PRODUCT MONOGRAPH

BeneFIX®

Coagulation Factor IX (Recombinant)

INN= Nonacog alfa

BeneFIX® Coagulation Factor IX (Recombinant), is prepared in four lyophilized powder dosage forms nominally containing 250, 500, 1000 and 2000 IU per vial. The reconstituted product contains approximately: 50, 100, 200 and 400 IU/mL, respectively.

World Health Organization (WHO) International Standard for Factor IX Concentrate

Antihemorrhagic Blood Coagulation Factor IX

Date of Approval:
March 21, 1997
Date of Revision:
April 5, 2007

Control#: 105598 **Date of Approval: April 13, 2007**

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BeneFIX®

Coagulation Factor IX (Recombinant)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous injection	Lyophilized powder nominally containing 250, 500, , 1000 and 2000 IU per vial. The reconstituted product contains approximately: 50, 100, 200 and 400 IU/mL, respectively.	Glycine Sucrose L-Histidine Polysorbate 80

DESCRIPTION

BeneFIX® is formulated as a sterile, nonpyrogenic, lyophilized powder preparation. It is a clear, colorless solution after reconstitution.

INDICATIONS AND CLINICAL USE

BeneFIX® Coagulation Factor IX (Recombinant), is indicated for the control and prevention of hemorrhagic episodes in patients with hemophilia B (congenital factor IX deficiency or Christmas disease), including control and prevention of bleeding in surgical settings.

BeneFIX® is not indicated for the treatment of other factor deficiencies (e.g., factors II, VII and X), nor for the treatment of hemophilia A patients with inhibitors to factor VIII, nor for the reversal of coumarin-induced anticoagulation, nor for the treatment of bleeding due to low levels of liver-dependent coagulation factors.

CONTRAINDICATIONS

Because BeneFIX® Coagulation Factor IX (Recombinant), is produced in a Chinese Hamster ovary cell line, it may be contraindicated in patients with a known history of hypersensitivity to hamster protein.

WARNINGS AND PRECAUTIONS

General

Allergic-type hypersensitivity reactions, including anaphylaxis, have been reported for all factor IX products. Frequently, these events have occurred in close temporal association with the development of factor IX inhibitors. Patients should be informed of the early symptoms and signs of hypersensitivity reactions including hives, generalized urticaria, chills (rigors), flushing, angioedema, chest tightness, dyspnea, wheezing, faintness, hypotension, tachycardia, and anaphylaxis. If allergic or anaphylactic reactions occur, administration of BeneFIX® should be stopped immediately, and appropriate medical management should be given, which may include treatment for shock. Patients should be advised to discontinue use of the product and contact their physician and/or seek immediate emergency care, depending on the type/severity of the reaction, if any of these symptoms occur.

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 has not been established.

Since the use of factor IX complex concentrates has historically been associated with the development of thromboembolic complications, the use of factor IX-containing products may be potentially hazardous in patients with signs of fibrinolysis and in patients with disseminated intravascular coagulation (DIC).

Historically, the administration of factor IX complex concentrates derived from human plasma, containing factors II, VII, IX and X, has been associated with the development of thromboembolic complications. Although BeneFIX®, Coagulaton Factor IX (Recombinant), contains no Coagulation factor other than factor IX, the potential risk of thrombosis and DIC observed with other products containing factor IX should be recognized. Because of the potential risk of thromboembolic complications, caution should be exercised when administering this product to patients with liver disease, to patients post-operatively, to neonates, or to patients at risk of thromboembolic phenomena or DIC. In each of these situations, the benefit of treatment with BeneFIX® should be weighed against the risk of these complications.

Twelve days after a dose of BeneFIX® for a bleeding episode, one hepatitis C antibody positive

patient developed a renal infarct. The relationship of the infarct to prior administration of BeneFIX® is uncertain but was judged to be unlikely by the investigator. The patient continued to be treated with BeneFIX®.

Dosing of BeneFIX® may differ from that of plasma-derived factor IX products.

Carcinogenesis and Mutagenesis
BeneFIX® has been shown to be nonmutagenic in the Ames assay and nonclastogenic in a chromosomal aberrations assay. No investigations on carcinogenesis or impairment of fertility have been conducted.

Cardiovascular
Historically, the administration of factor IX complex concentrates derived from human plasma, containing factors II, VII, IX and X, has been associated with the development of thromboembolic complications. Although BeneFIX®, Coagulaton Factor IX (Recombinant), contains no Coagulation factor other than factor IX, the potential risk of thrombosis and DIC observed with other products containing factor IX should be recognized. Because of the potential risk of thromboembolic complications, caution should be exercised when administering this product to patients with liver disease, to patients post-operatively, to neonates, or to patients at risk of thromboembolic phenomena or DIC. In each of these situations, the benefit of treatment with BeneFIX® should be weighed against the risk of these complications.

Hematologic
See CARDIOVASCULAR.

Hepatic/Biliary/Pancreas
See CARDIOVASCULAR.

Immune
Activity-neutralizing antibodies (inhibitors) have been detected in patients receiving factor IX-containing products. As with all factor IX products, patients using BeneFIX® should be monitored for the development of factor IX inhibitors. 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 inhibitor. Preliminary information suggests a relationship may exist between the presence of major deletion mutations in a patient's factor IX gene and an increased risk of inhibitor formation and of acute hypersensitivity reactions. Patients known to have major deletion mutations of the factor IX gene should be observed closely for signs and symptoms of acute hypersensitivity reactions, particularly during the early phases of initial exposure to product. In view 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.

Peri-Operative Considerations
See CARDIOVASCULAR.

Renal
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 has not been established.

Twelve days after a dose of BeneFIX® for a bleeding episode, one hepatitis C antibody positive patient developed a renal infarct. The relationship of the infarct to prior administration of BeneFIX® is uncertain but was judged to be unlikely by the investigator. The patient continued to be treated with BeneFIX®.

Respiratory
Patients should be informed of the early symptoms and signs of hypersensitivity reactions including hives, generalized urticaria, chills (rigors), flushing, angioedema, chest tightness, dyspnea, wheezing, faintness, hypotension, tachycardia, and anaphylaxis. Patients should be advised to discontinue use of the product and contact their physician and/or seek immediate emergency care, depending on the type/severity of the reaction, if any of these symptoms occur.

Sensitivity/Resistance
See GENERAL.

Sexual Function/Reproduction
See SPECIAL POPULATIONS.

Skin
See SENSITIVITY/RESISTANCE.

Special Populations

Pregnant and Nursing Women: 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 clearly indicated.

Pediatrics: Data from BeneFIX® safety, efficacy, and pharmacokinetic studies have been evaluated in previously treated and previously untreated pediatric patients.

