**BeneFIX® COAGULATION FACTOR IX (RECOMBINANT)**

**DESCRIPTION**

BeneFIX®, Coagulation Factor IX (Recombinant), is a purified protein produced by recombinant DNA technology for use in the management 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-transformed 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. The CHO 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 predomi-
nantly a single component by SDS-polyacrylamide gel elec-
trophoresis evaluation. The potency (in international units, I.U.) is determined using an in vivo one-stage clotting assay with the World Health Organization (WHO) International Standard for Factor IX concentrate. One inter-
national unit of the amount of factor IX activity present in 1 mL of pooled, normal human plasma. The specific activity of BeneFIX® is greater than 200 I.U./milligram of protein. BeneFIX® is not derived from human blood and contains no preservatives or added animal or human com-
ponents.

BeneFIX® is formulated as a sterile, nonpyrogenic, lyophilized powder preparation. BeneFIX® is intended for intravenous (IV) injection. It is available in single use vials containing the labeled amount of factor IX activity, expressed in international units (I.U.). Each vial contains nominally 250, 500, or 1000 I.U. of Coagulation Factor IX (Recombinant). After reconstitution of the lyophilized drug product, the concentrations of excipients in the 500 and 1000 I.U. dosage strengths are 10 mM L-histidine, 1% sucrose, 260 mM glycine, 0.005% polysorbate 80. The concentrations after reconstitution in the 250 I.U. dosage strength are half those of the other two dosage strengths. The pH of the 2500 I.U. dosage strength is acidic after reconstitution, and the 250 I.U. dosage strength has half the acidity 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 Xa in the intrinsic coagulation pathway. Activated factor IX, in combination with activated factor VIII, activates factor X. This results ultimately in the conversion of prothrombin to thrombin. Thrombin then converts fibrinogen to fibrin, and a clot can be formed.

Factor IX is the specific clotting factor deficient in patients with hemophilia B and in patients with acquired factor IX deficiencies. The administration of BeneFIX®, Coagulation Factor IX (Recombinant), increases plasma levels of factor IX and can temporarily correct the coagulation defect in these patients. After single intravenous (IV) doses of 50 I.U./kg of BeneFIX®, Coagulation Factor IX (Recombinant), in 36 patients, each given as a 10-minute infusion, the mean increase in circulating factor IX activity was 0.8 ± 0.2 I.U./dl per kg infused ( ranged from 0.4 to 1.4 I.U./dl per kg) and the mean biological half-life was 36 hours ( ranged from 11 to 36 hours). The in vivo recovery using BeneFIX® was statistically significantly less (28% lower) than the recovery using a high-purity plasma-derived factor IX product. There was no significant difference in biological half-life. In subsequent evaluations at 6 and 12 months, the pharmacoki-
etic parameters were similar to the initial results. In clinical studies of total of 84 patients (44 previously treated patients [PTPs], 11 previously untreated patients [PUPs], and the 9 patients participating only once) given a total of 7.7 million I.U. were administered over a period of up to 18 months. This included 57 HIV-negative and 7 HIV-positive patients. Forty-five patients were evaluated for efficacy, all of whom were treated successfully for bleeding episodes on an on-demand basis or for the prevention of bleeds. Bleeding episodes that were managed successfully included hemarthroses and bleeding in soft tissue and muscle. Management of hemostasis was evaluated in the surgical setting. Seventeen surgical procedures have been performed in 10 patients, with a cumulative dose ranging from 10,000 to 348,000 I.U. The 10 major procedures were performed using a pulse replacement regimen (N=7) or a continuous infusion regimen (N=3), and included a liver transplantation, a hernia repair, six orthopedic surgeries, and two dural extractions. Circulatory factor IX levels targeted to 10% of normal and maintained for 60 min. BeneFIX® has been used both in pulse replacement and continuous infusion regimens. Hemostasis was maintained throughout the surgical period, however, one patient required evacuation of a surgical wound site hematoma and another patient who received BeneFIX® after a tooth extraction required further surgical intervention due to oozing at the extraction site. There was no clinical evidence of thrombotic complications in any of these patients. In four patients for whom fibrinopeptide A and prothrombin fragment 1+ 2 were measured pre-infusion, at 4 to 8 hours, and then daily up to 96 hours, there was no evidence of significant increase in coagulation acti-
vation. Data from two additional patients were judged to be not evaluable.

A study of BeneFIX® has been initiated in patients who had not been treated previously with plasma-derived factor IX concentrate (PFCs). In preliminary data, 11 of the 20 patients enrolled in the study received at least one infusion of BeneFIX®. These 11 patients received a total of 27,208 I.U. During the study, 55 patients will be enrolled and followed for up to 5 years to complete evaluation of BeneFIX® in this patient population for safety, efficacy, and immunogenicity.

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

**INDICATIONS AND USAGE**

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

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

**CONTRAINDICATIONS**

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

**WARNINGS**

Allergic type hypersensitivity reactions, including anaphy-
laxis, have been reported for all factor IX products. Fre-
quently, these events occur in 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 anaphy-
laX. 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 reac-
tion, if any of these symptoms occur (see PRECAUTIONS).

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

Since the use of factor IX complex concentrates has histori-
cally been associated with the development of thrombo-
embolic complications, the use of factor IX-containing prod-
cuts may be potentially hazardous in patients with signs of fibrosis and in patients with disseminated intravascular coagulation (DIC).

