Nonacog alfa

BeneFIX

Coagulation Factor IX (Recombinant)

250, 500, 1000, and 2000 IU per vial

℞

1.0 PHARMACOLOGIC CATEGORY

Coagulation Factor IX

2.0 DESCRIPTION

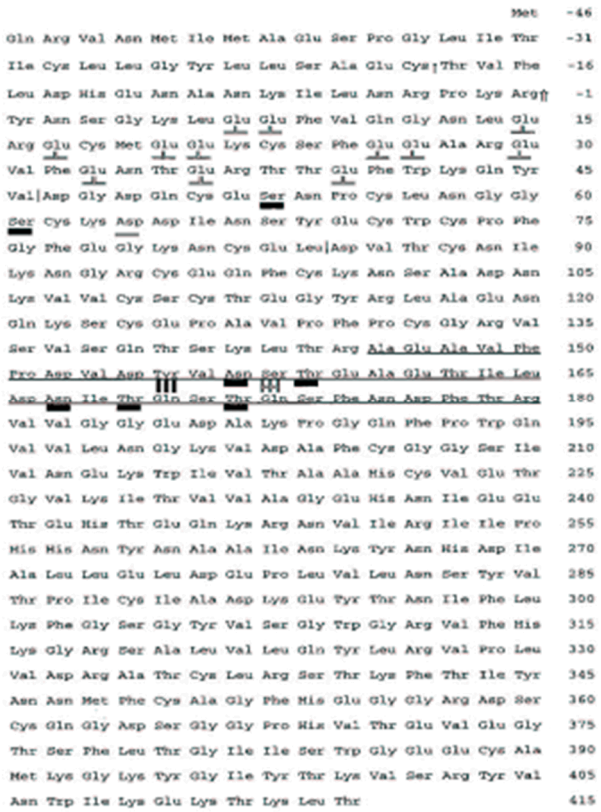
Nonacog alfa (BeneFIX) is formulated as a sterile, nonpyrogenic, lyophilized powder preparation. It is a clear, colorless solution after reconstitution.

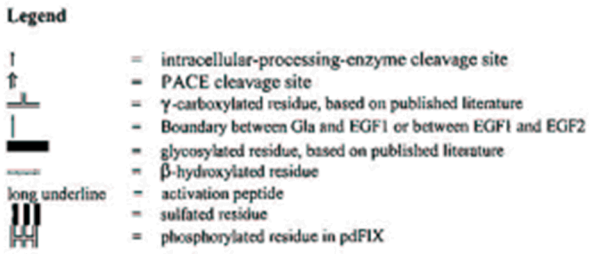
Proper name: Coagulation Factor IX (Recombinant)

Chemical name: Coagulation Factor IX (Recombinant)

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

Structural formula:





Physicochemical properties

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

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

3.0 FORMULATION/ COMPOSITION

Nonacog alfa (BeneFIX) 250 IU Lyophilized powder for solution for Injection: Each vial contains 250IU nonacog alfa.
Nonacog alfa (BeneFIX) 500 IU Lyophilized powder for solution for Injection: Each vial contains 500IU nonacog alfa.
Nonacog alfa (BeneFIX) 1000 IU Lyophilized powder for solution for Injection: Each vial contains 1000IU nonacog alfa.
Nonacog alfa (BeneFIX) 2000 IU Lyophilized powder for solution for Injection: Each vial contains 2000IU nonacog alfa.

4.0 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

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

4.2 Dosage and Method of Administration

Dosage

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

of hemophilia B.

Treatment with all factor IX products, including Nonacog alfa (BeneFIX), requires individualized dosage adjustment. The dosage and duration of treatment for all factor IX products depend on the severity of the factor IX deficiency, the location and extent of bleeding, and the patient's clinical condition. Dosing of Nonacog alfa (BeneFIX) may differ from that of plasma-derived factor IX products.