Nineteen (19) previously treated pediatric patients (range 4 to < 15 years) underwent pharmacokinetic evaluations for up to 24 months. The mean increase in circulating factor IX activity was 0.7 ± 0.2 IU/dL per IU/kg infused (range 0.3 to 1.1 IU/dL per IU/kg). The mean biological half-life was 20.2 ± 4.0 hours (range 14 to 28 hours).

Fifty-eight previously untreated patients [PUPs] less than 15 years of age at baseline [3 neonates (0-<1 month), 45 infants (≥1 month-<2 years), 9 children (≥2 years-<12 years) and 1 adolescent >12 years)] underwent at least one recovery assessment within 30 minutes post-infusion in the presence or absence of hemorrhage during the study. The mean increase in circulating FIX activity was 0.7 ± 0.3 IU/dL per IU/kg infused (range 0.2 to 2.1 IU/dL per IU/kg). In addition, there was no difference in the recoveries noted when data were evaluated by age group for infants (0.7 ± 0.4 IU/dL per IU/kg; range 0.2 to 2.1 IU/dL per IU/kg) and children (0.7 ±0.2 IU/dL per IU/kg; range 0.2 to 1.5 IU/dL per IU/kg). The recoveries in these age groups were consistent with the recovery for the PUP study as a whole. There was insufficient sample size in the neonate and adolescent age groups to perform an analysis in these groups. Data from 57 patients who underwent repeat recovery testing for up to 60 months demonstrated that the average incremental FIX recovery was consistent over time. Additional safety and efficacy studies are ongoing in previously treated, minimally treated, and previously untreated pediatric patients

Geriatrics: Clinical studies of BeneFIX® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. As with any patient receiving BeneFIX®, dose selection for an elderly patient should be individualized.

Monitoring and Laboratory Tests

Temporary correction of partial thromboplastin time (PTT) was observed. No effect on normal prothrombin time was seen. No significant increase in fibrinopeptide A or prothrombin fragment 1+2 was observed.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

As with the intravenous administration of any protein product, the following reactions may be observed after administration: headache, fever, chills, flushing, nausea, vomiting, lethargy, or manifestations of allergic reactions. Should evidence of an acute hypersensitivity reaction be

observed, the infusion should be stopped promptly and appropriate counter measures and supportive therapy should be administered.

Clinical Trial Adverse Drug Reactions

During uncontrolled open-label clinical studies with BeneFIX®, Coagulation Factor IX (Recombinant), conducted in previously treated patients (PTPs), 131 adverse reactions with definite, probable, possible or unknown relation to BeneFIX® therapy were reported among 27 of 65 patients (with some patients reporting more than one event) who received a total of 7573 infusions. These adverse reactions are summarized in Table 1 below.

Table 1: Adverse Events Reported for PTPs*

Reaction	Total number of events with definite, probable, possible or unknown relation to therapy (n=129)	Number and (%) of patients from which the reports originated (n=65)	Number and (%) of infusions temporally associated with the reaction[1] (n=7573)
Nausea	27	4 (6.2)	27 (0.36)
Taste perversion (Altered taste)	14	3 (4.6)	19 (0.25)
Hypoxia (Urge to cough with hypoxemia)	11	1 (1.5)	11 (0.15)
Injection site reaction	11	5 (7.7)	12 (0.16)
Injection site pain	10	4 (6.2)	16 (0.21)
Headache	10	7 (10.8)	13 (0.17)
Dizziness	7	5 (7.7)	8 (0.11)
Allergic rhinitis	7	3 (4.6)	9 (0.12)
Pain (Burning sensation in the jaw and skull)	6	1 (1.5)	7 (0.09)
Rash	6	5 (7.7)	7 (0.09)
Hives	3	2 (3.1)	3 (0.04)
Flushing	3	2 (3.1)	4 (0.05)
Fever	2	2 (3.1)	2 (0.03)
Shaking	2	2 (3.1)	1 (0.01)
Factor IX inhibitor[2]	1	1 (1.5)	2 (0.03)
Chest tightness	1	1 (1.5)	4 (0.05)
Drowsiness	1	1 (1.5)	1 (0.01)
Visual disturbance	1	1 (1.5)	1 (0.01)
Cellulitis at the IV site	1	1 (1.5)	7 (0.09)
Phlebitis at the IV site	1	1 (1.5)	7 (0.09)
Dry cough	1	1 (1.5)	0 (0.00)
Allergic reaction	1	1 (1.5)	1 (0.01)
Diarrhea	1	1 (1.5)	1 (0.01)
Lung disorder	1	1 (1.5)	1 (0.01)
Vomiting	1	1 (1.5)	1 (0.01)
Renal infarct[3]	1	1 (1.5)	1 (0.01)

Total	131	27/65 (41.5)	148/7573 (2.2)

* More than one event in the table could have been assoc. with an infusion; however, the total represents the actual number of infusions given.
1 Reaction occurring within 72 hours after infusion.
2 Low titer transient inhibitor formation
3 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. (See PRECAUTIONS, General).

One subject discontinued BeneFIX® due to pulmonary allergic-type symptoms.

In the 63 treated PUPS, who received a total of 5538 infusions, 22 adverse reactions were reported as having definite, probable, possible or unknown relationship to BeneFIX®. These events are summarized in Table 2 below.

Table 2: Adverse Events reported for PUPs*

Reaction	Total number of events with definite, probable, possible or unknown relation to therapy (n=22)	Number and (%) of patients from which the reports originated (n=63)	Number and (%) of infusions temporally associated with the reaction[1] (n=5538)
Diarrhea	5	1 (1.6)	11 (0.20)
Urticaria (hives)	3	3 (4.8)	3 (0.05)
Factor IX inhibitor[2]	2	2 (3.2)	4 (0.07)
Dyspnea (Respiratory distress)	2	2 (3.2)	2 (0.04)
Increased alkaline phosphatase	1	1 (1.6)	3 (0.05)
Elevated ALT	1	1 (1.6)	0 (0.00)
Rash (Body rash)	1	1 (1.6)	1 (0.02)
Elevated AST	1	1 (1.6)	0 (0.00)
Chills (Rigors)	1	1 (1.6)	3 (0.05)
Photosensitivity reaction	1	1 (1.6)	0 (0.00)
Injection site reaction	1	1 (1.6)	2 (0.04)
HAV seroconversion[3]	1	1 (1.6)	2 (0.04)
Parvovirus B19 seroconversion[4]	1	1 (1.6)	1 (0.02)
Asthma	1	1 (1.6)	1 (0.02)
Total	22	11/63 (17.5)	27/5538 (0.60)

* More than one event in the table could have been assoc. with an infusion; however, the total represents the actual number of infusions given.
1 Reaction occurring within 72 hours after infusion.
2 Two subjects developed high titer inhibitor formation during treatment with BeneFIX®.

3 Relationship of HAV seroconversion to BeneFIX® is unknown. HAV seroconversion was noted on 2 occasions in a single patient but was negative at final visit. The patient had no laboratory or clinical findings associated with active infection.

