

Benefix®

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Control and Prevention of Bleeding Episodes in Hemophilia B

Benefix®, Coagulation Factor IX (Recombinant), is indicated for the control and prevention of bleeding episodes in adult and pediatric patients with hemophilia B (congenital factor IX deficiency or Christmas disease).

1.2 Peri-operative Management in Patients with Hemophilia B

Benefix, Coagulation Factor IX (Recombinant), is indicated for peri-operative management in adult and pediatric patients with hemophilia B.

Benefix, Coagulation Factor IX (Recombinant), is **NOT** indicated for:

- a. treatment of other factor deficiencies (e.g., factors II, VII, VIII, and X),
- b. treatment of hemophilia A patients with inhibitors to factor VIII,
- c. reversal of coumarin-induced anticoagulation,
- d. treatment of bleeding due to low levels of liver-dependent coagulation factors.

2 DOSAGE AND ADMINISTRATION

2.1 General Considerations for Administration

For Intravenous Use after Reconstitution

- **Treatment with Benefix, Coagulation Factor IX (Recombinant), should be initiated under the supervision of a physician experienced in the treatment of hemophilia B.**
- **Each vial of Benefix has the rFIX potency in the International Units (IU) stated on the vial.**
- **Dosage and duration of treatment for all factor IX products depend on the severity of the factor IX deficiency, the location and extent of bleeding, and the patient's clinical condition, age and recovery of factor IX.**

To ensure that the desired factor IX activity level has been achieved, precise monitoring using the factor IX activity assay is advised. Doses should be titrated using the factor IX activity, pharmacokinetic parameters, such as half-life and recovery, as well as taking the clinical situation into consideration in order to adjust the dose as appropriate.

Dosing of Benefix may differ from that of plasma-derived factor IX products [see *Clinical Pharmacology* (12)]. Subjects at the low end of the observed factor IX recovery may require upward dosage adjustment of Benefix to as much as two times (2X) the initial empirically calculated dose in order to achieve the intended rise in circulating factor IX activity.

The safety and efficacy of BeneFIX administration by continuous infusion have not been established [see Warnings and Precautions (5)].

2.2 Method of Calculating Initial Estimated Dose

The method of calculating the factor IX dose is shown in Table 1.

Table 1

number of factor IX IU required (IU)	=	body weight (kg)	x	desired factor IX increase (% or IU/dL)	x	reciprocal of observed recovery (IU/kg per IU/dL)
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Average Recovery Adult Patients in Clinical Trial

In adult PTPs, on average, one International Unit (IU) of BeneFIX per kilogram of body weight increased the circulating activity of factor IX by 0.8 ± 0.2 IU/dL (range 0.4 to 1.2 IU/dL). The method of dose estimation is illustrated in Table 2. If you use 0.8 IU/dL average increase of factor IX per IU/kg body weight administered, then:

Table 2

number of factor IX IU required (IU)	=	body weight (kg)	x	desired factor IX increase (% or IU/dL)	x	1.3 (IU/kg per IU/dL)
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Average Recovery Pediatric Patients (<15 years) in Clinical Trial

In pediatric patients, on average, one international unit of BeneFIX per kilogram of body weight increased the circulating activity of factor IX by 0.7 ± 0.3 IU/dL (range 0.2 to 2.1 IU/dL; median of 0.6 IU/dL per IU/kg). The method of dose estimation is illustrated in Table 3. If you use 0.7 IU/dL average increase of factor IX per IU/kg body weight administered, then:

Table 3

number of factor IX IU required (IU)	=	body weight (kg)	x	desired factor IX increase (% or IU/dL)	x	1.4 (IU/kg per IU/dL)
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Doses administered should be titrated to the patient's clinical response. Patients may vary in their pharmacokinetic (e.g., half-life, *in vivo* recovery) and clinical responses to BeneFIX. Although the dose can be estimated by the calculations above, it is highly recommended that, whenever possible, appropriate laboratory tests, including serial factor IX activity assays, be performed.

2.3 Dosing Guide for Control and Prevention of Bleeding Episodes and Peri-operative Management

Table 4

Type of Hemorrhage	Circulating Factor IX Activity Required [% or (IU/dL)]	Dosing Interval [hours]	Duration of Therapy [days]
Minor			
Uncomplicated hemarthroses, superficial muscle, or soft tissue	20-30	12-24	1-2
Moderate			
Intramuscle or soft tissue with dissection, mucous membranes, dental extractions, or hematuria	25-50	12-24	Treat until bleeding stops and healing begins, about 2 to 7 days
Major			
Pharynx, retropharynx, retroperitoneum, CNS, surgery	50-100	12-24	7-10

Adapted from: Roberts and Eberst¹

2.4 Instructions for Use

BeneFIX is administered by intravenous (IV) infusion after reconstitution of the lyophilized powder with the supplied pre-filled diluent (0.234% sodium chloride solution) syringe.

Patients should follow the specific reconstitution and administration procedures provided by their physicians.

