BeneFIX®
COAGULATION FACTOR IX
(RECOMBINANT)

Rx only

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 known 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, 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.

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 (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.

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. 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 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) 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 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 bioequivalent 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. The mean (± SD) incremental recovery (K-value) values were 0.73 ± 0.20 IU/dL per IU/kg for BeneFIX® and 0.68 ± 0.18 IU/dL per IU/kg for previously marketed BeneFIX®. The mean (± SD) area under the curve (AUC) values were 940 ± 237 and 880 ± 220 IU·h/dL for BeneFIX® and previously marketed BeneFIX®, respectively. The mean (± SD) half-life values were 22.4 ± 5.3 hours for BeneFIX® and 23.4 ± 5.2 hours for previously marketed BeneFIX®. The pharmacokinetic parameters were followed-up in 23 previously treated patients (≥12 years) after repeated administration of BeneFIX® for six months and found to be unchanged compared with those obtained at the initial evaluation. The K-values, determined by age, were on average 0.78 ± 0.19 IU/dL per IU/kg (range 0.39 to 1.2 IU/dL per IU/kg) for those >15 years old (n=16), and 0.66 ± 0.16 IU/dL per IU/kg (range 0.44 to 0.92 IU/dL per IU/kg) for those ≤15 years old (n=7).

For specific information regarding pediatric pharmacology, see **PRECAUTIONS, Pediatric Use**.

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

In 4 clinical studies of BeneFIX®, a total of 128 subjects 56 previously treated patients [PTPs], 9 subjects 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 subjects.

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 ± 5.34 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 subjects were evaluable for efficacy. 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. The subject's dose had not been adequately titrated. The remaining 55 subjects 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 subject developed a low titer, transient inhibitor (maximum titer 1.5 BU). This subject 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 subject's factor IX inhibitor and its effect on the half-life of BeneFIX® resolved.

Forty-one of the subjects had measurements of fibrinopeptide A and prothrombin fragment 1 + 2 prior to infusion, 4 to 8 hours and then 24 hours following the infusion. Twenty-nine of the subjects had elevations in fibrinopeptide A with a maximum value of 35.3 nmol/L (22 of the 29 subjects had elevated baseline values). Ten of the subjects had elevated prothrombin fragment 1 + 2 with a maximum value of 1.82 nmol/L (3 of the 10 subjects had elevated baseline values).

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. Nineteen subjects were administered BeneFIX® for routine secondary prophylaxis (at least twice weekly) for a total of 345 patient-months with a median follow-up period of 24 months per subject. The average dose used by these 19 subjects was 40.3 IU/kg, ranging from 13 to 78 IU/kg. One additional subject 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 subjects. Thirteen (13) minor surgical procedures were performed in 12 subjects, 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 subjects including a liver transplant, splenectomy, 3 inguinal hernia repairs, 11 orthopedic procedures, a calf-debridement and 6 complicated dental extractions.

Twenty-three (23) subjects 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 in 8 subjects 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). Six of the 8 subjects who had received continuous infusion of BeneFIX® in conjunction with major surgeries were switched over to intermittent pulse regimens at a median dose of 56.3 IU/kg (range 33.6-89.1 IU/kg; mean 57.8 ± 18.1 IU/kg SD) for a median of 3.5 exposure days (range 1-5 days, mean 3.3 ± 1.4 SD) during the post-operative period. 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. Subjects administered BeneFIX® by continuous infusion for surgical prophylaxis also received intermittent bolus infusions of the product.

Among the 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 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 subject required evacuation of a surgical wound site hematoma and another 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. In seven subjects 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 subjects were judged to be not evaluable.

Sixty-three PUPs received approximately 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. Data concerning the severity of bleeding episodes were not reported. Seventy-five percent of all bleeding episodes were managed with a single infusion of BeneFIX®. Three of these 54 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. One subject developed a high titer inhibitor (maximum titer 42 BU) on exposure day 7. A second subject developed a high titer inhibitor (maximum titer 18 BU) after 15 exposure days. Both subjects experienced allergic manifestations in temporal association with their inhibitor development.

Thirty-two PUPs administered BeneFIX® for routine prophylaxis. Twenty-four PUPs administered BeneFIX® 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 BeneFIX® 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. 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. 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.