4 Relationship of Parvovirus B19 seroconversion to BeneFIX® is unknown. It was unlikely that seroconversion was related to BeneFIX® due to the frequency of community acquired infection and viral safeguards built into the manufacturing process.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

In the section below the following frequency categories and terms are used:

Uncommon:	≥ 0.1% and < 1%
Rare:	≥ 0.01% and < 0.1%
Very Rare:	< 0.01%

Body as a whole

Rare	**Hypersensitivity/allergic reactions**
Rare	**Anaphylaxis**

Nervous system disorders

Uncommon	**Dizziness, headache**

Cardiac disorders

Rare	**Hypotension, tachycardia**

Vascular disorders

Rare	**Phlebitis at the injection site**

Respiratory, thoracic and mediastinal disorders

Rare	**Respiratory distress**
Very Rare	**Dry cough**

Gastrointestinal disorders

Uncommon	**Nausea**
Rare	**Vomiting**

Skin

Rare	**Angioedema, cellulitis at the injection site, hives, rash**

Special senses

Uncommon	**Altered taste**

General disorder and administration site conditions

Uncommon	**Injection site reaction**
Rare	**Fever**

Abnormal Hematologic and Clinical Chemistry Findings

Temporary correction of partial thromboplastin time (PTT) was observed. No effect on normal prothrombin time was seen. No significant increase in fibrinopeptide A or prothrombin fragment 1+2 was observed.

Post-Market Adverse Drug Reactions

The following post-marketing adverse reactions have been reported for BeneFIX®, as well as for plasma-derived factor IX products: inadequate factor IX recovery, inadequate therapeutic response, inhibitor development, anaphylaxis, laryngeal edema, angioedema, cyanosis, dyspnea, hypotension, and thrombosis.

DRUG INTERACTIONS

Overview

No interactions of recombinant coagulation factor IX products with other medicinal products are known.

Drug-Laboratory Interactions

No interactions of recombinant coagulation factor IX products with laboratory methods are known.

DOSAGE AND ADMINISTRATION

Dosage

Treatment should be initiated under the supervision of a physician experienced in the treatment of hemophilia B.

Treatment with all factor IX products, including BeneFIX®, requires individualized dosage adjustment. The 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. Dosing of BeneFIX® may differ from that of plasma-derived factor IX products.

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

In an eleven patient, crossover, randomized PK evaluation of BeneFIX® and a single lot of high-

purity plasma-derived factor IX, the recovery was lower for BeneFIX®. In the clinical efficacy studies, patients were initially administered the same dose previously used for plasma-derived factor IX. Even in the absence of factor IX inhibitor, approximately half of the patients increased their dose in these studies. Titrate the initial dose upward if necessary to achieve the desired clinical response. As with some plasma-derived factor IX products, patients at the low end of the observed factor IX recovery may require upward dosage adjustment to as much as two times (2X) the initial empirically calculated dose in order to achieve the intended rise in circulating factor IX activity.

Method of Calculating Dose
The method of calculating the factor IX dose is shown in the following equation:

Number of factor IX IU required (IU)	=	**Body weight (kg)**	×	**Desired factor IX increase (% or IU/dL)**	×	**Reciprocal of observed recovery (IU/kg per IU/dL)**

In the presence of an inhibitor, higher doses may be required.

Adult Patients

In adult PTPs, on average, one international unit of BeneFIX® per kilogram of body weight increased the circulating activity of factor IX by 0.8 ± 0.2 (range 0.4 to 1.4) IU/dL. The method of dose estimation is illustrated in the following example. If you use 0.8 IU/dL average increase of factor IX per IU/kg body weight administered, then:

Number of factor IX IU required (IU)	=	**Body weight (kg)**	×	**Desired factor IX increase (% or IU/dL)**	×	**1.2 (IU/kg per IU/dL)**

Pediatric Patients (< 15 years)

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 (range 0.2 to 2.1) IU/dL. The method of dose estimation is illustrated in the following example. If you use 0.7 IU/dL average increase of factor IX per IU/kg body weight administered, then:

Number of factor IX IU required (IU)	=	**Body weight (kg)**	×	**Desired factor IX increase (% or IU/dL)**	×	**1.4 (IU/kg per IU/dL)**

Dosing for Bleeding Episodes and Surgery

The following chart[3] may be used to guide dosing in bleeding episodes and surgery:

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 Eberst[3]

Administration (Intravenous Injection)

BeneFIX® is administered by intravenous (IV) infusion after reconstitution with 0.234% sodium chloride solution.

BeneFIX® should be administered using the infusion set 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.

Detailed instructions for preparation and administration are contained in Part III: Consumer Information.

Reconstitute lyophilized BeneFIX® powder for injection with the supplied diluent (0.234% sodium chloride solution) from the pre-filled syringe provided. Gently rotate the vial until all powder is dissolved.

After reconstitution, the solution is drawn back into the syringe. The solution should be clear and colorless. The solution should be discarded if visible particulate matter or discoloration is observed.

Note: 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.

After reconstitution, BeneFIX® should be injected intravenously over several minutes. The rate of administration should be determined by the patient's comfort level.

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 in DOSAGE AND ADMINISTRATION be followed closely.

Dispose of all unused solution, empty vials, and used needles and syringes in an appropriate container for throwing away waste that might hurt others if not handled properly.

The administration of BeneFIX® by continuous infusion has not been sufficiently evaluated in clinical trials to justify its use in this manner. BeneFIX® should only be reconstituted with the diluent provided. BeneFIX® should not be mixed with 5% dextrose or other parenteral infusion solutions.

OVERDOSAGE

No symptoms of overdose are known.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

BeneFIX® contains recombinant coagulation factor IX, (nonacog alfa). Recombinant coagulation factor IX is a single chain glycoprotein with an approximate molecular mass of 55,000 Daltons that is a member of the serine protease family of vitamin K-dependent coagulation factors. Recombinant coagulation factor IX is a recombinant DNA-based protein therapeutic, which has structural and functional characteristics comparable to endogenous factor IX. Factor IX is activated by factor VII/tissue factor complex in the extrinsic pathway as well as factor XIa in the intrinsic coagulation pathway. Activated factor IX, in combination with activated factor VIII, activates factor X. This results ultimately in the conversion of prothrombin to thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed. Factor IX activity is absent or greatly reduced in patients with hemophilia B and substitution therapy may be required.

Hemophilia B is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor IX and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma levels of factor IX are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

Pharmacodynamics

Factor IX is activated by factor VII/tissue factor complex in the extrinsic coagulation pathway as well as by factor XIa in the intrinsic coagulation pathway. Activated factor IX, in combination with activated factor VIII, activates factor X. This results ultimately in the conversion of prothrombin to thrombin. Thrombin then converts fibrinogen to fibrin, and a clot can be formed.