Reconstitution, product administration, and handling of the administration set must be done with caution. Discard all equipment, including any reconstituted BeneFIX product, in an appropriate container. Place needles used for venipuncture in a sharps container after single use. Percutaneous puncture with a needle contaminated with blood from an infected patient can transmit infectious viruses including HIV (AIDS) and hepatitis. Obtain immediate medical attention if injury occurs.

2.5 Preparation and Reconstitution

The procedures below are provided as general guidelines for the reconstitution and administration of BeneFIX.

Preparation

1. Always wash your hands before performing the following procedures.
2. Aseptic technique (meaning clean and germ-free) should be used during the reconstitution procedure.

3. Use all components in the reconstitution and administration of this product as soon as possible after opening their sterile containers to minimize unnecessary exposure to the atmosphere.

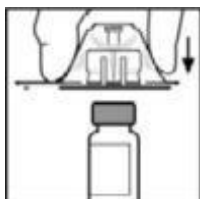
Note: If you use more than one vial of BeneFIX per infusion, each vial should be reconstituted according to the following instructions. The diluent syringe should be removed leaving the vial adapter in place, and a separate large luer lock syringe may be used to draw back the reconstituted contents of each vial. Do not detach the diluent syringes or the large luer lock syringe until you are ready to attach the large luer lock syringe to the next vial adapter.

Reconstitution

1. If refrigerated allow the vial of lyophilized BeneFIX and the pre-filled diluent syringe to reach room temperature.
2. Remove the plastic flip-top cap from the BeneFIX vial to expose the central portions of the rubber stopper.



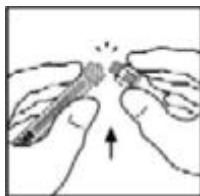
3. Wipe the top of the vial with the alcohol swab provided, or use another antiseptic solution, and allow to dry. After cleaning, do not touch the rubber stopper with your hand or allow it to touch any surface.
4. Peel back the cover from the clear plastic vial adapter package. **Do not remove the adapter from the package.**
5. Place the vial on a flat surface. While holding the adapter in the package, place the vial adapter over the vial and press down firmly on the package until the adapter spike penetrates the vial stopper.



6. Grasp the plunger rod as shown in the diagram. Avoid contact with the shaft of the plunger rod. Attach the threaded end of the plunger rod to the diluent syringe plunger by pushing and turning firmly.



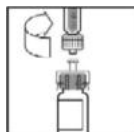
7. Break off the tamper-resistant plastic-tip cap from the diluent syringe by snapping the perforation of the cap. Do not touch the inside of the cap or the syringe tip. The diluent syringe may need to be recapped (if not administering reconstituted BeneFIX immediately), so place the cap on its top on a clean surface in a spot where it would be least likely to become environmentally contaminated.



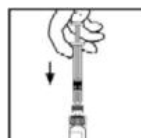
8. Lift the package away from the adapter and discard the package.



9. Place the vial on a flat surface. Connect the diluent syringe to the vial adapter by inserting the tip into the adapter opening while firmly pushing and turning the syringe clockwise until secured.



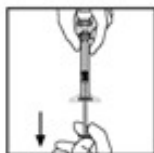
10. Slowly depress the plunger rod to inject all the diluent into the BeneFIX vial.



11. Without removing the syringe, **gently** swirl the contents of the vial until the powder is dissolved.

Note: The final solution should be inspected visually for particulate matter before administration. The solution should appear clear and colorless. If it is not, the solution should be discarded and a new kit should be used.

12. Invert the vial and slowly draw the solution into the syringe.



13. Detach the syringe from the vial adapter by gently pulling and turning the syringe counter-clockwise. Discard the vial with the adapter attached.

Note: If the solution is not to be used immediately, the syringe cap should be carefully replaced. Do not touch the syringe tip or the inside of the cap.

BeneFIX, when reconstituted, contains polysorbate-80, which is known to increase the rate of di-(2-ethylhexyl)phthalate (DEHP) extraction from polyvinyl chloride (PVC). This should be considered during the preparation and administration of BeneFIX, including storage time elapsed in a PVC container following reconstitution. It is important that the recommendations for dosage and administration be followed closely [see Dosage and Administration (2)].

Note: The tubing of the infusion set included with this kit does not contain DEHP.

2.6 Administration (Intravenous Injection)

For Intravenous Use only after Reconstitution

BeneFIX is administered by intravenous (IV) infusion after reconstitution with the pre-filled diluent (0.234% sodium chloride solution) syringe.

- BeneFIX should be inspected for particulate matter and discoloration prior to administration, whenever solution and container permit.
- The reconstituted solution may be stored at room temperature prior to administration, but BeneFIX should be administered within 3 hours. BeneFIX should be administered using the tubing provided in this kit, and the pre-filled diluent syringe provided, or a single sterile disposable plastic syringe. In addition, the solution should be withdrawn from the vial using the vial adapter.
- A dose of BeneFIX may be administered over a period of several minutes. The rate of administration, however, should be adapted to the comfort level of each individual patient.

