

**BeneFIX<sup>®</sup>**  
**COAGULATION FACTOR IX**  
**(RECOMBINANT)**

**Rx only**

**DESCRIPTION**

BeneFIX<sup>®</sup>, 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<sup>148</sup> allelic form of plasma-derived factor IX, and has structural and functional characteristics similar to those of endogenous factor IX.

BeneFIX<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> is greater than or equal to 200 IU per milligram of protein. BeneFIX<sup>®</sup> is not derived from human blood and contains no preservatives or added animal or human components.

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

BeneFIX<sup>®</sup> is formulated as a sterile, nonpyrogenic, lyophilized powder preparation. BeneFIX<sup>®</sup> 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, or 1000 IU of Coagulation Factor IX (Recombinant). After reconstitution of the lyophilized drug product, the concentrations of excipients in the 500 and 1000 IU dosage strengths are 10 mM L-histidine, 1% sucrose, 260 mM glycine, 0.005% polysorbate 80. The concentrations after reconstitution in the 250 IU dosage strength are half those of the other two dosage strengths. The 500 and 1000 IU dosage strengths are isotonic after reconstitution, and the 250 IU 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. The administration of BeneFIX<sup>®</sup>, 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 BeneFIX<sup>®</sup>, 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  $0.8 \pm 0.2$  IU/dL per IU/kg infused (range 0.4 to 1.4 IU/dL per IU/kg) and the mean biologic half-life was  $18.8 \pm 5.4$  hours (range 11 to 36 hours). In the randomized, cross-over pharmacokinetic study in previously treated patients (PTPs), the *in vivo* recovery using BeneFIX<sup>®</sup> 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<sup>®</sup> 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.

For specific information regarding pediatric pharmacology, see [PRECAUTIONS, Pediatric Use](#).

### Clinical Studies

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

In 4 clinical studies of BeneFIX<sup>®</sup>, 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<sup>®</sup> 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  $23.4 \pm 5.34$  months). Fifty-five of these PTPs received a median of 42.8 IU/kg (range 6.5 to 224.6 IU/kg; mean  $46.6 \pm 23.5$  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<sup>®</sup>. 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<sup>®</sup> with no anamnestic rise in inhibitor or anaphylaxis, however, increased frequency of BeneFIX<sup>®</sup> administration was required; subsequently the subject's factor IX inhibitor and its effect on the half-life of BeneFIX<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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  $85 \pm 32.8$  IU/kg (range 25-154.9 IU/kg). The mean total post-operative (inpatient and outpatient) dose was  $63.1 \pm 22.0$  IU/kg (range 28.6-129.0).

Total BeneFIX<sup>®</sup> 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<sup>®</sup> was administered at a median rate of 6.7 IU/kg/hr (range of average rates: 4.3-8.6 IU/kg/hr; mean  $6.4 \pm 1.5$  IU/kg/hr) for a median duration of 5 days (range 1-11 days; mean  $4.9 \pm 3.1$ ). Six of the 8 subjects who had received continuous infusion of BeneFIX<sup>®</sup> 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  $57.8 \pm 18.1$  IU/kg SD) for a median of 3.5 exposure days (range 1-5 days, mean  $3.3 \pm 1.4$  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<sup>®</sup> 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<sup>®</sup> 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  $0.8 \pm 0.2$  IU/dL per IU/kg). The median elimination half-life for the surgery subjects was 19.4 hours (range 10-37 hours; mean  $21.3 \pm 8.1$  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<sup>®</sup> 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<sup>®</sup> 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  $38.1 \pm 16.4$  months). Fifty-four of these PUPs received a median dose of 62.7 IU/kg (range 8.2 to 292.0 IU/kg; mean  $75.6 \pm 42.5$  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<sup>®</sup>. 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<sup>®</sup> for routine prophylaxis. Twenty-four PUPs administered BeneFIX<sup>®</sup> at least twice weekly for a total of 2587 infusions. The mean dose per infusion was  $72.5 \pm 37.1$  IU/kg, and the mean duration of prophylaxis was  $13.4 \pm 8.2$  months. Eight PUPs administered BeneFIX<sup>®</sup> once weekly for a total of 571 infusions. The mean dose per infusion was  $75.9 \pm 17.9$  IU/kg, and the mean duration of prophylaxis was  $17.6 \pm 7.4$  months. Five PUPs experienced a total of 6 spontaneous bleeding episodes within 48 hours after an infusion.

Twenty-three PUPs received BeneFIX<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup>, 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<sup>®</sup>, 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<sup>®</sup>, 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**).

The diluent vial accompanying this product may contain dry natural rubber that may cause hypersensitivity reactions when handled by or administered to persons with known or possible latex sensitivity.

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<sup>®</sup> 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.<sup>1</sup> Although BeneFIX<sup>®</sup> 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<sup>®</sup> should be weighed against the risk of these complications.