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, VIII, 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

The safety and efficacy of BeneFIX® administration by continuous infusion have not been established (see **DOSAGE AND ADMINISTRATION** and **INSTRUCTIONS FOR USE, Administration**). 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, Post-marketing Experience** section).

Factor IX complex concentrates have historically been associated with the development of thromboembolic complications[1]. The use of factor IX-containing products, including BeneFIX®, may be potentially hazardous in patients at risk of thromboembolic phenomena, including patients with signs of fibrinolysis or disseminated intravascular coagulation (DIC), patients with liver disease or post-surgical patients.

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.

Allergic type hypersensitivity reactions, including anaphylaxis, have been reported with factor IX products including BeneFIX®. 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**).

PRECAUTIONS

General

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 non-clastogenic 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
Additional safety and efficacy studies are ongoing in previously treated, minimally treated, and previously untreated pediatric patients (see **CLINICAL PHARMACOLOGY**, **WARNINGS** and **DOSAGE AND ADMINISTRATION**).

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; median of 0.6 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; median of 0.6 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 subjects who underwent repeat recovery testing for up to 60 months demonstrated that the average incremental FIX recovery was consistent over time.

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. As with any patient receiving BeneFIX®, dose selection for an elderly patient should be individualized (see **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS
See also **CLINICAL PHARMACOLOGY: Clinical Studies**.

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 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 subjects (with some subjects 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 %)

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)
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.

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%)

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)
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 (see **DESCRIPTION**).

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.

Post-marketing Experience
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, 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**). 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 **INSTRUCTIONS FOR USE, Administration**).

DOSAGE AND ADMINISTRATION
The safety and efficacy of BeneFIX® administration by continuous infusion have not been established (see **WARNINGS**).

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 subject, 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, subjects 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 subjects 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, subjects 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 0.234% sodium chloride solution.

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)**	x	**Desired factor IX increase (% or IU/dL)**	x	**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 0.78 ± 0.19 (range 0.39 to 1.2) IU/dL. The

method of dose estimation is illustrated in the following example. If you use 0.78 IU/dL average increase of factor IX per IU/kg body weight administered, then:

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)**

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; median of 0.6 IU/dL per IU/kg). 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)**	**x**	**desired factor IX increase (% or IU/dL)**	**x**	**1.4 (IU/kg per IU/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 (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

Type of Hemorrhage	Circulating Factor IX Activity Required [% or (IU/dL)]	Dosing Interval [hours]	Duration of Therapy [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
Detailed instructions for preparation and administration are contained in the Patient Package Insert provided with BeneFIX®.

Reconstitute lyophilized BeneFIX® powder for injection with the supplied diluent (0.234% sodium chloride solution) from the pre-filled syringe provided. Once the diluent has been injected into the vial, 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.

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

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.

Administration (Intravenous Injection)
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.

> *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**). The safety and efficacy of administration by continuous infusion have not been established (see **WARNINGS** and **ADVERSE REACTIONS, Post-marketing Experience**).

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 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.

HOW SUPPLIED

BeneFIX®, Coagulation Factor IX (Recombinant), is supplied in single use vials which contain nominally 250, 500, 1000 or 2000 IU per vial (NDC # 58394-003-06, 58394-002-06, 58394-001-06, and 58394-008-02, respectively) 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.

United States Patent Numbers: 4,994,371; 5,171,569; 5,714,583; 6,372,716; 6,627,737.

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.

This product's label may have been updated. For current package insert and further product information, please visit www.wyeth.com or call our medical communications department toll-free at 1-800-934-5556.

Wyeth®

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INFORMATION FOR PATIENTS

BeneFIX®
(BEN-uh-fiks)
COAGULATION FACTOR IX
(RECOMBINANT)

Rx only

Please read this Patient Insert carefully before using BeneFIX®. This guide is a summary of the important information you need to know about your medicine. This Patient Insert does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about BeneFIX®?
The use of BeneFIX® has been associated with reports of blood clot complications in patients at risk of developing blood clots, including patients with indwelling venous catheters receiving BeneFIX® by continuous infusion. The safety and efficacy of administration of BeneFIX by continuous infusion have not been established. Continuous infusion is not an approved way to administer BeneFIX.

You should talk with your doctor before using BeneFIX® if you suffer from liver disease or have recently had surgery, as these factors may increase your risk of blood clotting complications.