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

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

Method of Calculating Dose

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

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

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

Patients ≥ 15 years

In patients ≥ 15 years, on average, one international unit of Nonacog alfa (BeneFIX) per kilogram of body weight increased the circulating activity of factor IX by 0.8 ± 0.2 (range 0.4 to 1.4) IU/dL. The method of dose estimation is illustrated in the following example. If you use 0.8 IU/dL average increase of factor IX per IU/kg body weight administered, then:

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

**Reciprocal of observed recovery (IU/kg per IU/dL)*

Patients < 15 years

In patients <15 years, on average, one international unit of Nonacog alfa (BeneFIX) per kilogram of body weight increased the circulating activity of factor IX by 0.7 ± 0.3 (range 0.2 to 2.1) IU/dL. The method of dose estimation is illustrated in the following example. If you use 0.7 IU/dL average increase of factor IX per IU/kg body weight administered, then:

$$\text{Number of factor IX IU required (IU)} = \text{Body weight (kg)} \times \text{Desired factor IX increase (\% or IU/dL)} \times \text{1.4 (IU/kg per IU/dL)}^{*}$$

**Reciprocal of observed recovery (IU/kg per IU/dL)*

Dosage for Bleeding Episodes and Surgery

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

Table 1: Dosing Guide for Control and Prevention of 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			
Intramuscular or soft tissue with dissection, mucous membranes, dental extractions, or hematuria	25–50	12–24	Treat until bleeding stops and healing begins; about 2 to 7 days
Major			
Pharynx, retropharynx, retroperitoneum, CNS, surgery	50–100	12-24	7–10
Adapted from: Roberts and Eberst			

Dosage for Prophylaxis

For long term prophylaxis against bleeding in patients with severe hemophilia B, Nonacog alfa (BeneFIX) may be administered. In a clinical study for routine secondary prophylaxis the average dose for previously treated adult patients (PTP) was 40 IU/kg (range 13 to 78 IU/kg) at intervals of 3 or 4 days. In younger patients, shorter dosage intervals or higher doses may be necessary (see section **5.1 Pharmacodynamic Properties**).

Administration (Intravenous Injection)

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

Nonacog alfa (BeneFIX) should be administered using the infusion set provided in this kit, and the pre-filled diluent syringe provided or a single sterile disposable plastic syringe. In addition, the solution should be withdrawn from the vial using the vial adapter.

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

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

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

Note: Agglutination of red blood cells in the tubing/syringe has been reported with the administration of Nonacog alfa (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 Nonacog alfa (BeneFIX) solution) and resume administration with a new package.

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

The reconstituted solution may be stored at room temperature prior to administration. However, Nonacog alfa (BeneFIX) should be administered within 3 hours after reconstitution.

Nonacog alfa (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 Nonacog alfa (BeneFIX), including storage time elapsed in a PVC container following reconstitution. It is important that the recommendations in section **4.2 Dosage and Method of Administration** be followed closely.

Note: The tubing of the infusion set included with this kit does not contain DEHP.

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

The administration of Nonacog alfa (BeneFIX) by continuous infusion has not been sufficiently evaluated in clinical trials to justify its use in this manner. Nonacog alfa (BeneFIX) should only

be reconstituted with the diluent provided. Nonacog alfa (BeneFIX) should not be mixed with 5% dextrose or other parenteral infusion solutions.

4.3 Contraindications

Because Nonacog alfa (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.

4.4 Special Warnings and Precautions for Use

General

Hypersensitivity

Allergic-type hypersensitivity reactions, including anaphylaxis, have been reported for all factor IX products, including Nonacog alfa (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, chills (rigors), flushing, angioedema, chest tightness, laryngospasm, bronchospasm, dyspnea, wheezing, faintness, hypotension, tachycardia, blurred vision, and anaphylaxis. If allergic or anaphylactic reactions occur, administration of Nonacog alfa (BeneFIX) should be stopped immediately, and appropriate medical management should be given, which may include treatment for shock. Patients should be advised to discontinue use of the product and contact their physician and/or seek immediate emergency care, depending on the type/severity of the reaction, if any of these symptoms occur.

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

In case of severe allergic reactions, alternative hemostatic measures should be considered.

Dosing of Nonacog alfa (BeneFIX) may differ from that of plasma-derived factor IX products.

Cardiovascular

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

The safety and efficacy of Nonacog alfa (BeneFIX) administration by continuous infusion have not been established. There have been post-marketing reports of thrombotic events in patients receiving continuous-infusion Nonacog alfa (BeneFIX) through a central venous catheter, including life-threatening superior vena cava (SVC) syndrome in critically ill neonates.

Hematologic

See **Cardiovascular**.

Hepatic/Biliary/Pancreas

See **Cardiovascular**.