1. Attach the syringe to the luer end of the infusion set tubing provided.

2. Apply a tourniquet and prepare the injections site by wiping the skin well with an alcohol swab provided in the kit.



3. Perform venipuncture. Insert the needle on the infusion set tubing into the vein, and remove the tourniquet. 3. The reconstituted BeneFIX product should be injected intravenously over several minutes. The rate of administration should be determined by the patient's comfort level.



Reconstituted BeneFIX should not be administered in the same tubing or container with other medicinal products.

Agglutination of red blood cells in the tubing/syringe has been reported with the administration of BeneFIX. No adverse events have been reported in association with this observation. To minimize the possibility of agglutination, it is important to limit the amount of blood entering the tubing. Blood should not enter the syringe. If red blood cell agglutination is observed in the tubing or syringe, discard all material (tubing, syringe and BeneFIX solution) and resume administration with a new package.

Following completion of BeneFIX treatment, remove the infusion set and discard. Dispose of all unused solution, empty vial(s), and used needles and syringes in an appropriate container for throwing away waste that might hurt others if not handled properly.

The safety and efficacy of administration by continuous infusion have not been established [see Warnings and Precautions (5)].

3 DOSAGE FORMS AND STRENGTHS

BeneFIX is supplied as a white lyophilized powder in the following dosages:

- 250 IU
- 500 IU
- 1000 IU
- 2000 IU

4 CONTRAINDICATIONS

BeneFIX is contraindicated in patients who have manifested life-threatening, immediate hypersensitivity reactions, including anaphylaxis, to the product or its components, including hamster protein.

5 WARNINGS AND PRECAUTIONS

5.1 General

The clinical response to BeneFIX may vary. If bleeding is not controlled with the recommended dose, the plasma level of factor IX should be determined, and a sufficient dose of BeneFIX should be administered to achieve a satisfactory clinical response. If the patient's plasma factor IX level fails to increase as expected or if bleeding is not controlled after the expected dose, the presence of an inhibitor (neutralizing antibodies) should be suspected, and appropriate testing performed [*see Warnings and Precautions (5.6)*].

5.2 Anaphylaxis and Severe Hypersensitivity Reactions

Allergic type hypersensitivity reactions, including anaphylaxis, have been reported with BeneFIX and have manifested as pruritus, rash, urticaria, hives, facial swelling, dizziness, hypotension, nausea, chest discomfort, cough, dyspnea, wheezing, flushing, discomfort (generalized) and fatigue. Frequently, these events have occurred in close temporal association with the development of factor IX inhibitors. Advise patients to discontinue use of the product and contact their physician and/or seek immediate emergency care.

BeneFIX contains trace amounts of hamster (CHO) proteins. Patients treated with this product may develop hypersensitivity to these non-human mammalian proteins.

5.3 Thromboembolic Complications

The safety and efficacy of BeneFIX administration by continuous infusion have not been established [*see Dosage and Administration (2)*]. There have been post-marketing reports of thrombotic events in patients receiving continuous-infusion BeneFIX through a central venous catheter, including life-threatening superior vena cava (SVC) syndrome in critically ill neonates [*see Adverse Reactions (6)*].

5.4 Nephrotic Syndrome

Nephrotic syndrome has been reported following immune tolerance induction with factor IX products in hemophilia B patients with factor IX inhibitors and a history of allergic reactions to factor IX. The safety and efficacy of using BeneFIX for immune tolerance induction have not been established.

5.5 Neutralizing Antibodies (Immunogenicity)

Patients using BeneFIX should be monitored for the development of factor IX inhibitors by appropriate clinical observations and laboratory tests. Inhibitors have been reported following administration of BeneFIX [*see Clinical Pharmacology (12)*]. If expected plasma factor IX activity levels are not attained, or if bleeding is not controlled with an expected dose, an assay that measures factor IX inhibitor concentration should be performed.

Patients with factor IX inhibitors may be at an increased risk of anaphylaxis upon subsequent challenge with factor IX.² Patients experiencing allergic reactions should be evaluated for the

presence of an inhibitor. Patients should be observed closely for signs and symptoms of acute hypersensitivity reactions, particularly during the early phases of initial exposure to product. **Because of the potential for allergic reactions with factor IX concentrates, the initial (approximately 10 - 20) administrations of factor IX should be performed under medical supervision where proper medical care for allergic reactions could be provided.**

5.6 Monitoring Laboratory Tests

- Patients should be monitored for factor IX activity levels by the one-stage clotting assay to confirm that adequate factor IX levels have been achieved and maintained, when clinically indicated [*see Dosage and Administration (2)*].
- Patients should be monitored for the development of inhibitors if expected factor IX activity plasma levels are not attained, or if bleeding is not controlled with the recommended dose of BeneFIX. Assays used to determine if factor IX inhibitor is present should be titrated in Bethesda Units (BUs).

6 ADVERSE REACTIONS

The most serious adverse reactions are systemic hypersensitivity reactions, including bronchospastic reactions and/or hypotension and anaphylaxis and the development of high-titer inhibitors necessitating alternative treatments to factor IX replacement therapy.