Factor IX is the specific clotting factor deficient in patients with hemophilia B and in patients with acquired factor IX deficiencies. The administration of BeneFIX® Coagulation Factor IX (Recombinant), increases plasma levels of factor IX and can temporarily correct the coagulation defect in these patients.

Pharmacokinetics

After single intravenous (IV) doses of 50 IU/kg of BeneFIX®, Coagulation Factor IX (Recombinant), 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 subsequent evaluations for up to 24 months, the pharmacokinetic parameters were similar to the initial results.

In the randomized, cross-over pharmacokinetic study in previously treated patients (PTPs), the *in vivo* recovery using BeneFIX® was statistically significantly less (28% lower) than the recovery using a highly purified plasma-derived factor IX product. There was no significant difference in biological half-life. Structural differences of the rFIX molecule compared with pdFIX were shown to contribute to the lower recovery.

For specific information regarding pediatric pharmacology, see WARNINGS & PRECAUTIONS, SPECIAL POPULATIONS.

Special Populations and Conditions

Pediatrics: See WARNINGS & PRECAUTIONS, SPECIAL POPULATIONS.

Geriatrics: See WARNINGS & PRECAUTIONS, SPECIAL POPULATIONS.

Hepatic Insufficiency: See WARNINGS & PRECAUTIONS, HEPATIC/BILIARY/PANCREAS.

Renal Insufficiency: See WARNINGS & PRECAUTIONS, HEPATIC/BILIARY/PANCREAS.

STORAGE AND STABILITY

Product as packaged for sale: BeneFIX®, Coagulation Factor IX (Recombinant), should be stored under refrigeration at a temperature of 2 to 8ºC (36 to 46ºF). Prior to the expiration date, BeneFIX® may also be stored at room temperature not to exceed 25ºC (77ºF) for up to 6 months. The patient should make note of the date the product was placed at room temperature in the space provided on the outer carton. Freezing should be avoided to prevent damage to the diluent syringe.

Do not use BeneFIX® after the expiry date on the label.

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

SPECIAL HANDLING INSTRUCTIONS

Reconstituted Solutions

Detailed instructions for preparation and administration are contained in Part III: Consumer Information. Patients should follow the specific reconstitution and administration procedures provided by their physicians.

Always wash your hands before performing the following procedures. Aseptic technique should be used during the reconstitution procedure.

BeneFIX®, Coagulation Factor IX (Recombinant), will be administered by intravenous (IV) infusion after reconstitution with 0.234% sodium chloride solution(diluent).

BeneFIX® should be administered within 3 hours after reconstitution. The reconstituted solution may be stored at room temperature prior to administration.

Parenteral Products (for reconstitution before use)

Vial Size	Volume of Diluent to be Added to Vial	Nominal Concentration per mL
250 IU	5 mL	50 IU
500 IU	5 mL	100 IU
1000 IU	5 mL	200 IU
2000 IU	5 mL	400 IU

Reconstitute with 0.234% sodium chloride solution (USP)

DOSAGE FORMS, COMPOSITION AND PACKAGING

BeneFIX® Coagulation Factor IX (Recombinant), is supplied in single use vials which contain nominally 250, 500, 1000 and 2000 IU per vial, one pre-filled syringe of solvent (5 ml sterile 0.234% sodium chloride solution for injection for reconstitution) with one plunger rod, one sterile vial adapter reconstitution device, one sterile infusion set, and two (2) alcohol swabs, one plaster and one gauze pad. Actual factor IX activity in IU is stated on the label of each vial. Prior to use, the 250-, 500-, 1000 and 2000IU per vial dosage forms are reconstituted in 5-mL of 0.234% sodium chloride solution. The reconstituted product contains approximately: 50, 100, 200 and 400 IU/mL Factor IX, respectively.

After reconstitution of the lyophilized drug product, the concentrations of the excipients are 0.234% sodium chloride, 8m M L-histidine, 0.8% sucrose, 208 mM glycine and 0.004% polysorbate 80.

The container closure system for BeneFIX® consists of a 10mL USP Type I glass vial, a 20-mm-grey rubber stopper, and a 20 mm-diameter flip-off crimp seal.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

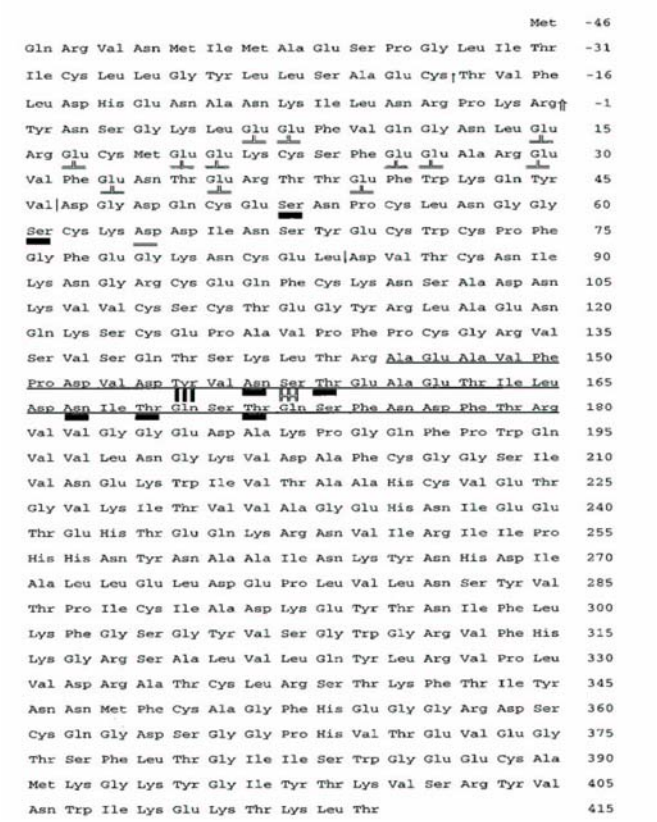
Drug Substance

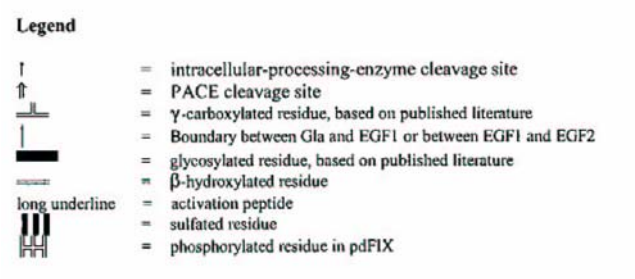
Proper name: Coagulation Factor IX (Recombinant)

Chemical name: Coagulation Factor IX (Recombinant)

Molecular formula and molecular mass: The molecular formula for BeneFIX®, assuming 11 disulfide bonds, 12 Gla residues, and no other posttranslational modifications, is $C_{2053}H_{3114}N_{558}O_{665}S_{25}$. Coagulation Factor IX (Recombinant) is a glycoprotein with an approximate molecular mass of 55,000 Da consisting of 415 amino acids in a single chain.