BeneFIX® can cause serious allergic reactions. You should be aware of the early symptoms of an allergic reaction and in severe cases, anaphylaxis (severe allergic reaction). These include hives, swelling, chest tightness, difficulty breathing, wheezing, faintness, rapid heart rate and low blood pressure. If any of these symptoms occur, stop using BeneFIX® immediately and contact a doctor or seek emergency medical care. The initial administrations of BeneFIX® should be administered under proper medical supervision, where proper medical care for severe allergic reactions could be provided.

Your body may produce inhibitors against BeneFIX®. Inhibitors are antibodies produced by your immune system that can lead to a decreased response, or no response, to BeneFIX® therapy. Check with your doctor to make sure you are closely monitored with blood tests for the presence of inhibitors. Notify your doctor if you are unable to prevent or control episodes of bleeding with your normal dose of BeneFIX®.

What is BeneFIX®?
Coagulation Factor IX is a protein that is necessary for blood to clot. People who have the hereditary bleeding disease (Hemophilia B) lack this clotting factor, causing their blood to take longer to form a clot. BeneFIX® is a genetically engineered form of coagulation Factor IX. Administering BeneFIX® increases blood levels of Factor IX and helps prevent and control bleeding episodes in patients with Hemophilia B. BeneFIX® is produced by a genetically engineered Chinese hamster ovary (CHO) cell line. These cells produce the human coagulation Factor IX protein, which is purified and separated from the hamster cell components. BeneFIX® has the same clot-promoting effects as Factor IX protein made from human plasma. In the manufacturing process for BeneFIX®, no preservatives or materials of human or animal origin

are added. Because BeneFIX® is not derived from human blood, it is free from the risk of transmission of human blood-borne pathogens such as HIV, hepatitis viruses, and parvovirus.

Who should not receive BeneFIX®?
You should not receive BeneFIX® unless your doctor confirms you have Hemophilia B. BeneFIX® should not be used for the treatment of other clotting factor deficiencies such as Hemophilia A.

BeneFIX® is produced in hamster cells and may contain hamster proteins. Patients who have a history of allergic reactions to hamster proteins should not take BeneFIX®.

Pregnant women should use BeneFIX® only if clearly needed since it is not known whether it can harm your unborn child. It is also not known whether BeneFIX® affects a woman's ability to have children or whether BeneFIX® affects a nursing infant. If you are breastfeeding, pregnant, or considering becoming pregnant, you should talk to your doctor before using this product.

How should I administer BeneFIX®?
You should always follow the specific instructions given by your doctor. The steps listed below are general guidelines for using BeneFIX®. If you are unsure of the procedures, please call your doctor or pharmacist before using.

The dose of BeneFIX® you are receiving has been specially determined for you by your doctor depending on the degree of Factor IX deficiency, the location and extent of bleeding, and your age and state of health. Your doctor may occasionally need to take blood tests to make sure that the level of Factor IX in your blood is high enough to allow normal blood clotting. Contact your doctor immediately if bleeding is not controlled after using BeneFIX®.

It is important to always wash your hands before performing the following steps. Aseptic (clean and germ-free) techniques 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 supplied in a sterile powder form, and it is intended for intravenous (IV) injection. Before it can be administered by injection, the powder must be reconstituted by mixing the liquid diluent supplied (0.234% sodium chloride diluent) to make it an injectable liquid. BeneFIX® should be reconstituted and administered using the infusion set, diluent, syringe and adapter provided in this kit, and by following the directions below.

The safety and efficacy of administration of BeneFIX by continuous infusion have not been established.

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) in the pre-filled syringe.

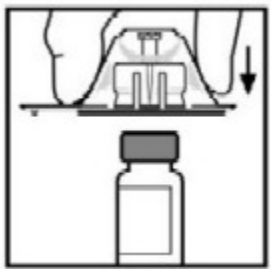
1. Allow the vial of lyophilized BeneFIX® and the pre-filled diluent syringe to reach room temperature.

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.

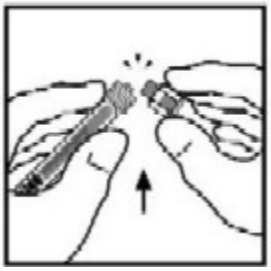
4. Peel back the cover from the clear plastic vial adapter package. **Do not remove the adapter from the package**.

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.