The most common adverse reactions observed in clinical trials (frequency > 5% of PTPs or PUPs) were headaches, dizziness, nausea, injections site reaction, injection site pain and skin-related hypersensitivity reactions (e.g., rash, hives).

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

During uncontrolled open-label clinical studies with BeneFIX, Coagulation Factor IX (Recombinant), conducted in previously treated patients (PTPs), 113 adverse reactions with known or unknown relation to BeneFIX therapy were reported among 38.5% (25 of 65) of subjects (with some subjects reporting more than one event) who received a total of 7,573 infusions. These adverse reactions are summarized in Table 5.

Table 5: Adverse Reactions Reported for PTPs*

Body System	Adverse Reaction	Number of patients (%)
Blood and lymphatic system disorders	Factor IX inhibition ¹	1 (1.5%)
Eye disorders	Blurred vision	1 (1.5%)
Gastrointestinal disorders	Nausea	4 (6.2%)
	Vomiting	1 (1.5%)
General disorders and administration site conditions	Injection site reaction	5 (7.7%)
	injection site pain	4 (6.2%)
	Fever	2 (3.1%)
Infections and infestations	Cellulitis at IV site	1 (1.5%)
	Phlebitis at IV site	1 (1.5%)

Table 5: Adverse Reactions Reported for PTPs*

Body System	Adverse Reaction	Number of patients (%)
Nervous system disorders	Headache	7 (10.8%)
	Dizziness	5 (7.7%)
	Taste perversion (altered taste)	3 (4.6%)
	Shaking	1 (1.5%)
	Drowsiness	1 (1.5%)
Renal and urinary disorders	Renal infarct ²	1 (1.5%)
Respiratory, thoracic and mediastinal disorders	Dry cough	1 (1.5%)
	Hypoxia	1 (1.5%)
	Chest tightness	1 (1.5%)
Skin and subcutaneous disorders	Rash	4 (6.2%)
	Hives	2 (3.1%)
Vascular disorders	Flushing	2 (3.1%)

*Adverse reactions reported within 72 hours of an infusion of BeneFIX.

¹ Low-titer transient inhibitor formation.

² The renal infarct developed in a hepatitis C antibody-positive patient 12 days after a dose of BeneFIX for a bleeding episode. The relationship of the infarct to the prior administration of BeneFIX is uncertain.

In the 63 previously untreated patients (PUPs), who received a total of 5,538 infusions, 10 adverse reactions were reported among 9.5% of the patients (6 out of 63) having known or unknown relationship to BeneFIX. These events are summarized in Table 6.

Table 6: Adverse Reactions Reported for PUPs*

Body System	Adverse Reaction	Number of Patients (%)
Blood and lymphatic system disorders	Factor IX inhibition ¹	2 (3.2%)
General disorders and administration site conditions	Injection site reaction	1 (1.6%)
	Chills	1 (1.6%)
Respiratory, thoracic and mediastinal disorders	Dyspnea (respiratory distress)	2 (3.2%)
	Hives	3 (4.8%)
Skin and subcutaneous disorders	Rash	1 (1.6%)

*Adverse reactions reported within 72 hours of an infusion of BeneFIX.

¹ Two subjects developed high-titer inhibitor formation during treatment with BeneFIX.

For adverse reactions thought to be related to the administration of BeneFIX, the rate of infusion should be decreased or the infusion stopped.

Immunogenicity

In clinical studies with 65 PTPs (defined as having more than 50 exposure days), a low-titer inhibitor was observed in one patient. The inhibitor was transient, the patient continued on

study and had normal factor IX recovery pharmacokinetics at study completion (approximately 15 months after inhibitor detection).

In clinical studies with pediatric PUPs, inhibitor development was observed in 2 out of 63 patients (3.2%), both were high-titer (> 5 BU) inhibitors detected after 7 and 15 exposure days, respectively. Both patients were withdrawn from the study.

6.2 Post-marketing Experience

The following post-marketing adverse reactions have been reported for BeneFIX: inadequate factor IX recovery, inadequate therapeutic response, inhibitor development [*see Clinical Pharmacology (12)*], anaphylaxis [*see Warnings and Precautions (5.2)*], angioedema, dyspnea, hypotension, and thrombosis.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The safety and efficacy of BeneFIX administration by continuous infusion have not been established [*see Warnings and Precautions (5.3)*]. There have been post-marketing reports of thrombotic events, including life-threatening SVC syndrome in critically ill neonates, while receiving continuous-infusion BeneFIX through a central venous catheter. Cases of peripheral thrombophlebitis and DVT have also been reported. In some, BeneFIX was administered via **continuous infusion, which is not an approved method of administration** [*see Dosage and Administration (2)*].

7 DRUG INTERACTIONS

None known.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproduction and lactation studies have not been conducted with BeneFIX, Coagulation Factor IX (Recombinant). It is not known whether BeneFIX can affect reproductive capacity or cause fetal harm when given to pregnant women. BeneFIX should be administered to pregnant and lactating women only if needed.