Structural formula:





Physicochemical properties: Coagulation Factor IX (Recombinant) drug substance is a solution containing rFIX, Glycine, Histidine, Sucrose and Polysorbate 80. The solution is clear and colorless and essentially free of plainly visible particulate matter.

In lyophilized form, rFIX drug product is present as a white cake containing rFIX and excipients (Glycine, Histidine, Sucrose, and Polysorbate 80); it is essentially free from plainly visible particulate matter. After reconstitution, rFIX drug product is a clear, colorless solution that is essentially free from plainly visible particulate matter.

Product Characteristics

Coagulation Factor IX (Recombinant) is a glycoprotein with an approximate molecular mass of 55,000 Da consisting of 415 amino acids in a single chain. It has a primary amino acid sequence that is identical to the Ala^{148} allelic form of plasma-derived factor IX, and has structural and functional characteristics comparable to those of endogenous factor IX.

BeneFIX® Coagulation Factor IX (Recombinant), is produced by a genetically engineered Chinese hamster ovary (CHO) cell line that is extensively characterized and shown to be free of infectious agents. The stored cell banks are free of 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 and yields a high-purity, active product. A membrane filtration step that has the ability to retain molecules with apparent molecular weights >70,000 Da (such as large proteins and viral particles) is included for additional viral safety. BeneFIX® is predominantly 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 not derived from human blood and contains no preservatives or added animal or human components.

BeneFIX® is inherently free from the risk of transmission of human blood-borne pathogens such as HIV, hepatitis viruses, and parvovirus.

CLINICAL TRIALS

In 4 clinical studies of BeneFIX® Coagulation Factor IX (Recombinant), a total of 128 patients (56 previously treated patients [PTPs], 9 patients participating only in the surgical study, and 63 previously untreated patients [PUPs]), received more than 28 million IU administered over a period of up to 64 months. The studies included 121 HIV-negative and 7 HIV-positive patients.

Fifty-six PTPs received approximately 20.9 million IU of BeneFIX® in two clinical studies. The median number of exposure days was 83.5. These PTPs who were treated for bleeding episodes on an on-demand basis or for the prevention of bleeds were followed over a median interval of 24 months (range 1 to 29 months; mean 23.4 ± 5.3 months). Fifty-five of these PTPs received a median of 42.8 IU/kg (range 6.5 to 224.6 IU/kg; mean 46.6 ± 23.5 IU/kg) per infusion for bleeding episodes. All patients were evaluable for efficacy. One patient discontinued the study after one month of treatment due to bleeding episodes that were difficult to control; he did not have a detectable inhibitor. The patient's dose had not been adequately titrated. The remaining 55 patients were treated successfully. Bleeding episodes that were managed successfully included hemarthroses and bleeding in soft tissue and muscle. Data concerning the severity of bleeding episodes were not reported. Eighty-eight percent of the total infusions administered for bleeding episodes were rated as providing an "excellent" or "good" response. Eighty-one percent of all bleeding episodes were managed with a single infusion of BeneFIX®. One patient developed a low titer, transient inhibitor (maximum titer 1.2 BU). This patient had previously received plasma-derived products without a history of inhibitor development. He was able to continue treatment with BeneFIX® with no anamnestic rise in inhibitor or anaphylaxis, however, increased frequency of BeneFIX® administration was required; subsequently the patient's factor IX inhibitor and its effect on the half-life of BeneFIX® resolved.

A total of 20 PTPs were treated with rFIX for secondary prophylaxis at some regular interval during the study. Nineteen patients were administered rFIX for routine secondary prophylaxis (at least twice weekly) for a total of 345 patient-months. The average dose used by these 19 patients was 40.3 IU/kg, ranging from 13 to 78 IU/kg. One additional patient was treated weekly, using an average dose of 33.3 IU/kg, over a period of 21 months. Ninety-three percent of the responses were rated as "excellent" or "effective". These 20 PTPs received a total of 2985 infusions of BeneFIX® for routine prophylaxis. Seven of these PTPs experienced a total of 26 spontaneous bleeding episodes within 48 hours after an infusion.

Management of hemostasis was evaluated in the surgical setting. Thirty-six surgical procedures have been performed in 28 patients. Thirteen (13) minor surgical procedures were performed in 12 patients, including 7 dental procedures, 1 punch biopsy of the skin, 1 cyst removal, 1 male sterilization, 1 nevus ablation, and 2 ingrown toenail removals. Twenty-three (23) major surgical

procedures were performed in 19 patients including a liver transplant, splenectomy, 3 inguinal hernia repairs, 11 orthopedic procedures, a calf-debridement and 6 complicated dental extractions.

Twenty-three (23) patients underwent 27 surgical procedures with a pulse-replacement regimen. The mean perioperative (preoperative and intraoperative) dose for these procedures was 85 ± 32.8 IU/kg (range 25-154.9 IU/kg). The mean total post-operative (inpatient and outpatient) dose was 63.1 ± 22.0 IU/kg (range 28.6-129.0).

Total BeneFIX® coverage during the surgical period for the major procedures ranged from 4230 to 385,800 IU**.** The pre-operative dose for the major procedures ranged from 75 to 155 IU/kg. Nine of the major surgical procedures were performed using a continuous infusion regimen. Following pre-operative bolus doses (94.1-144.5 IU/kg), continuous infusion of BeneFIX® was administered at a median rate of 6.7 IU/kg/hr (range of average rates: 4.3-8.6 IU/kg/hr; mean 6.4 ± 1.5 IU/kg/hr) for a median duration of 5 days (range 1-11 days; mean 4.9 ± 3.1). Circulatory factor IX levels targeted to restore and maintain hemostasis were achieved with both pulse replacement and continuous infusion regimens.

Among the surgery patients, 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 surgery subjects was 19.4 hours (range 10-37 hours; mean 21.3 ± 8.1 hours).

Hemostasis was maintained throughout the surgical period, however, one patient required evacuation of a surgical wound site hematoma and another patient 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 patients. In seven patients for whom fibrinopeptide A and prothrombin fragment 1 + 2 were measured pre-infusion, at 4 to 8 hours, and then daily up to 96 hours, there was no evidence of significant increase in coagulation activation. Data from two other patients were judged to be not evaluable.