Immune

Activity-neutralizing antibodies (inhibitors) have been detected in patients receiving factor IX-containing products. As with all factor IX products, patients using Nonacog alfa (BeneFIX) should be monitored for the development of factor IX inhibitors. Patients with factor IX inhibitors may be at an increased risk of anaphylaxis upon subsequent challenge with factor IX[2]. Patients experiencing allergic reactions should be evaluated for the presence of inhibitor. Preliminary information suggests a relationship may exist between the presence of major deletion mutations in a patient's factor IX gene and an increased risk of inhibitor formation and of acute hypersensitivity reactions. Patients known to have major deletion mutations of the factor IX gene should be observed closely for signs and symptoms of acute hypersensitivity reactions, particularly during the early phases of initial exposure to product. In view of the potential for allergic reactions with factor IX concentrates, the initial (approximately 10 - 20) administrations of factor IX should be performed under medical supervision where proper medical care for allergic reactions could be provided.

Peri-Operative Considerations

See **Cardiovascular**.

Renal

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

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

Respiratory

Patients should be informed of the early symptoms and signs of hypersensitivity reactions including hives, generalized urticaria, chills (rigors), flushing, angioedema, chest tightness, dyspnea, wheezing, faintness, hypotension, tachycardia, and anaphylaxis. Patients should be

advised to discontinue use of the product and contact their physician and/or seek immediate emergency care, depending on the type/severity of the reaction, if any of these symptoms occur.

Sensitivity/Resistance

See **General**.

Sexual Function/Reproduction

See section **4.6 Pregnant and Nursing Women**.

Skin

See **Sensitivity/Resistance**

Pediatrics

Data from Nonacog alfa (BeneFIX) safety, efficacy, and pharmacokinetic studies have been evaluated in previously treated and previously untreated pediatric patients.

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

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

Geriatrics

Clinical studies of Nonacog alfa (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 Nonacog alfa (BeneFIX), dose selection for an elderly patient should be individualized.

Monitoring and Laboratory Tests

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

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Overview

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

Drug-Laboratory Interactions

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

4.6 Fertility, Pregnancy and Lactation

Pregnant and Nursing Women

Animal reproduction and lactation studies have not been conducted with Nonacog alfa (BeneFIX) Coagulation Factor IX (Recombinant). It is not known whether Nonacog alfa (BeneFIX) can affect reproductive capacity or cause fetal harm when given to pregnant women. Nonacog alfa (BeneFIX) should be administered to pregnant and lactating women only if clearly indicated.

4.7 Effects on Ability to Drive and Use Machines

On the basis of the pharmacodynamic and pharmacokinetic profile and reported adverse reactions Nonacog alfa (BeneFIX) has no or negligible influence on the ability to drive or use machines.

4.8 Undesirable Effects

Adverse Drug Reaction Overview

As with the intravenous administration of any protein product, the following reactions may be observed after administration: headache, fever, chills, flushing, nausea, vomiting, lethargy, or manifestations of allergic reactions. Should evidence of an acute hypersensitivity reaction be observed, the infusion should be stopped promptly and appropriate counter measures and supportive therapy should be administered.

Clinical Trial Adverse Drug Reactions

The table below lists adverse reactions reported in the clinical trials of previously treated patients (PTPs) and previously untreated patients (PUPs). The frequencies are based on all causality treatment emergent events in pooled clinical trials with 287 subjects.

Table 2: Adverse Reactions Reported for PTPs and PUPs

System Organ Class	ADR Term	Frequency (%)
Infections and infestations	Infusion-site cellulitis	0.7

System Organ Class	ADR Term	Frequency (%)
Blood and lymphatic system disorders	Factor IX inhibition	1.4
Immune system disorders	Hypersensitivity	6.6
Nervous system disorders	Headache	23.0
	Dizziness	3.1
	Dysgeusia	1.4
	Somnolence	0.7
	Tremor	0.3
Eye disorders	Visual impairment	0.7
Cardiac disorders	Tachycardia	0.7
Vascular disorders	Flushing	1.4
	Hypotension	1.0
	Phlebitis	1.0
Respiratory, thoracic and mediastinal disorders	Cough	19.2
	Respiratory distress	0.3
Gastrointestinal disorders	Vomiting	12.2
	Nausea	7.3
Skin and subcutaneous disorders	Rash	9.4
	Urticaria	4.5
Renal and urinary disorders	Renal infarct	0.3
General disorders and administration site conditions	Pyrexia	24.0
	Infusion-site pain	2.1
	Infusion-site reaction	2.1
	Chest discomfort	1.4
	Chills	0.7

One subject discontinued Nonacog alfa (BeneFIX) due to pulmonary allergic-type symptoms.