8.2 Labor and Delivery

There is no information available on the effect of factor IX replacement therapy on labor and delivery. Use only if needed.

8.3 Nursing Mothers

It is not known whether this drug is excreted into human milk. Because many drugs are excreted into human milk, caution should be exercised if BeneFIX is administered to nursing mothers.

Use only if needed.

8.4 Pediatric Use

Safety, efficacy, and pharmacokinetics of BeneFIX have been evaluated in previously treated (PTP) and previously untreated pediatric patients (PUP) [*see Dosage and Administration (2), Clinical Pharmacology (12), Clinical Studies (14) and Adverse Reactions (6)*]. On average, lower recovery has been observed in pediatric patients (<15 years). A dose adjustment may be needed [*see Dosage and Administration (2) and Clinical Pharmacology (12)*].

8.5 Geriatric Use

Clinical studies of BeneFIX did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Dose selection for an elderly patient should be individualized [*see Dosage and Administration (2)*].

10 OVERDOSAGE

No symptoms of overdose have been reported.

11 DESCRIPTION

BeneFIX, Coagulation Factor IX (Recombinant), is a purified protein produced by recombinant DNA. It has a primary amino acid sequence that is identical to the Ala¹⁴⁸ allelic form of plasma-derived factor IX, and has structural and functional characteristics similar to those of endogenous factor IX. BeneFIX is produced by a genetically engineered Chinese hamster ovary (CHO) cell line that is extensively characterized. No human or animal proteins are added during the purification and formulation processes of BeneFIX.

BeneFIX is not derived from human blood and contains no preservatives, and the manufacture of BeneFIX includes no added animal or human components. The stored cell banks are free of human blood or plasma products. The CHO cell line secretes recombinant factor IX into a defined cell culture medium that does not contain any proteins derived from animal or human sources, and the recombinant factor IX is purified by a chromatography purification process that does not require a monoclonal antibody step. The process also includes a membrane nanofiltration step that has the ability to retain molecules with apparent molecular weights >70,000 Da (such as large proteins and viral particles). BeneFIX is a single component by SDS-polyacrylamide gel electrophoresis evaluation. The potency (in International Units, IU) is determined using an *in vitro* one-stage clotting assay against the World Health Organization (WHO) International Standard for Factor IX concentrate. One International Unit is the amount of factor IX activity present in 1 mL of pooled, normal human plasma. The specific activity of BeneFIX is greater than or equal to 200 IU per milligram of protein.

BeneFIX is formulated as a sterile, nonpyrogenic, lyophilized powder preparation. BeneFIX is intended for intravenous (IV) injection. It is available in single-use vials containing the labeled amount of factor IX activity, expressed in IU. Each vial contains nominally 250, 500, 1000 or 2000 IU of Coagulation Factor IX (Recombinant). After reconstitution of the lyophilized drug product, the concentrations of excipients are 0.234% sodium chloride, 8 mM L-histidine, 0.8% sucrose, 208 mM glycine, 0.004% polysorbate 80. All dosage strengths yield a clear, colorless solution upon reconstitution.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

BeneFIX temporarily replaces the missing clotting factor IX that is needed for effective hemostasis.

12.2 Pharmacodynamics

The activated partial thromboplastin time (aPTT) is prolonged in people with hemophilia B. Treatment with factor IX concentrate may normalize the aPTT by temporarily replacing the factor IX. The administration of BeneFIX, Coagulation Factor IX (Recombinant), increases plasma levels of factor IX, and can temporarily correct the coagulation defect in these patients.

12.3 Pharmacokinetics

After single intravenous (IV) doses of 50 IU/kg of previously marketed BeneFIX, Coagulation Factor IX (Recombinant) [reconstituted with Sterile Water for Injection], in 37 previously treated adult patients (>15 years), each given as a 10-minute infusion, the mean increase from pre-infusion level in circulating factor IX activity was 0.8 ± 0.2 IU/dL per IU/kg infused (range 0.4 to 1.4 IU/dL per IU/kg) and the mean biologic half-life was 18.8 ± 5.4 hours (range 11 to 36 hours). In the original randomized, cross-over pharmacokinetic study in previously treated patients (PTPs), the *in vivo* recovery using previously marketed BeneFIX was statistically significantly less (28% lower, $p < 0.05$) than the recovery using a highly purified plasma-derived factor IX product (pdFIX). A summary of pharmacokinetic data for BeneFIX and pdFIX are presented in Table 7.

Table 7: Pharmacokinetic Parameter Estimates for BeneFIX and pdFIX in Previously Treated Patients with Hemophilia B

Parameter	BeneFIX, n = 11 Mean \pm SD	pdFIX, n = 11 Mean \pm SD
AUC _∞ (IU·hr/dL)	548 \pm 92	928 \pm 191
t _{1/2} (hr)	18.1 \pm 5.1	17.7 \pm 5.3
CL (mL/hr/kg)	8.62 \pm 1.7	6.00 \pm 1.4
K-value (IU/dL per IU/kg)	0.84 \pm 0.30	1.17 \pm 0.26
<i>In vivo</i> Recovery (%)	37.8 \pm 14.0	52.6 \pm 12.4

Abbreviations: AUC_∞ = area under the plasma concentration-time curve from time zero to infinity; K-value = incremental recovery; t_{1/2} = plasma elimination half-life; CL = clearance; SD = standard deviation.