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

Activity-neutralizing antibodies (inhibitors) have been detected in patients receiving factor IX-containing products. As with all factor IX products, patients using BeneFIX<sup>®</sup> 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<sup>2</sup>. 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<sup>®</sup> 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<sup>®</sup>, 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<sup>®</sup>, Coagulation Factor IX (Recombinant). It is not known whether BeneFIX<sup>®</sup> can affect reproductive capacity or cause fetal harm when given to pregnant women. BeneFIX<sup>®</sup> 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<sup>®</sup> 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  $0.7 \pm 0.2$  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  $20.2 \pm 4.0$  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  $0.7 \pm 0.3$  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 ( $0.7 \pm 0.4$  IU/dL per IU/kg; range 0.2 to 2.1 IU/dL per IU/kg) and children ( $0.7 \pm 0.2$  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<sup>®</sup> 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<sup>®</sup>, 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<sup>®</sup>, Coagulation Factor IX (Recombinant), conducted in previously treated patients (PTPs), 131 adverse reactions with definite, probable, possible or unknown relation to BeneFIX<sup>®</sup> 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 <sup>1</sup> (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 <sup>2</sup>              | 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 <sup>1</sup> (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 <sup>3</sup> | 1   | 1 (1.5 %)   | 1 (0.01 %)  |
| <b>Total</b>               | <b>131</b>  | <b>27/65 (41.5 %)</b>   | <b>148/7573 (2.2 %)</b>   |

\*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<sup>®</sup> for a bleeding episode. The relationship of the infarct to the prior administration of BeneFIX<sup>®</sup> is uncertain. (See **PRECAUTIONS, General**).

One subject discontinued BeneFIX<sup>®</sup> 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<sup>®</sup>. 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 <sup>1</sup> (n=5538) |
|----------------------------------|--|---|---|
| Diarrhea                         | 5  | 1 (1.6 %)   | 11 (0.20%)  |
| Urticaria (hives)                | 3  | 3 (4.8 %)   | 3 (0.05%)   |
| Factor IX inhibitor <sup>2</sup> | 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 <sup>1</sup> (n=5538) |
|--|--|---|---|
| HAV seroconversion <sup>3</sup>            | 1  | 1 (1.6 %)   | 2 (0.04%)   |
| Parvovirus B19 seroconversion <sup>4</sup> | 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<sup>®</sup>.

3 Relationship of HAV seroconversion to BeneFIX<sup>®</sup> 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<sup>®</sup> is unknown. It was unlikely that seroconversion was related to BeneFIX<sup>®</sup> due to the frequency of community acquired infection and viral safeguards built into the manufacturing process (See **DESCRIPTION**).

The following post-marketing adverse reactions have been reported for BeneFIX<sup>®</sup>, 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.

If any adverse reaction takes place that is thought to be related to the administration of BeneFIX<sup>®</sup>, the rate of infusion should be decreased or the infusion stopped.

#### **DOSAGE AND ADMINISTRATION**

Treatment with BeneFIX<sup>®</sup>, 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<sup>®</sup> and a single lot of high-purity plasma-derived factor IX, the recovery was lower for BeneFIX<sup>®</sup> (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<sup>®</sup> 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:

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|   |   |                         |   |  |   |  |
|---|---|-------------------------|---|--|---|--|
| <b>number of factor IX IU required (IU)</b> | = | <b>body weight (kg)</b> | x | <b>Desired factor IX increase (% or IU/dL)</b> | x | <b>reciprocal of observed recovery (IU/kg per IU/dL)</b> |
|---|---|-------------------------|---|--|---|--|

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

#### **Adult Patients**

In adult PTPs, on average, one international unit of BeneFIX<sup>®</sup> 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:

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|   |   |                         |   |  |   |                              |
|---|---|-------------------------|---|--|---|------------------------------|
| <b>number of factor IX IU required (IU)</b> | = | <b>body weight (kg)</b> | x | <b>desired factor IX increase (% or IU/dL)</b> | x | <b>1.2 (IU/kg per IU/dL)</b> |
|---|---|-------------------------|---|--|---|------------------------------|

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#### **Pediatric Patients (<15 years)**

In pediatric patients, on average, one international unit of BeneFIX<sup>®</sup> 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:

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$$\text{number of factor IX IU required (IU)} = \text{body weight (kg)} \times \text{desired factor IX increase (\% or IU/dL)} \times 1.4 \text{ (IU/kg per IU/dL)}$$


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The following chart<sup>3</sup> 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]                                       |
|--|--|-------------------------|--|
| <b>Minor</b>   |  |                         |  |
| Uncomplicated hemarthroses, superficial muscle, or soft tissue                                 | 20-30  | 12-24                   | 1-2  |
| <b>Moderate</b>  |  |                         |  |
| 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 |
| <b>Major</b>   |  |                         |  |
| Pharynx, retropharynx, retroperitoneum, CNS, surgery   | 50-100   | 12-24                   | 7-10   |

Adapted from: Roberts and Eberst<sup>3</sup>

### INSTRUCTIONS FOR USE

The procedures below are provided as general guidelines for the reconstitution and administration of BeneFIX<sup>®</sup>. 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<sup>®</sup>, 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<sup>®</sup> and diluent to reach room temperature.
2. Remove the plastic flip-top caps from the BeneFIX<sup>®</sup> 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<sup>®</sup> vial.

*Note: Point the double-ended needle toward the wall of the BeneFIX<sup>®</sup> vial to prevent excessive foaming.*

6. The vacuum will draw the diluent into the BeneFIX<sup>®</sup> vial.
7. Once the transfer is complete, remove the long end of the needle from the BeneFIX<sup>®</sup> vial, and properly discard the needle with the diluent vial.

*Note: If the diluent does not transfer completely into the BeneFIX<sup>®</sup> 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<sup>®</sup> should appear clear and colorless.

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

BeneFIX<sup>®</sup>, 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<sup>®</sup>, 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<sup>®</sup>, 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<sup>®</sup> vial. This may cause partial loss of product.*

2. Insert the filter spike end into the stopper of the BeneFIX<sup>®</sup> 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<sup>®</sup>, 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<sup>®</sup>. 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<sup>®</sup> solution) and resume administration with a new package.*

After reconstitution, BeneFIX<sup>®</sup> 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<sup>®</sup>, 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup>, Coagulation Factor IX (Recombinant), is supplied in single use vials which contain nominally 250, 500, or 1000 IU 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 IU 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.



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



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