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

In the section below the following frequency categories and terms are used:
Uncommon: ≥ 0.1% and < 1%
Rare: ≥ 0.01% and < 0.1%
Very Rare: < 0.01%

Body as a whole

Rare — Hypersensitivity/allergic reactions (including, but not limited to hives, generalized urticaria, chills (rigors), flushing, angioedema, chest tightness, laryngospasm, bronchospasm, dyspnea, wheezing, faintness, hypotension, tachycardia, anaphylaxis)

Nervous system disorders

Uncommon — Dizziness, headache, somnolence, tremor

Cardiac disorders

Rare — Hypotension, tachycardia

Vascular disorders

Rare	Phlebitis at the injection site

Respiratory, thoracic and mediastinal disorders

Rare	Respiratory distress
Very Rare	Dry cough

Gastrointestinal disorders

Uncommon	Nausea
Rare	Vomiting

Renal and urinary disorders

Uncommon	Renal infarct

Eye disorders

Uncommon	Visual impairment

Skin

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

Special senses

Uncommon	Altered taste

General disorder and administration site conditions

Uncommon	Injection site reaction (including infusion site pruritis, infusion site erythema), infusion site pain (including infusion site irritation)
Rare	Fever

Post-Market Adverse Drug Reactions

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

There have been post-marketing reports of thrombotic events in patients receiving continuous-infusion Nonacog alfa (BeneFIX) through a central venous catheter, including life-threatening superior vena cava (SVC) syndrome in critically ill neonates. Cases of peripheral thrombophlebitis and deep vein thrombosis (DVT) have also been reported. In some, Nonacog alfa (BeneFIX) was administered via continuous infusion, which is not an approved method of administration.

If any adverse reaction takes place that is thought to be related to the administration of Nonacog alfa (BeneFIX), the rate of infusion should be decreased or the infusion stopped.

4.9 Overdose and Treatment

No symptoms of overdose are known.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Mechanism of Action

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

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

Pharmacodynamics

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

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

Clinical Trials

In 4 clinical studies of Nonacog alfa (BeneFIX) Coagulation Factor IX (Recombinant), a total of 128 patients (56 previously treated patients [PTPs], 9 patients participating only in the

surgical study, and 63 previously untreated patients [PUPs]), received more than 28 million IU administered over a period of up to 64 months. The studies included 121 HIV-negative and 7 HIV-positive patients.

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

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

Management of hemostasis was evaluated in the surgical setting. Thirty-six surgical procedures have been performed in 28 patients. Thirteen (13) minor surgical procedures were performed in 12 patients, including 7 dental procedures, 1 punch biopsy of the skin, 1 cyst removal, 1 male sterilization, 1 nevus ablation, and 2 ingrown toenail removals. Twenty-three (23) major surgical procedures were performed in 19 patients including a liver transplant, splenectomy, 3 inguinal hernia repairs, 11 orthopedic procedures, a calf-debridement and 6 complicated dental extractions.

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

Total Nonacog alfa (BeneFIX) coverage during the surgical period for the major procedures ranged from 4230 to 385,800 IU**.** The pre-operative dose for the major procedures ranged from 75 to 155 IU/kg. Nine of the major surgical procedures were performed using a continuous infusion regimen. Following pre-operative bolus doses (94.1-144.5 IU/kg), continuous infusion

of Nonacog alfa (BeneFIX) was administered at a median rate of 6.7 IU/kg/hr (range of average rates: 4.3-8.6 IU/kg/hr; mean 6.4 ± 1.5 IU/kg/hr) for a median duration of 5 days (range 1-11 days; mean 4.9 ± 3.1). Circulatory factor IX levels targeted to restore and maintain hemostasis were achieved with both pulse replacement and continuous infusion regimens.

Among the surgery patients, the median increase in circulating factor IX activity was 0.7 IU/dL per IU/kg infused (range 0.3-1.2 IU/dL; mean 0.8 ± 0.2 IU/dL per IU/kg). The median elimination half-life for the surgery subjects was 19.4 hours (range 10-37 hours; mean 21.3 ± 8.1 hours).

Hemostasis was maintained throughout the surgical period, however, one patient required evacuation of a surgical wound site hematoma and another patient who received Nonacog alfa (BeneFIX) after a tooth extraction required further surgical intervention due to oozing at the extraction site. There was no clinical evidence of thrombotic complications in any of the patients. In seven patients for whom fibrinopeptide A and prothrombin fragment 1 + 2 were measured pre-infusion, at 4 to 8 hours, and then daily up to 96 hours, there was no evidence of significant increase in coagulation activation. Data from two other patients were judged to be not evaluable.