There was no significant difference in biological half-life. Structural differences of the BeneFIX molecule compared with pdFIX were shown to contribute to the lower recovery. In subsequent evaluations for up to 24 months, the pharmacokinetic parameters were similar to the initial results.

In a subsequent randomized, cross-over pharmacokinetic study, BeneFIX reconstituted in 0.234% sodium chloride diluent was shown to be pharmacokinetically equivalent to the previously marketed BeneFIX (reconstituted with Sterile Water for Injection) in 24 previously treated patients (≥ 12 years) at a dose of 75 IU/kg. In addition, pharmacokinetic parameters

were followed up in 23 previously treated patients after repeated administration of BeneFIX for six months and found to be unchanged compared with those obtained at the initial evaluation. A summary of pharmacokinetic data are presented in Table 8:

Table 8: Pharmacokinetic Parameter Estimates for BeneFIX at Baseline (Cross-over phase) and Month 6 (Follow-up phase) in Previously Treated Patients with Hemophilia B

Parameter	Parameters at Initial Visit (Cross-over phase), n = 24	Parameters at Month 6 (Follow-up phase), n = 23
	Mean \pm SD	Mean \pm SD
C _{max} (IU/dL)	54.5 \pm 15.0	57.3 \pm 13.2
AUC _∞ (IU·hr/dL)	940 \pm 237	923 \pm 205
t _{1/2} (hr)	22.4 \pm 5.3	23.8 \pm 6.5
CL (mL/hr/kg)	8.47 \pm 2.12	8.54 \pm 2.04
K-value (IU/dL per IU/kg)	0.73 \pm 0.20	0.76 \pm 0.18
<i>In vivo</i> Recovery (%)	34.5 \pm 9.3	36.8 \pm 8.7

Abbreviations: AUC_∞ = area under the plasma concentration-time curve from time zero to infinity; AUC_t = area under the plasma concentration-time curve from zero to the last measurable concentration; C_{max} = peak concentration; K-value = incremental recovery; t_{1/2} = plasma elimination half-life; CL = clearance; SD = standard deviation.

Pediatric Patients (≤15 years)

Nineteen (19) previously treated pediatric patients (range 4 to ≤15 years) underwent pharmacokinetic evaluations for up to 24 months. Fifty-eight previously untreated patients [PUPs] less than 15 years of age at baseline underwent at least one recovery assessment within 30 minutes post-infusion in the presence or absence of hemorrhage during the study. A total of 202 recovery assessments collected during the 60-month period from these 58 PUPs are combined with 19 recovery assessments from PTPs and were summarized by age group in Table 9. There was one recovery assessment in a neonate, which had a value of 0.46 IU/dL per IU/kg. The overall mean recovery and FIX elimination half-life values were 0.7 \pm 0.3 IU/dL per IU/kg and 20.2 \pm 4.0 hours, respectively.

Table 9: Summary of BeneFIX Pharmacokinetic Parameters in Pediatric Patients

Age Group	n	K-value (IU/dL per IU/kg)	t _{1/2} (h)
Infants (≥1 month to <2 years)	33	0.7 \pm 0.4 (0.2, 2.1)	ND
Children (≥2 years to <12 years)	61	0.7 \pm 0.2 (0.2, 1.5)	19.8 \pm 4.0 (14, 27) ^a
Adolescents (≥12 years to ≤15 years)	9	0.8 \pm 0.3 (0.4, 1.4)	21.1 \pm 4.5 (15, 28) ^b

^a n = 13

^b n = 6

Data presented are mean \pm standard deviation (min, max).

Abbreviations: ND = not determined; K-value = incremental recovery; t_{1/2} = terminal phase elimination half-life.

Note: The columns are not mutually exclusive; individual patients may be listed under more than 1 age category.

Data from 57 PUP subjects who underwent repeat recovery testing for up to 60 months demonstrated that the average incremental FIX recovery was consistent over time, as shown in Figure 1.