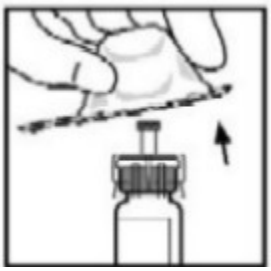


6. Grasp the plunger rod as shown in the diagram. Avoid contact with the shaft of the plunger rod. Attach the threaded end of the plunger rod to the diluent syringe plunger by pushing and turning firmly.

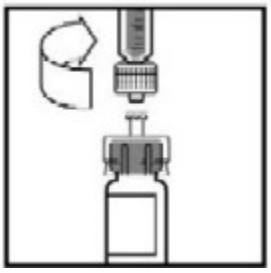
7. Remove the tamper-resistant, plastic-tip cap from the diluent syringe by bending the cap up and down to break the perforation. Do not touch the inside of the cap or the syringe tip. Place the cap on its side on a clean surface in a spot where it would be least likely to become environmentally contaminated.



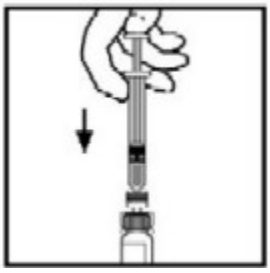
8. Lift the package away from the adapter and discard the package.



9. Place 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.



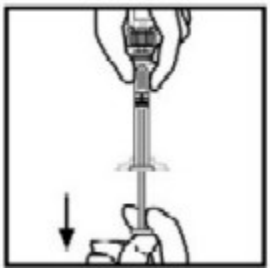
11. With the syringe still connected to the adapter, **gently** swirl the contents of the vial until the powder is dissolved.

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)
Continuous infusion is not an approved way to administer BeneFIX.

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.

What should I avoid while taking BeneFIX®?
Check with your doctor if you are pregnant or become pregnant while taking BeneFIX®. BeneFIX® has not been studied in pregnant women, and its risks to the unborn child are not known.

What are the possible or reasonably likely side effects of BeneFIX®?
BeneFIX® can cause serious allergic reactions. Your body can also produce inhibitors, or antibodies, against BeneFIX®. See "**What is the most important information I should know about BeneFIX®** ?"

BeneFIX® may increase the risk of thromboembolism (abnormal blood clots) in your body if you have risk factors for developing blood clots, including an indwelling venous catheter through which BeneFIX® is given by continuous infusion. There have been reports of severe blood clotting events, including life-threatening blood clots in critically ill neonates, while receiving continuous infusion BeneFIX® through a central venous catheter. The safety and efficacy of BeneFIX® administration by continuous infusion have not been established.

Some other side effects of BeneFIX® include: It is not uncommon for patients to react to intravenous administration of protein products such as BeneFIX®. The following reactions may be observed: headache, fever, chills, flushing, nausea, vomiting, lethargy, or symptoms of an allergic reaction. The symptoms of an allergic reaction include hives, swelling of the face and rash. Serious anaphylactic symptoms can also occur with an allergic reaction. These symptoms include wheezing, difficulty breathing, chest tightness, a bluish tinge, fast heartbeat, faintness, and decreased blood pressure. If you experience any of these symptoms, stop BeneFIX® infusion immediately and contact your doctor.

How should I store BeneFIX®?
The BeneFIX® product and diluent syringe should be stored under refrigeration at a temperature of 2° to 8°C (36° to 46°F). BeneFIX® may also be stored at room temperature not to exceed 25°C (77°F) for up to 6 months, until the expiration date. You should write the date the product

was placed at room temperature in the space provided on the outer carton. At the end of the 6-month period, the product should not be put back into the refrigerator, but should be used immediately or discarded. Freezing should be avoided to prevent damage to the pre-filled diluent syringe. Do not use after the expiration date stated on the label.

BeneFIX® does not contain a preservative. Use the reconstituted solution immediately or within 3 hours. Do not use BeneFIX® if the reconstituted solution is not clear and colorless.

General Information about BeneFIX®
Medicines are sometimes prescribed for purposes other than those listed here. Do not use BeneFIX® for a condition for which it was not prescribed. Do not share BeneFIX® with other people, even if they have the same symptoms that you have.

If you have any questions or concerns about BeneFIX®, ask your doctor or healthcare provider. This Patient Insert summarizes the most important information about BeneFIX®. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about BeneFIX® that was written for healthcare professionals.

This product's label may have been updated. For current package insert and further product information, please visit www.wyeth.com or call our medical communications department toll-free at 1-800-934-5556.

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