg dose of BeneFIX or a single intravenous 75 ± 5 IU/kg dose of IB1001. A pre-infusion level of factor IX and the presence of inhibitors and non-inhibitory antibodies was assessed, after which the test dose of factor IX was infused and factor IX levels were determined at the following time points post-infusion: 30 minutes ± 5 minutes, 1 hour ± 5 minutes, 3 hours ± 30 minutes, 6 hours ± 1 hour, 9 hours ± 1 hour, 12 hours ± 2 hours, 24 hours ± 3 hours, 36 hours ± 3 hours, 48 hours ± 3 hours, 60 hours ± 3 hours, and 72 hours ± 3 hours. Thrombogenic markers (D dimer, F1+2, and TAT) were evaluated pre-infusion; and at 30 minutes ± 5 minutes, 3 hours ± 30 minutes, and 24 hours ± 3 hours post-infusion. After a minimum washout of 5 days and up to a maximum of 28 days after the last assessment (assuming no other treatment with factor IX), a single intravenous 75 ± 5 IU/kg dose of the opposite product that was received by a subjects in the first cross-over period was administered, and an identical set of factor IX and thrombogenic markers was assessed. In the event that factor IX was required for treatment of a bleeding episode during the 5- to 28-day interval, the second evaluation was scheduled 5 to 28 days after the last infusion.

The comparability between IB1001 and BeneFIX was evaluated by 2-sided 90% confidence intervals on log transformed AUC data. Non-inferiority was declared if the lower 95% CI was above 80%. All other PK parameters were reported as descriptive statistics.

Factor IX activity in plasma PK samples was performed at the central lab (b)(4) by one stage assay on a (b)(4). Samples were measured in 3 independent dilutions against an in-house plasma standard, derived from pooled plasma from 55 healthy individuals which was calibrated against the most recent World Health Organization (WHO) standard for factor IX in plasma. Each individual run consisted of a calibrator, internal control and maximal 10 plasma samples at the time. Potencies of the individual plasma samples were expressed against the standard using a parallel line model and each result was submitted to an analysis of variance.

The pharmacokinetic parameters of IB1001 and BeneFIX are presented in Table 1. Plasma concentrations-time profile of IB1001 and BeneFIX are shown in Figure 1. The results of the PK

analysis indicate that IB1001 and BeneFIX are comparable in terms of pharmacokinetics. The 2-sided 90% confidence intervals on log transformed $AUC_{(0-infinity)}$ ranged from 0.886 to 1.004, indicating that IB1001 and BeneFIX are pharmacokinetically equivalent.

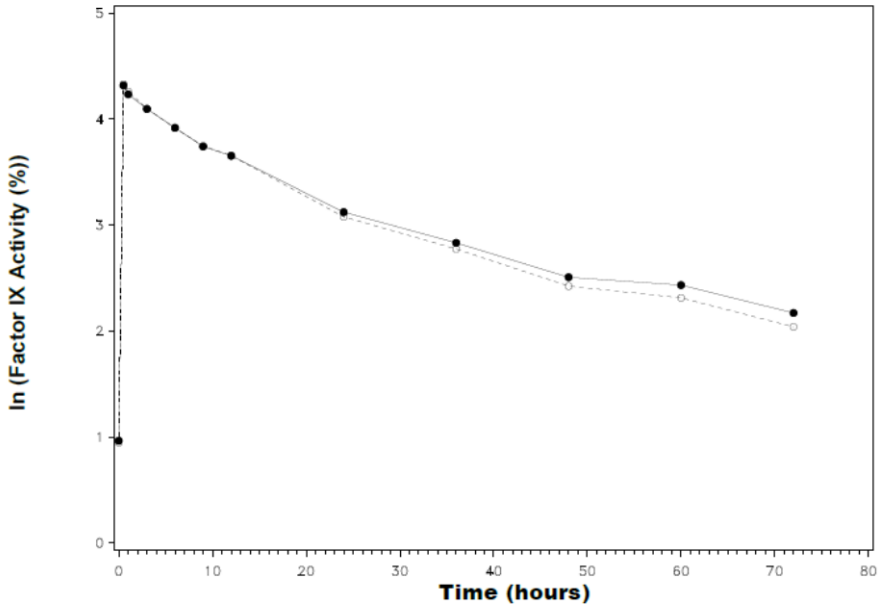
Table 1: Pharmacokinetic parameters (mean ± sd) of IB1001

Parameters	BeneFIX (n =32)	IB1001 (n =32)
$AUC_{(0-\infty)}$ (IUxhr/dL)	1656 ± 469	1573 ± 451
Clearance (mL/hr per kg)	5.0 ± 1.2	5.1 ± 1.3
Half-life (hrs)	26 ± 14	24 ± 7
MRT (hrs)*	35 ± 19	32 ± 6
Vss (mL/kg)**	181 ± 57	175 ± 57

* Mean residence time, ** Volume of distribution at steady state

Figure 1: Mean Factor IX Activity by Time and Treatment (Log-linear)

(IB1001, dashed line; BeneFIX, solid line)



Multiple or Repeat Dose Pharmacokinetics:

Four to 18 months after completing the BeneFIX/IB1001 PK Study, 13 subjects participated in a follow-up PK study with IB1001. While the intent was to include these subjects between 3 and 6 months after their initial PK, three subjects were beyond the six month window; two subjects had been on prophylaxis for 15-18 months and one subject had been on prophylaxis for 6 months followed by 8 months of on demand use. The results of the repeat dose PK studies are summarized in Table 2. The results suggest that there is no accumulation of IB1001 following multiple dosing.

Table 2: Pharmacokinetic parameters (mean ± sd) of IB1001

Parameters	IB1001 (n =13) initial PK	IB1001 (n =13) Repeat PK
$AUC_{(0-\infty)}$ (IUxhr/dL)	1438 ± 409	1530 ± 435
Clearance (mL/hr per kg)	5.6 ± 1.3	5.3 ± 1.5
Half-life (hrs)	24 ± 7	24 ± 6
MRT (hrs)*	30 ± 6	31 ± 5
Vss (mL/kg)**	193 ± 62	185 ± 70

* Mean residence time, ** Volume of distribution at steady state

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PK and Body Mass Index:

The PK data were divided into two subgroups of subjects with a BMI ≤30 (n = 26) or BMI >30 (n = 6). The $AUC_{(0-\infty)}$ and C_{max} values were 40% and 34% higher in subjects with BMI >30 than BMI ≤30. There were no significant differences between BeneFIX and IB1001 in the subgroup of subjects with a BMI ≤30 in regards to $AUC_{(0-\infty)}$ (90% CI 0.87-0.99) or C_{max} (90% CI 0.97-1.04). Likewise, no significant difference was observed in the subjects with a BMI >30 in regards to $AUC_{(0-\infty)}$ (90% CI 0.90-1.14), or C_{max} (90% CI 0.93-1.18).

Conclusions

- The pharmacokinetics of IB1001 are comparable to the pharmacokinetics of BeneFIX and based on the 90% confidence interval, both products are pharmacokinetically equivalent.
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- Although, the sample size for subjects BMI >30 (n = 6) was small but it seems that the obese may be receiving higher doses than needed.