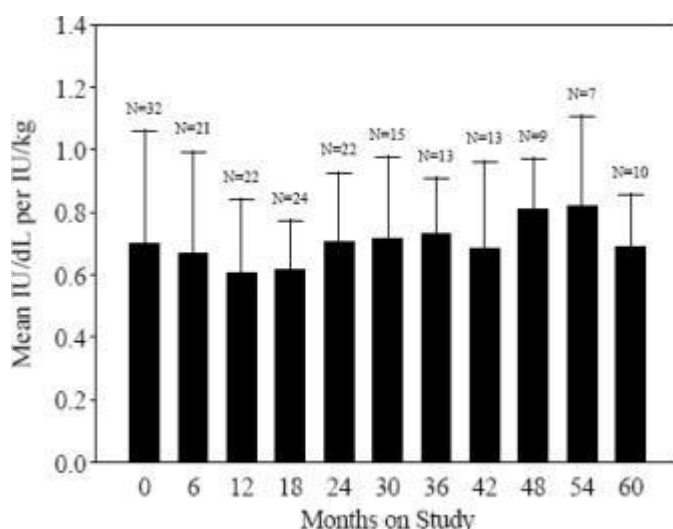


Figure 1. Average Incremental rFIX Recovery over Time

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

BeneFIX, Coagulation Factor IX (Recombinant), has been shown to be nonmutagenic in the Ames assay and non-clastogenic in a chromosomal aberrations assay. No investigations on carcinogenesis or impairment of fertility have been conducted.

14 CLINICAL STUDIES

Efficacy of BeneFIX has been evaluated in clinical studies in which a total of 128 subjects received BeneFIX either for the treatment of bleeding episodes on an on-demand basis, for the prevention of bleeds (prophylaxis) or for management of hemostasis in the surgical setting (surgical prophylaxis).

Fifty-six PTPs and sixty-three PUPs were treated for bleeding episodes on an on-demand basis or for the prevention of bleeds (see Tables 9 and 10). The PTPs were followed over a median interval of 24 months (mean 23.4 ± 5.3 months) and for a median of 83.5. The PUPs were followed over a median interval of 37 months (mean 38.1 ± 16.4 months) and for a median of 89 exposure days.

Fifty-five PTPs and fifty-four PUPs received BeneFIX for the treatment of bleeding episodes (see Table 10). Bleeding episodes that were managed successfully included hemarthrosis and bleeding in soft tissue and muscle. Data concerning the severity of bleeding episodes were not reported. In the PTPs, 88% of total infusions administered for on-demand treatment were rated as an “excellent” or “good” response.

Table 10: Efficacy of BeneFIX for on-demand treatment of PTPs and PUPs

	Median dose: IU/kg (range)	Rate of bleeds resolved with 1 infusion	Response to 1 st Infusion Rating ^c		
			Excellent/Good	Moderate	No Response
PTPs N=55 ^a	42.8 (6.5 - 224.6)	81 %	90.9%	7.1%	0.7%
PUPs N=54 ^b	62.7 (8.2 - 292)	75 %	94.1%	2.9%	1.0%

^a One subject discontinued the study after one month of treatment due to bleeding episodes that were difficult to control; he did not have a detectable inhibitor.

^b Three subjects were not successfully treated including one episode in a subject due to delayed time to infusion and insufficient dosing and in 2 subjects due to inhibitor formation.

^c Response ratings not provided for 1.3% and 2% of 1st infusions for PTPs and PUPs, respectively.

A total of 20 PTPs were treated with BeneFIX for secondary prophylaxis (the regular administration of FIX replacement therapy to prevent bleeding in patients who may have already demonstrated clinical evidence of hemophilic arthropathy or joint disease) at some regular interval during the study with a mean of 2.0 infusions per week (see Table 11). Thirty-two PUPs were administered BeneFIX for routine (primary and secondary) prophylaxis (see Table 11). Twenty-four PUPs were administered BeneFIX at least twice weekly, and eight PUPs were administered BeneFIX once weekly. Seven PTPs experienced a total of 26 spontaneous bleeding episodes within 48 hours after an infusion. Six spontaneous bleeds within 48 hours after an infusion were reported in 5 PUPs. Prophylaxis therapy was rated as “excellent” or “effective” in 93% of PTPs receiving prophylaxis one to two times per week.

Table 11: Efficacy of Prophylaxis of BeneFIX in PTPs and PUPs

Total exposure (infusions)		Duration of prophylaxis (months) (mean ± SD)	Dose IU/kg (mean ± SD)	Spontaneous bleeds within 48 hrs of infusion	Response rating ^a		
					Excellent	Effective	Inadequate
PTPs							
20	2985	18.2 ± 8.4 ^b	40.3 ± 15.2 ^b	28	56.0%	37.1%	4.3%
PUPs							
32	3158	14.4 ± 8.1	73.3 ± 33.1	6	91.3%	6.4%	1.7%

^a Response ratings provided at approximately 3-month intervals. In total, 116 and 172 assessments reported for PTPs and PUPs, respectively. Response ratings not provided for 2.6% and 0.6% of intervals for PTPs and PUPs, respectively.

^b N = 19

Management of hemostasis was evaluated in the surgical setting in both PTPs and PUPs (see Table 12). Thirty-six surgical procedures have been performed in 28 PTPs with 23 major

surgical procedures performed (including 6 complicated dental extractions). Thirty surgical procedures have been performed in 23 PUPs. Twenty-eight of these procedures were considered minor. Hemostasis was maintained throughout the surgical period; however, one PTP subject required evacuation of a surgical wound-site hematoma, and another PTP subject who received BeneFIX after a tooth extraction required further surgical intervention due to oozing at the extraction site. There was no clinical evidence of thrombotic complications in any of the subjects.