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

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

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

Prophylaxis

Study 400-WW was a randomized, open-label, 4-period study of Nonacog alfa (BeneFIX) in 50 subjects aged 6 to 65 years (study population range 6 to 64 years) with a documented history of moderately severe or severe haemophilia B (FIX:C ≤2%). Subjects were to use Nonacog alfa (BeneFIX) in an on-demand manner for 4 months, followed by random assignment to 1 of 2 prophylaxis regimens for 4 months. This was followed by a 2-month period when subjects again used Nonacog alfa (BeneFIX) in an on-demand-only manner. Subjects then crossed over to the alternate prophylaxis regimen for 4 months. Dosing with Nonacog alfa (BeneFIX) during the on-demand treatment periods, as well as treatment of any bleeding episodes occurring during the prophylaxis periods, was at the discretion of the investigator.

In Study 400-WW, both prophylaxis regimens showed better efficacy compared with the on-demand regimen. No statistically significant differences in the annualized bleed rate (ABR) were observed between the 2 prophylaxis regimens (100 IU/kg once weekly and 50 IU/kg twice weekly). The mean (± standard deviation) ABR during the on-demand treatment period 1 and 2 were 34.3 (±21.8) and 31.1 (±22.0) vs prophylaxis regimens: 4.4 (±10.0) in 100 IU/kg once weekly and 2.8 (±5.7) in 50 IU/kg twice weekly.

However, the efficacy of Nonacog alfa (BeneFIX) prophylaxis in reducing the number of bleeding episodes was variable among the subjects. During 50 IU/kg twice weekly prophylaxis period (ranged 84-127 days), 28/43 (65.1%) patients had no bleeding episodes; and 15/43 (35.9%) patients had bleeding episodes (ABR ranged: 2.99 – 24.12). During 100 IU/kg weekly prophylaxis period (ranged 78 - 139 days), 25/44(56.8%) patients had no bleeding episodes, and 19/44 (43.2%) patients had bleeding episodes (ABR ranged: 2.59 – 50.51). There were 35 bleeding episodes reported during 50 IU/kg twice weekly treatment period, and 52 bleeding episodes reported during100 IU/kg once weekly treatment period.

In study B1821010, another open-label study of 25 patients (range 12-54 years; 5 subjects <18 years) comparing on-demand treatment versus prophylaxis when administered at a dose of 100 IU/kg once weekly for approximately 52 weeks, the annualized bleed rate (ABR) for the prophylaxis period was significantly lower ($p < 0.0001$) than the ABR for the on-demand period (mean: 3.6 ± 4.6, median: 2.0, min-max: 0.0 - 13.8 versus mean: 32.9 ± 17.4, median: 33.6, min-max: 6.1 - 69.0, respectively). Twelve subjects (48%) experienced no spontaneous bleeds during the prophylaxis period while 13 subjects experienced (52%) experience one or more bleeds during the prophylaxis period. There were 64 spontaneous bleeds during the prophylaxis period in these 13 patients. Three subjects experienced 1 spontaneous bleeding episode each within 48 hours of a previous prophylaxis infusion. All of these bleeding episodes were associated with confounding factors and were not considered occurrences of LETE. The majority of spontaneous bleeds in the prophylaxis period (47 of 64 bleeds, 73.4%) occurred >72 hours from the previous prophylaxis infusion.

5.2 Pharmacokinetic Properties

After single intravenous (IV) doses of 50 IU/kg of Nonacog alfa (BeneFIX), Coagulation Factor IX (Recombinant), in 37 previously treated adult patients (>15 years), each given as a 10-minute infusion, the mean increase from pre-infusion level in circulating factor IX activity was 0.8 ± 0.2 IU/dL per IU/kg infused (range 0.4 to 1.4 IU/dL per IU/kg) and the mean biologic

half-life was 18.8 ± 5.4 hours (range 11 to 36 hours). In subsequent evaluations for up to 24 months, the pharmacokinetic parameters were similar to the initial results.

In a randomized, cross-over pharmacokinetic study, Nonacog alfa (BeneFIX) reconstituted in 0.234% sodium chloride diluent was shown to be pharmacokinetically equivalent to the previously marketed Nonacog alfa (BeneFIX) (reconstituted with Sterile Water for Injection) in 24 PTP patients (≥12 years) at a dose of 75 IU/kg. In addition, pharmacokinetic parameters were followed up in 23 of the same PTP after repeated administration of Nonacog alfa (BeneFIX) for six months and found to be unchanged compared with those obtained at the initial evaluation.