Sixty-three PUPs received more than 6.2 million IU of BeneFIX® in an open-label safety and efficacy study over 89 median exposure days. These PUPs were followed over a median interval of 37 months (range 4 to 64 months; mean 38.1 ± 16.4 months). Fifty-four of these PUPs received a median dose of 62.7 IU/kg (range 8.2 to 292.0 IU/kg; mean 75.6 ± 42.5 IU/kg) per infusion for bleeding episodes. Fifty-one of these 54 patients were treated successfully. Bleeding episodes that were managed successfully included hemarthroses and bleeding in soft tissue and muscle. Data concerning the severity of bleeding episodes were not reported. Ninety-four percent of the infusions administered to initiate treatment of bleeding were rated as providing an "excellent" or "good" response. Seventy-five percent of all bleeding episodes were managed with a single infusion of BeneFIX®. Three of these 54 patients were not successfully treated; including one episode in a patient due to delayed time to infusion and insufficient dosing and in 2 patients due to inhibitor formation. One patient developed a high titer inhibitor (maximum titer 42 BU) on exposure day 7. A second patient developed a high titer inhibitor (maximum titer 18 BU) after 15

exposure days. Both patients experienced allergic manifestations in temporal association with their inhibitor development.

Thirty-two PUPs administered BeneFIX® for routine prophylaxis. Twenty-four PUPs administered rFIX at least twice weekly for a total of 2587 infusions. The mean dose per infusion was 72.5 ± 37.1 IU/kg, and the mean duration of prophylaxis was 13.4 ± 8.2 months. Eight PUPs administered rFIX once weekly for a total of 571 infusions. The mean dose per infusion was 75.9 ± 17.9 IU/kg, and the mean duration of prophylaxis was 17.6 ± 7.4 months. Ninety-eight percent of the responses were rated as "excellent" or "effective". Five PUPs experienced a total of 6 spontaneous bleeding episodes within 48 hours after an infusion.

Twenty-three PUPs received BeneFIX® for surgical prophylaxis in 30 surgical procedures. All surgical procedures were minor except 2 hernia repairs. The preoperative bolus dose ranged from 32.3 IU/kg to 247.2 IU/kg. The perioperative total dose ranged from 385 to 23280 IU. Five of the surgical procedures were performed using a continuous infusion regimen over 3 to 5 days. Surgical hemostasis with BeneFIX® was achieved and efficacy was excellent or good in all rated assessments.

There are ongoing safety and efficacy studies of BeneFIX® in previously treated, previously untreated, and minimally treated patients.

DETAILED PHARMACOLOGY

See ACTION AND CLINICAL PHARMACOLOGY.

MICROBIOLOGY

Not applicable.

TOXICOLOGY

Summary of Preclinical Toxicity Studies of BeneFIX® Coagulation Factor IX (Recombinant) [FIX]

Study	Test Article/System	Test Animal, Dose, Duration, and Site or Route	Results
Biological Test Center P0795002[a,e] *Seven Day Evaluation of Test Article 0715B01 Following a Single Intraperitoneal Injection in Mice*	rFIX (Lot 0715B01)/ in vivo	ICR mouse; vehicle control, 1, 2, 10, 20, 35, and 50 IU rFIX/mouse, n = 20/group, single dose IP injection, sacrifices on Days 2 and 8	One death at 50 IU/kg/day on Day 2. Dose-related and reversible decreases in platelet counts and increases in fibrinogen at ≥ 35 IU/mouse. Peri-ocular hemorrhage at ≥ 20 IU/mouse. Histologic lesions of thrombosis and hemorrhage at ≥ 20 IU/mouse. Treatment related thrombosis with consumptive coagulopathy at doses of ≥ 20 IU/mouse. In this study, no toxic-effect dose was 10 IU/mouse (500 IU/kg).

Summary of Preclinical Toxicity Studies of BeneFIX® Coagulation Factor IX (Recombinant) [FIX]			
Study	**Test Article/System**	**Test Animal, Dose, Duration, and Site or Route**	**Results**
Bio-Research Laboratories Ltd. Study 54823[b,f] *A Toxicity and Pharmacokinetic Study of Recombinant Human Factor IX Administered by Intraperitoneal Injection in the Albino Mouse for 1 to 7 Consecutive Days*	rFIX (Lot 0715C01)/ in vivo	CD-1 mouse; rFIX 100, 500, 1000, and 2500 IU/kg/day (Swiss Crl:CD^{R} -1 (ICR) mice), IP injection, n= 32/sex/group, sacrifices on Days 2 and 8	At doses of 500, 1000, and 2500 IU/kg/day there were treatment-related deaths, signs of deteriorating condition of surviving animals, various changes in clinical pathology and ophthalmological changes. Microscopic thrombosis at dosages of 500, 1000 and 2500 IU/kg/day was observed in heart, liver, lungs and lymph nodes. Lesions suspected to be secondary were hemorrhage as a result of consumptive coagulopathy, ischemic degeneration/necrosis in numerous organs and tissues, compensatory splenic and hepatic extramedullary hematopoiesis and increased erythropoiesis in the bone marrow. 100 IU/kg/day was the no-effect level after 1 to 7 days of dosing.
P96056-21 *Toxicokinetics of rFIX in Male CD-1 Mice After IP Injection* (Bio-Research Laboratories Ltd. Study 54823)	rFIX (Lot 0715C01)/ in vivo	CD-1 mice (vehicle n=3; 100, 500, 1000, 2500 IU/kg n=39), IP injection for 7 days	FIX concentrations in plasma were undetectable at 100 IU/kg. Day 1 $AUC_{0\rightarrow\infty}$ was 6786 (500 IU/kg), 23918 (1000 IU/kg), and 50256 ng x hr/mL (2500 IU/kg). Day 6 accumulation factors for the 500, 1000, and 2500 IU/kg doses indicate no excessive accumulation. rFIX $AUC_{0\rightarrow\infty}$ of 6786 ng x hr/mL was associated with serious toxicity in the mouse. The toxicologic effects in the mouse are likely to have minimal predictive value with respect to human risk assessment.
Biological Test Center P0296002[a,e] *Seven Day Evaluation of Test Article 0715E01 and 216001A Following a Single Intraperitoneal Injection in Mice*	rFIX (Lot 0715E01 and 216001A)/ in vivo	ICR male mice (n=20/lot/dose: doses of 50, 35, 20, 10, and 2 IU/mouse), single-dose IP injection, sacrifice on Day 8.	Five deaths occurred in the 200 mice dosed: 4 mice treated with Lot 0715E01 (2 at 35 IU/mouse and 2 at 10 IU/mouse) and 1 mouse treated with Lot 216001A at 50 IU/mouse. The most common clinical observation was hemorrhage in one or both of an animal's eyes (16/200 animals).
Bio-Research Laboratories Ltd. Study 54595[c,f] *A 4-Week Intravenous Bolus Injection Toxicity Study of Recombinant Human Factor IX in the Albino Rat Followed by a 4-Week Recovery Period*	rFIX (Lot 0725C02)/ in vivo	Sprague-Dawley rat, saline control (n=10), vehicle control (n=20), 50 IU/kg (n=10), 100 IU/kg (n=10), and 200 IU/kg (n=20) x 4 weeks, IV bolus	Moderate dose exaggeration (2-4x human dose) for 28 consecutive days with no observed toxicity. No-effect dose was 200 IU/kg in the rat. Minimal antibody response to rFIX with just 2 animals at high dose developing low titer and transient antibody responses.

