BeneFix®
COAGULATION FACTOR IX (RECOMBINANT)

DESCRIPTION

BeneFix®, Coagulation Factor IX (Recombinant), is a purified protein produced by recombinant DNA technology for use in therapy of factor IX deficiency, known as hemophilia B or Christmas disease. 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 similar to those of endogenous factor IX.

BeneFix® 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 (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, I.U.) 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 I.U. 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.

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 international units (I.U.). Each vial contains nominally 250, 500, or 1000 I.U. of Coagulation Factor IX (Recombinant). After reconstitution of the lyophilized drug product, the concentrations of excipients in the 500 and 1000 I.U. dosage strengths are 10 mM L-histidine, 1% sucrose, 260 mM glycine, 0.005% polysorbate 80. The concentrations after reconstitution in the 250 I.U. dosage strength are half those of the other two dosage strengths. The 500 and 1000 I.U. dosage strengths are isotonic after reconstitution, and the 250 I.U. dosage strength has half the tonicity of the other two dosage strengths after reconstitution. All dosage strengths yield a clear, colorless solution upon reconstitution.

CLINICAL PHARMACOLOGY

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.

After single intravenous (IV) doses of 50 I.U./kg of BeneFix®, Coagulation Factor IX (Recombinant), in 36 patients, each given as a 10-minute infusion, the mean increase in circulating factor IX activity was 0.8 ± 0.2 I.U./dL per I.U./kg infused (ranged from 0.4 to 1.4 I.U./dL per I.U./kg) and the mean biologic half-life was 19.4 ± 5.4 hours (ranged from 11 to 36 hours). 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. In subsequent evaluations at 6 and 12 months, the pharmacokinetic parameters were similar to the initial results.

In clinical studies of BeneFix® involving a total of 64 patients (44 previously treated patients [PTPs], 11 previously untreated patients [PUPs], and the 9 patients participating only in the surgical study), more than 7 million I.U. were administered over a period of up to 18 months. This includes 57 HIV-negative and 7 HIV-positive patients. Forty-five patients were evaluated for efficacy, all of whom were treated successfully for bleeding episodes on an on-demand basis or for the prevention of bleeds. Bleeding episodes that were managed successfully included hemarthroses and bleeding in soft tissue and muscle.

Management of hemostasis was evaluated in the surgical setting. Thirteen surgical procedures have been performed in 12 patients, with a cumulative dose ranging from 10,000 to 348,000 I.U. The 10 major procedures were performed using a pulse replacement regimen (N=7) or a continuous infusion regimen (N=3), and included a liver transplantation, a hernia repair, six orthopedic surgeries, and two dental extractions. Circulatory factor IX levels targeted to restore and maintain hemostasis were achieved with both pulse replacement and continuous infusion regimens. 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 these patients. In four 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 additional patients were judged to be not evaluable.

A study of BeneFix® has been initiated in patients who had not been treated previously with plasma-derived factor IX concentrate (PUPs). In preliminary data, 11 of the 20 patients enrolled in the study received at least one infusion of BeneFix®. These 11 patients received a total of 27,208 I.U. in 42 infusions. Thirty to 50 patients will be enrolled and followed for up to 5 years to complete evaluation of BeneFix® in this patient population for safety, efficacy, and immunogenicity.

A low-level inhibitor developed in 1 of 44 BeneFix® patients who had previously received plasma-derived products. This patient had an extensive previous history of exposure to plasma-derived factor IX products, including a single subcutaneous exposure, without history of inhibitor development. Antibodies were detected in this patient after 9 months of treatment (39 exposure days) with BeneFix®. This patient was able to continue treatment with BeneFix® with no anamnestic rise in inhibitor or anaphylaxis.

INDICATIONS AND USAGE

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®, Coagulation Factor IX (Recombinant), 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

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, 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 (see **PRECAUTIONS**).

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).

PRECAUTIONS

General

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.[1] Although BeneFix® 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®.

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 (see **CLINICAL PHARMACOLOGY** and **WARNINGS**). 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.

Dosing of BeneFix® may differ from that of plasma-derived factor IX products (see **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

Information for Patients

Patients should be informed of the early symptoms and signs of hypersensitivity reactions including hives, generalized urticaria, 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. Patients experiencing allergic reactions should be evaluated for the presence of inhibitor.

Carcinogenesis, Mutagenesis, Impairment of Fertility

BeneFix®, Coagulation Factor IX (Recombinant), 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.

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 clearly indicated.

Pediatric Use

Safety and efficacy studies are ongoing in previously treated children and adolescents and in previously untreated children (see **CLINICAL PHARMACOLOGY, WARNINGS** and **PRECAUTIONS**).

ADVERSE REACTIONS

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.

During clinical studies with BeneFix®, Coagulation Factor IX (Recombinant), conducted in previously-treated patients (PTPs), 60 mild adverse reactions definitely, probably, or possibly related to therapy were reported for 2,548 infusions. These were nausea (16), discomfort at the IV site (13), altered taste (10), burning sensation in the jaw and skull (6), allergic rhinitis (3), light-headedness (2), headache (2), dizziness (1), chest tightness (1), fever (1), phlebitis/cellulitis at IV site (1), drowsiness (1), dry cough/sneeze (1), rash (1), and a single hive (1). 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®.