**PRECAUTIONS**

**General**

Historically, the administration of factor IX complex con-
centrates derived from human plasma, containing factors II, VII, IX, and X, has been associated with the development of thromboembolic complications. Although BeneFIX®, con-
tains no coagulation factor other than factor IX, the poten-
tial risk of thrombosis and DIC observed with other prod-
cuts 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 neoplastic patients, or to patients at risk of thromboembolic phenom-
ena or DIC. In each of these situations, the benefit of treat-
ment with BeneFIX® should be weighed against the risk of these complications.

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

**ADVERSE REACTIONS**

As with any new product administration of any protein prod-
uct, the following reactions may be observed after adminis-
tration: 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 admin-
istered.

During clinical studies with BeneFIX®, Coagulation Factor IX (Recombinant), conducted in previously treated patients (PTPs), there were no adverse events definitely, probably, or possibly related to therapy were reported for 2,548 infu-
sions. These were nausea (16), discomfort at the IV site (13), burning sensation in the jaw and skull (6), allergic rhinitis (3), light-headedness (2), headache (2), dizziness (1), chest tightness (1), fever (1), palpitations, arthralgias at IV site (1), drowsiness (1), dry cough/sneeze (1), rash (1), and a single hive (1). Twelve days after a dose of BeneFIX® for a bleeding episode, one hepatitis B antibody positive patient developed a renal infarct. The relationship of the infarct to prior administration of BeneFIX® is uncertain but was judged to be unlikely by the investigator. The patient continued to be treated with BeneFIX®.
The following post-marketing adverse reactions have been reported for BeneFix® as well as for plasma-derived factor IX products: inadequate factor IX recovery, inadequate therapeutic response, inhibitor development (see CLINICAL PHARMACOLOGY), anaphylaxis (see WARNINGS), laryngeal edema, angioedema, cyanosis, dyspnea, hypotension, thrombosis. If any adverse reaction takes place that is thought to be related to the administration of BeneFix®, the rate of infusion should be decreased or the infusion stopped.

DOSE AND ADMINISTRATION

Treatment with BeneFix®, Coagulation Factor IX (Recombinant), should be initiated under the supervision of a physician experienced in the treatment of hemophilia B. Dosage and duration of treatment for all factor IX products depend on the severity of the factor IX deficiency, the location and extent of bleeding, and the patient's clinical condition, age, and recovery of factor IX.

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

In an eleven patient, crossover, randomized PK evaluation following example. If you use 0.8 I.U./dL average increase I.U./dL. The method of dose estimation is illustrated in the following equation:

\[
\text{number of factor IX I.U. required (I.U.)} = \text{weight (kg) x desired factor IX increase (I.U./dL) x 1.4 (I.U./kg).}
\]

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

<table>
<thead>
<tr>
<th>Type of Hemorrhage</th>
<th>Circulating Factor IX Activity Required (I.U./dL)</th>
<th>Dosing Interval of Therapy (hours)</th>
<th>Duration of Therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor</td>
<td>20-30</td>
<td>12-24</td>
<td>1-2</td>
</tr>
<tr>
<td>Moderate</td>
<td>25-50</td>
<td>12-24</td>
<td>7-10</td>
</tr>
<tr>
<td>Major</td>
<td>50-100</td>
<td>12-24</td>
<td>2 to 7 days</td>
</tr>
</tbody>
</table>

Adapted from: Roberts and Eberst®

INSTRUCTIONS FOR USE

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

Reconstitution

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

BeneFix®, Coagulation Factor IX (Recombinant), will be administered by intravenous (IV) infusion after reconstitution with Sterile Water for Injection (USP). The reconstituted solution may be stored at room temperature prior to administration.

Administration (Intravenous Injection)

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

1. Using aseptic technique, attach the sterile filter spike to the vial. Note: Do NOT inject air into the BeneFix® vial. This may cause partial loss of product.

2. Insert the filter spike end into the stopper of the BeneFix® vial.

3. Invert the vial and withdraw the reconstituted solution into the syringe.

4. Remove and discard the filter spike.

5. Attach the syringe to the Luer end of the infusion set.

After reconstitution, BeneFix® should be injected intravenously over several minutes. The rate of administration should be determined by the patient’s comfort level (see ADVERSE REACTIONS).

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

Storage

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

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

How Supplied

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

REFERENCES


Manufactured by:
Genetics Institute, Inc.
Cambridge MA 02140-2387, USA

US License Number 1163
Telephone: 1-800-934-5556

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

INSTRUCTIONS FOR USE

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

\[
\text{number of factor IX I.U. required (I.U.)} = \text{weight (kg) x desired factor IX increase (I.U./dL) x 1.4 (I.U./kg).}
\]

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

Adult Patients

In adult PTPs, on average, one international unit of BeneFix® per kilogram of body weight increased the circulating activity of factor IX by 0.8 ± 0.2 (ranged from 0.3 to 1.4) I.U.dL. The method of dose estimation is illustrated in the following example. If you use 0.8 I.U.dL average increase of factor IX per I.U.kg body weight administered, then:

\[
\text{number of factor IX I.U. required (I.U.)} = \text{weight (kg) x desired factor IX increase x 1.2 (I.U./kg).}
\]

Pediatric Patients (< 15 years)

In pediatric patients, on average, one international unit of BeneFix® per kilogram of body weight increased the circulating activity of factor IX by 0.7 ± 0.2 (ranged from 0.3 to 1.1) I.U.dL. The method of dose estimation is illustrated in the following example. If you use 0.7 I.U.dL average increase of factor IX per kg body weight administered, then:

\[
\text{number of factor IX I.U. required (I.U.)} = \text{weight (kg) x desired factor IX increase x 1.4 (I.U./kg).}
\]