Summary of Preclinical Toxicity Studies of BeneFIX® Coagulation Factor IX (Recombinant) [FIX]			
Study	**Test Article/System**	**Test Animal, Dose, Duration, and Site or Route**	**Results**
Bio-Research Laboratories Ltd. Study 53865[d,f] *A 14-Day Intravenous Bolus Injection Toxicity Study of Recombinant Human Factor IX in the Beagle Dog, Followed by a 14-Day Recovery Period*	rFIX (Reference Material RB2455-069)	Beagle dog, vehicle (n=10) or rFIX 50 (n=6), 100 (n=6), or 200 (n=10) IU/kg x 14 days, IV bolus-recovery 14 days in vehicle and 200 IU/kg dose groups (n = 2/sex).	No mortalities; no treatment-related effects on body weight, food consumption, ophthalmoscopy, cardiovascular parameters, hematology, clinical chemistry, urinalysis, organ weights, or gross or histopathologic examinations. Clinical signs (lying on cage floor, decreased physical activity, salivation, decreased muscle tone, pale gums, absence of toe pinch) were observed during Week 2 and correlated with the presence of anti-human FIX antibodies. The dosage of 200 IU/kg was considered to be the no-toxic-effect dose.

[a] Biological Test Center Study P0795002 was conducted in compliance with U.S. Good Laboratory Practice Regulations set forth in 21 CFR 58.

[b] Bio-Research Study 54823 was conducted in compliance with U.S. Good Laboratory Practice Regulations set forth in 21 CFR 58.

[c] Bio-Research Study 54595 was conducted in compliance with U.S. Good Laboratory Practice Regulations set forth in 21 CFR 58, Good Laboratory Practice Regulations of the Japan Ministry of Health and Welfare (Notification No. 313), Japanese Toxicity Guidelines (Notification No. 88), and OECD Principles of Good Laboratory Practices.

[d] Bio-Research Study 53865 was conducted in compliance with U.S. Good Laboratory Practice Regulations set forth in 21 CFR 58.

[e] Biological Test Center, 2525 McGaw Avenue, Post Office Box 19791, Irvine, CA 92713-9791 U.S.A.

[f] Bio-Research Laboratories Ltd., 87 Senneville Road, Senneville, Quebec, Canada H9X3R3.

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1. Lusher JM, Thrombogenicity associated with factor IX complex concentrates. *Semin. Hematol.* 1991; 28 (3 Suppl. 6) : 3-5.

2. Shapiro AD, Ragni MV, Lusher JM, et al. Safety and efficacy of monoclonal antibody purified factor IX concentrate in previously untreated patients with hemophilia B. *Thromb Haemost.* 1996;75(1):30-35.

3. Roberts HR, Eberst ME. Current management of hemophilia B. *Hematol Oncol Clin North Am.* 1993; 7(6):1269–1280.

PART III: CONSUMER INFORMATION

BeneFIX®
Coagulation Factor IX (Recombinant)

This leaflet is part III of a three-part "Product Monograph and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about BeneFIX®. Contact your doctor or hemophilia treatment centre if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- The control and treatment of bleeding and the prevention of bleeding in people with hemophilia B.
- BeneFIX® has been approved for use in hemophilia B for adults and children.
- Ask your doctor if you have any questions about why BeneFIX® has been prescribed for you.

What it does:

- Factor IX is a protein produced naturally in the body. It helps the blood form clots to stop bleeding.
- People with hemophilia B (Christmas disease) are deficient in coagulation factor IX.
- When the body does not make enough factor IX, and you become injured, your blood will not form clots as it should, and you may bleed into and damage your muscles and joints.
- Injections of factor IX are used to treat hemophilia B.
- BeneFIX® is created using recombinant technology that allows it to be made without human blood or plasma products, making it naturally free of blood borne pathogens.

When it should not be used:

- Do not use BeneFIX® for the treatment of other coagulation factor deficiencies (e.g., factors II, VII and X), for the treatment of hemophilia A, in patients with inhibitors to factor VIII, for the reversal of coumarin-induced anticoagulation, nor for the treatment of bleeding due to low levels of liver-dependent coagulation factors.
- Do not use BeneFIX® if you are allergic to hamster proteins or any of the nonmedicinal ingredients listed below.
- Do not use BeneFIX® after the expiry date (printed on the bottle). If you take this medicine after the expiry date has passed, it may not work well.
- Do not use BeneFIX® if the packaging is torn or shows signs of tampering.

If you are not sure whether you should use BeneFIX®, talk to your doctor.

What the medicinal ingredient is:

- Recombinant coagulation Factor IX (Nonacog alfa)

What the important nonmedicinal ingredients are:

- Glycine
- Sucrose
- Histidine
- Polysorbate 80
- Sodium chloride solution

What dosage forms it comes in:

BeneFIX® comes as a white powder in a glass vial, nominally containing 250, 500, 1000 and 2000 IU per vial. The actual amount of Factor IX is stated on the label of each bottle. BeneFIX® must be reconstituted (dissolved) with the diluent syringe and the product contains approximately: 50, 100, 200 and 400 IU/mL, respectively.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

STOP taking BeneFIX® and contact your doctor immediately if

- **You experience allergic reactions such as skin rash, itching, chest tightness, wheezing, dizziness, hives, faintness, rapid heartbeat, shortness of breath, and/or a swollen face. Severe allergic reactions to BeneFIX® and other Factor IX products have been reported.**

Contact your doctor immediately if

- **Your bleeding does not stop as expected**

BEFORE you use BeneFIX® talk to your doctor or hemophilia treatment centre if you:

- Are pregnant or planning to become pregnant
- Are breast feeding or planning to breast feed
- Are at risk of developing blood clots
- Have liver disease
- Have recently had surgery or are planning to have surgery, including dental surgery

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with BeneFIX® include:

- There are no known interactions of BeneFIX® with other medications.
- Tell your doctor or pharmacist if you are taking any other medicines, including any you buy without a prescription, including natural health products.

PROPER USE OF THIS MEDICATION

Usual dose:

- Your doctor will decide the dose of BeneFIX® you will receive.
- BeneFIX® is injected directly into the bloodstream.
- The dose, duration and frequency of infusion will depend on your individual needs for replacement factor IX and may be influenced by your age, weight, activity level and severity of bleed.
- Your doctor may periodically need to check laboratory blood test results following infusion to be sure that blood level of factor IX is high enough to allow satisfactory blood clotting.
- If you have been using plasma-derived factor IX, the dose of BeneFIX® may differ from the dose of plasma-derived factor IX.
- Do not lower the dose of BeneFIX® without checking with your doctor, unless you are having an allergic reaction.