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 (see **CLINICAL PHARMACOLOGY**), anaphylaxis (see **WARNINGS**), laryngeal edema, angioedema, cyanosis, dyspnea, hypotension, thrombosis.

If any adverse reaction takes place that is thought to be related to the administration of BeneFix® the rate of infusion should be decreased or the infusion stopped.

DOSAGE AND ADMINISTRATION

Treatment with BeneFix®, Coagulation Factor IX (Recombinant), should be initiated under the supervision of a physician experienced in the treatment of hemophilia B.

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.

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® (see **CLINICAL PHARMACOLOGY**). 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.

BeneFix® is administered by IV infusion over several minutes after reconstitution of the lyophilized powder with Sterile Water for Injection (USP).

Method of Calculating Dose

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

number of factor IX I.U. required (I.U.)	=	body weight (kg)	x	desired factor IX increase (% or I.U./dL)	x	reciprocal of observed recovery (I.U./kg per I.U./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 (ranged from 0.3 to 1.4) I.U./dL. The method of dose estimation is illustrated in the following example. If you use 0.8 I.U./dL average increase of factor IX per I.U./kg body weight administered, then:

number of factor IX I.U. required (I.U.)	=	body weight (kg)	x	desired factor IX increase (% or I.U./dL)	x	1.2 (I.U./kg per I.U./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 ± 0.2 (ranged from 0.3 to 1.1) I.U./dL. The method of dose estimation is illustrated in the following example. If you use 0.7 I.U./dL average

increase of factor IX per I.U./kg body weight administered, then:

number of factor IX I.U. required (I.U.)	=	body weight (kg)	x	desired factor IX increase (% or I.U./dL)	x	1.4 (I.U./kg per I.U./dL)

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

Type of Hemorrhage	Circulating Factor IX Activity Required [% or (I.U./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]			

INSTRUCTIONS FOR USE

The procedures below are provided as general guidelines for the reconstitution and administration of BeneFix®. Patients should follow the specific reconstitution and administration procedures provided by their physicians.

Reconstitution

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 Sterile Water for Injection (diluent).

1. Allow the vials of lyophilized BeneFix® and diluent to reach room temperature.
2. Remove the plastic flip-top caps from the BeneFix® vial and the diluent vial to expose the central portions of the rubber stoppers.
3. Wipe the tops of both vials with the alcohol swab provided, or use another antiseptic solution, and allow to dry.
4. Remove the protective cover from the short end of the sterile double-ended needle and insert the short end into the diluent vial at the center of the stopper.
5. Remove the protective cover from the long end of the needle. Invert the solvent vial and, to minimize leakage, quickly insert the long end of the needle through the center of the stopper of the upright BeneFix® vial.

   Note: Point the double-ended needle toward the wall of the BeneFix® vial to prevent excessive foaming.

6. The vacuum will draw the diluent to into the BeneFix® vial.
7. Once the transfer is complete, remove the long end of the needle from the BeneFix® vial, and properly discard the needle with the diluent vial.

   Note: If the diluent does not transfer completely into the BeneFix® vial, DO NOT USE the contents of the vial. Note that it is acceptable for a small amount of fluid to remain in the diluent vial after transfer.
8. Gently rotate the vial to dissolve the powder.
9. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Reconstituted BeneFix® should appear clear and colorless.

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

Administration (Intravenous Injection)

BeneFix®, Coagulation Factor IX (Recombinant), should be administered using a single sterile disposable plastic syringe. In addition, the solution should be withdrawn from the vial using the sterile filter spike.

1. Using aseptic technique, attach the sterile filter spike to the sterile disposable syringe.

   Note: Do NOT inject air into the BeneFix® vial. This may cause partial loss of product.
2. Insert the filter spike end into the stopper of the BeneFix® vial.
3. Invert the vial and withdraw the reconstituted solution into the syringe.
4. Remove and discard the filter spike.

   Note: If you use more than one vial of BeneFix®, the contents of multiple vials may be drawn into the same syringe through a separate, unused filter spike.
5. Attach the syringe to the Luer end of the infusion set tubing and perform venipuncture as instructed by your physician.

   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 (see **ADVERSE REACTIONS**).

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.

Storage

Product as packaged for sale: BeneFix®, Coagulation Factor IX (Recombinant), should be stored under refrigeration at a temperature of 2 to 8°C (36 to 46°F). Prior to the expiration date, BeneFix®, may also be stored at room temperature not to exceed 25°C (77°F) 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 vial. 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.

How Supplied

BeneFix®, Coagulation Factor IX (Recombinant), is supplied in single use vials which contain nominally 250, 500, or 1000 I.U. per vial (NDC # 58394-003-01, 58394-002-01, and 58394-001-01, respectively) with sterile diluent, sterile double-ended needle for reconstitution, sterile filter spike for withdrawal, sterile infusion set, and two (2) alcohol swabs. Actual factor IX activity in I.U. is stated on the label of each vial.

REFERENCES

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.

Manufactured by:

Genetics Institute, Inc.
Cambridge MA 02140-2387, USA
US License Number 1163
Telephone: 1-800-934-5556

Imported and Distributed in Canada by:
WYETH-AYERST CANADA INC.
Montreal, Canada

KEY CODE
03477 Rev. 2/01