A summary of pharmacokinetic data are presented in Table 3:

Table 3: Pharmacokinetic Parameter Estimates for Nonacog alfa (BeneFIX) (75 IU/kg) at Baseline and Month 6 in Previously Treated Patients with Hemophilia B

Parameter	**Baseline n = 24 Mean ± SD**	**Month 6 n = 23 Mean ± SD**
C_{max} (IU/dL)	54.5 ± 15.0	57.3 ± 13.2
AUC_{∞} (IU·hr/dL)	940 ± 237	923 ± 205
$t_{1/2}$ (hr)	22.4 ± 5.3	23.8 ± 6.5
CL (mL/hr/kg)	8.47 ± 2.12	8.54 ± 2.04
Recovery (IU/dL/IU/kg)	0.73 ± 0.20	0.76 ± 0.18

Abbreviations: AUC_{∞} = area under the plasma concentration-time curve from time zero to infinity; C_{max} = peak concentration; $t_{1/2}$ = plasma elimination half-life; CL = clearance; SD = standard deviation.

5.3 Preclinical Safety Data

Carcinogenesis and Mutagenesis

Nonacog alfa (BeneFIX) has been shown to be nonmutagenic in the Ames assay and nonclastogenic in a chromosomal aberrations assay. No investigations on carcinogenesis or impairment of fertility have been conducted.

6.0 PHARMACEUTICAL PARTICULARS

6.1 Shelf-Life

Please see outer package for the expiry date.

6.2 Storage Conditions

Product as packaged for sale: Nonacog alfa (BeneFIX), Coagulation Factor IX (Recombinant), can be stored at room temperature or under refrigeration, at a temperature between 2°C to 8°C.

Freezing should be avoided to prevent damage to the diluent syringe.

Do not use Nonacog alfa (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.

6.3 Availability

Nonacog alfa (BeneFIX) Coagulation Factor IX (Recombinant), is supplied in single use vials which contain nominally 250, 500, 1000 and 2000 per vial, one pre-filled syringe of solvent (5 ml sterile 0.234% sodium chloride solution for injection for reconstitution) with one plunger rod, one sterile vial adapter reconstitution device, one sterile infusion set, and two (2) alcohol swabs, one plaster and one gauze pad. Actual factor IX activity in IU is stated on the label of each vial. Prior to use, the 250, 500, 1000 and 2000 IU per vial dosage forms are reconstituted in 5-mL of 0.234% sodium chloride solution. The reconstituted product contains approximately: 50, 100, 200, 300, 400 and 600 IU/mL Factor IX, respectively.

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

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

6.4 Special Precautions for Disposal and Other Handling

Reconstituted Solutions

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

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

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

Parenteral Products (for reconstitution before use)

Vial Size	Volume of Diluent to be Added to Vial	Nominal Concentration per mL
250 IU	5 mL	50 IU
500 IU	5 mL	100 IU
1000 IU	5 mL	200 IU
2000 IU	5 mL	400 IU
Reconstitute with 0.234% sodium chloride solution (USP)		

7.0 FDA REGISTRATION NUMBER

Nonacog alfa (BeneFIX) 250 IU Lyophilized Powder for Solution for Injection: BR-1427
Nonacog alfa (BeneFIX) 500 IU Lyophilized Powder for Solution for Injection: BR-1428
Nonacog alfa (BeneFIX) 1000 IU Lyophilized Powder for Solution for Injection: BR-1429
Nonacog alfa (BeneFIX) 2000 IU Lyophilized Powder for Solution for Injection: BR-1430

8.0 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Nonacog alfa (BeneFIX) 250 IU Lyophilized Powder for Solution for Injection: 08 November 2022
Nonacog alfa (BeneFIX) 500 IU Lyophilized Powder for Solution for Injection: 08 November 2022
Nonacog alfa (BeneFIX) 1000 IU Lyophilized Powder for Solution for Injection: 08 November 2022
Nonacog alfa (BeneFIX) 2000 IU Lyophilized Powder for Solution for Injection: 08 November 2022

Keep out of reach of children.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of any adverse drug reaction.

CAUTION: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Manufactured by:

BeneFIX Lyophilized Powder:
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