Overdose:

- No symptoms of overdose are known.

Missed Dose:

- If you miss a dose of this medicine, check with your doctor as soon as possible for instructions.

- **Preparation and Administration:**

RECONSTITUTION

Always wash your hands before performing the following procedures. Aseptic technique (meaning clean and germ-free) should be used during the reconstitution procedure. All components used in the reconstitution and administration of this product should be used as soon as possible after opening their sterile containers to minimize unnecessary exposure to the atmosphere.

BeneFIX® is administered by intravenous (IV) infusion after reconstitution with the supplied diluent (0.234% sodium chloride diluent).

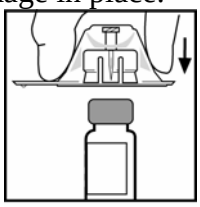
1. Allow the vial of lyophilized BeneFIX® and the pre-filled diluent syringe to reach room temperature.

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.

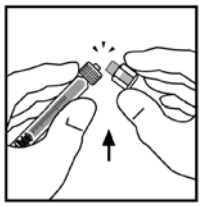
4. Peel back the cover from the clear plastic vial adapter package. **Do not remove the adapter from the package**.

5. Place the vial on a flat surface. While holding the adapter in the package, place the vial adapter over the vial. Press down firmly on the package until the adapter snaps into place on top of the vial, with the adapter spike penetrating the vial stopper. Leave the adapter package in place.



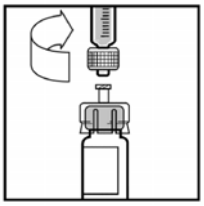
6. Grasp the plunger rod as shown in the diagram. Avoid contact with the shaft of the plunger rod. Attach the threaded end of the plunger rod to the diluent syringe plunger by pushing and turning firmly.

7. Remove the tamper-resistant, plastic-tip cap from the diluent syringe by bending the cap up and down to break the perforation. Do not touch the inside of the cap or the syringe tip. The cap may need to be replaced, so place the cap on its side on a clean surface in a spot where it would be least likely to become environmentally contaminated.

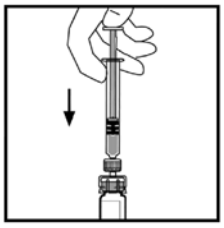


8. Lift the package away from the adapter and discard the package.

9. With the vial on a flat surface, connect the diluent syringe to the vial adapter by inserting the tip of the syringe into the adapter opening while firmly pushing and turning the syringe clockwise until the connection is secured.



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



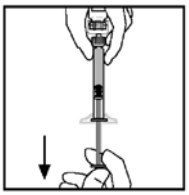
11. With the syringe still connected to the adapter, **gently** swirl the contents of the vial until the powder is dissolved.

12. Inspect the final solution for specks before administration. The solution should appear clear and colorless.

Note: If you use more than one vial of BeneFIX® per infusion, reconstitute each vial by following the previous instructions.

13. Ensuring that the syringe plunger rod is still fully depressed, invert the vial. Slowly draw the solution into the syringe.

    Note: If you prepared more than one vial of BeneFIX®, remove the diluent syringe from the vial adapter, leaving the vial adapter attached to the vial. Quickly attach a separate large luer lock syringe and draw back the reconstituted contents as instructed above. Repeat this procedure with each vial in turn. 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.



14. Detach the syringe from the vial adapter by gently pulling and turning the syringe counterclockwise. 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® should be administered within 3 hours after reconstitution. The reconstituted solution may be stored at room temperature prior to administration.

ADMINISTRATION (Intravenous Injection)

1. Attach the syringe to the luer end of the provided infusion set tubing and infuse BeneFIX® as instructed by your doctor or healthcare provider.

   Once you learn how to self infuse you can follow the instructions in this insert.

   After reconstitution, BeneFIX® should be injected intravenously over several minutes. Your comfort level should determine the rate of administration.

   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.

   Note: If red blood cell agglutination is observed in the tubing or syringe, discard all material (tubing, syringe and BeneFIX® solution) and continue administration with a new package.

2. After injecting BeneFIX®, remove the infusion set and discard. The amount of drug product left in the infusion set will not affect your treatment. Dispose of all unused solution, the empty vial(s), and the used needles and syringes in an appropriate container used for throwing away waste that might hurt others if not handled properly.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

- During your treatment with BeneFIX®, your blood will be checked for inhibitors to factor IX activity. Inhibitors are antibodies against Factor IX, which are made by your immune system. The inhibitors stop the factor IX from working as well as it used to.

Tell your doctor immediately if you are using increasing amounts of BeneFIX® in order to control a bleed.

- Injection of any medicine intravenously may have side effects. Often they are not serious but sometimes they can be. You may need medical treatment if you experience some of the side effects in the table below.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM	
Symptom / effect	**STOP taking BeneFIX® and call your doctor immediately**
The following side effects could mean you are having an allergic reaction. **These side effects are rare.**	
• A skin rash	✓
• Itching	✓
• Chest tightness	✓
• Wheezing	✓
• Dizziness	✓
• Hives	✓
• Faintness	✓
• Rapid heartbeat	✓
• Shortness of breath	✓
• A swollen face	✓

Tell your doctor if you notice any of the following side effects and they worry you:

- *Headache*
- *Runny or blocked nose*
- *Light-headedness*
- *Fever*
- *Chills*
- *Flushing*
- *Nausea*
- *Vomiting*
- *Diarrhea*
- *Feeling tired, drowsy or a lack of energy*
- *Discomfort or swelling at the injection site*
- *Altered taste*
- *Coughing*
- *Burning sensation in the jaw or skull*
- *Changes in your vision*

These are all mild side effects of BeneFIX® injection and will usually disappear on their own. Tell your doctor if you are concerned or if they continue.

***This is not a complete list of side effects. For any unexpected effects while taking BeneFIX®, contact your** doctor or hemophilia treatment centre.*

HOW TO STORE IT

Before preparation (BeneFIX® powder):

Keep BeneFIX® in the refrigerator (2°C to 8°C).

DO NOT freeze.

If stored at room temperature below 25°C, BeneFIX® must be used within 6 months. Write the date on the package when you first store BeneFIX® at room temperature.

Keep BeneFIX® (and needles) where young children cannot reach it.

BeneFIX® must be used by the expiry date on the label. Do not use BeneFIX® beyond the date (month and year) printed on the label after the word "Expires", even if it has been stored properly.

After preparation (BeneFIX® solution):

To avoid bacterial contamination of the solution, use the reconstituted BeneFIX® as soon as possible or within 3 hours.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs . If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

Toll-free telephone: 866-234-2345
Toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness
Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician** or hemophilia treatment centre**.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be requested by contacting the sponsor, Wyeth Canada:

Medical Information: 1-800-461-8844
After Hours Emergency: 1-800-361-1336

This leaflet was prepared by Wyeth Canada.

Last revised: 08/03/2006