Among the PTP surgery subjects, the median increase in circulating factor IX activity was 0.7 IU/dL per IU/kg infused (range 0.3 – 1.2 IU/dL; mean 0.8 ± 0.2 IU/dL per IU/kg). The median elimination half-life for the PTP surgery subjects was 19.4 hours (range 10 – 37 hours; mean 21.3 ± 8.1 hours).

Table 12: Efficacy of BeneFIX for Surgical Procedures in PTPs and PUPs

Surgery Type	Number of Procedures (Number of Subjects)	Response		
		Excellent/Good	Moderate	No Response
Previously Treated Patients				
Ankle surgery	2 (2)	2 (100%)	-	-
Hip prosthesis implant (right)	1 (1)	1 (100%)	-	-
Knee arthroplasty (2 bilateral, 1 right)	3 (3)	3 (100%)	-	-
Knee arthroscopic synovectomy	2 (2) ^a	1 (50%)	-	-
Liver transplantation (orthotopic)	1 (1)	1 (100%)	-	-
Splenectomy	1 (1)	1 (100%)	-	-
External fixation device removal (wrist)	1 (1)	1 (100%)	-	-
Hernia repair	3 (2)	3 (100%)	-	-
Subacromial decompression (left)	1 (1)	1 (100%)	-	-
Calf debridement, dental extraction ^b	1 (1)	1 (100%)	-	-
Lymph node removal, dental extraction ^b	1 (1)	1 (100%)	-	-
Left heel cord lengthening	1 (1)	1 (100%)	-	-
Dental procedures ^c	12 (11)	11 (92%)	1 (8%)	-
Minor procedures	6 (6)	6 (100%)	-	-
Previously Untreated Patients				
Hernia repair	2 (2)	2 (100%)	-	-
Minor procedures	28 (21) ^a	27 (96%)	-	-

^a Response assessment not provided for 1 procedure.

^b Includes pulse and continuous-infusion regimens; CI counted as 1 procedure in this summary.

^c Includes complicated extractions (6), clearance, and fillings.

Nine of the major surgical procedures were performed in 8 PUPs using a continuous-infusion regimen. Five of the surgical procedures were performed in PUPs using a continuous-infusion regimen over 3 to 5 days. Although circulating factor IX levels targeted to restore and maintain hemostasis were achieved with both pulse replacement and continuous infusion regimens, clinical trial experience with continuous infusion of BeneFIX for surgical prophylaxis in hemophilia B has been too limited to establish the safety and clinical efficacy of administration of the product by continuous infusion.

All subjects participating in the PTP, PUP and surgery studies were monitored for clinical evidence of thrombosis [see *Warnings and Precautions* (5)]. No thrombotic complications were reported in PUPs or surgery subjects. One PTP subject experienced a renal infarct 12 days after a dose of BeneFIX for a bleeding episode; the relationship of the infarct to the prior administration of BeneFIX is uncertain. Laboratory studies of thrombogenicity (fibrinopeptide A and prothrombin fragment 1 + 2) were obtained in 41 PTPs and 7 surgery subjects prior to infusion and up to 24 hours following infusion. The results of these studies were inconclusive. Out of 29 PTP subjects noted to have elevated fibrinopeptide A levels post-infusion of BeneFIX, 22 also had elevated levels at baseline. Surgery subjects showed no evidence of significant increase in coagulation activation.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

BeneFIX, Coagulation Factor IX (Recombinant), is supplied in kits that include single-use vials which contain nominally 250, 500, 1000, or 2000 IU per vial with sterile pre-filled diluent syringe, vial adapter reconstitution device, sterile infusion set, and two (2) alcohol swabs, one bandage, and one gauze pad. Actual factor IX activity in IU is stated on the label of each vial.

16.2 Storage and Handling

Product kit as packaged for sale: BeneFIX, Coagulation Factor IX (Recombinant), can be stored at room temperature or under refrigeration, at a temperature of 2 to 30°C (36 to 86°F). Do not use BeneFIX after the expiration date, on the label.

Do not freeze to prevent damage to the diluent syringe.

Product after reconstitution: The product does not contain a preservative and should be used within 3 hours.

17 PATIENT COUNSELING INFORMATION

Advise patients to report any adverse reactions or problems following BeneFIX administration to their physician or healthcare provider.

- Allergic-type hypersensitivity reactions are possible. Inform patients of the early signs of hypersensitivity reactions [including hives (rash with itching), generalized urticaria, tightness of the chest, wheezing, hypotension] and anaphylaxis. Advise patients to discontinue use of the product and contact their physicians if these symptoms occur.
- Advise patients to contact their physician or treatment facility for further treatment and/or assessment if they experience a lack of a clinical response to factor IX replacement therapy, as in some cases this may be a manifestation of an inhibitor.

18 MANUFACTURER

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The format of this leaflet has been defined by the Ministry of Health; its content has been checked and approved- December 2010.