1. NAME OF THE MEDICINAL PRODUCT

BeneFIX 250 IU powder and solvent for solution for injection.
BeneFIX 500 IU powder and solvent for solution for injection.
BeneFIX 1000 IU powder and solvent for solution for injection.
BeneFIX 2000 IU powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BeneFIX 250 IU powder and solvent for solution for injection
Each vial contains nominally 250 IU nonacog alfa (recombinant coagulation factor IX). After reconstitution with the accompanying 5 ml (0.234%) sodium chloride solution for injection, each ml of the solution contains approximately 50 IU nonacog alfa.

BeneFIX 500 IU powder and solvent for solution for injection
Each vial contains nominally 500 IU nonacog alfa (recombinant coagulation factor IX). After reconstitution with the accompanying 5 ml (0.234%) sodium chloride solution for injection, each ml of the solution contains approximately 100 IU nonacog alfa.

BeneFIX 1000 IU powder and solvent for solution for injection
Each vial contains nominally 1000 IU nonacog alfa (recombinant coagulation factor IX). After reconstitution with the accompanying 5 ml (0.234%) sodium chloride solution for injection, each ml of the solution contains approximately 200 IU nonacog alfa.

BeneFIX 2000 IU powder and solvent for solution for injection
Each vial contains nominally 2000 IU nonacog alfa (recombinant coagulation factor IX). After reconstitution with the accompanying 5 ml (0.234%) sodium chloride solution for injection, each ml of the solution contains approximately 400 IU nonacog alfa.

Excipients

For a full list of excipients, see section 6.1 **List of Excipients**.

3. PHARMACEUTICAL FORM

White/almost white powder and clear and colorless solvent for solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Treatment and prophylaxis of bleeding in patients with hemophilia B (congenital factor IX deficiency).

4.2 Posology and method of administration

Dosage

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

Treatment with all factor IX products, including BeneFIX, requires individualized dosage adjustment. The dosage and duration of treatment for all factor IX products depends on the severity of the factor IX deficiency, the location and extent of bleeding, and the patient's clinical condition. Dosing of 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.

The number of units of factor IX administered is expressed in International Units (IU), which are related to the current WHO standard for factor IX products. Factor IX activity in plasma is expressed either as a percentage (relative to normal human plasma) or in International Units (relative to an international standard for factor IX in plasma). One International Unit (IU) of factor IX activity is equivalent to that quantity of factor IX in one ml of normal human plasma. Estimation of the required dose of BeneFIX can be based on the finding that one unit of factor IX activity per kg body weight is expected to increase the circulating level of factor IX, an average of 0.8 IU/dL (range from 0.4 to 1.4 IU/dL) in adult patients (≥15 years). Pharmacokinetics have to be assessed regularly in each patient and posology has to be adjusted accordingly.

Number of factor IX IU required	=	body weight (kg)	x	desired factor IX increase (%) or (IU/dL)	x	reciprocal of observed recovery

Use in Adults

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 (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)	x	desired factor IX increase (%) or (IU/dL)	x	1.2 IU/kg

Dosage for Bleeding Episodes and Surgery

In the case of the hemorrhagic events listed in the table below, the factor IX activity should not fall below the given plasma activity levels (in % of normal or in IU/dL) in the corresponding period.

Degree of hemorrhage/Type of surgical procedure	Factor IX level required (%) or (IU/dL)	Frequency of doses (hours)/Duration of Therapy (days)
Hemorrhage		
Early hemarthrosis, muscle bleeding or oral bleeding	20 – 40	Repeat every 24 hours. At least 1 day, until the bleeding episode as indicated by pain is resolved or healing is achieved.
More extensive hemarthrosis, muscle bleeding or hematoma	30 – 60	Repeat infusion every 24 hours for 3 --4 days or more until pain and acute disability are resolved.
Life-threatening hemorrhages	60 – 100	Repeat infusion every 8 to 24 hours until threat is resolved.
Surgery		
Minor: Including tooth extraction	30 – 60	Every 24 hours, at least 1 day, until healing is achieved.
Major	80 – 100 (pre- and post-operative)	Repeat infusion every 8 – 24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a factor IX activity of 30% to 60% (IU/dL).

Dosage for Prophylaxis

For long-term prophylaxis against bleeding in patients with severe hemophilia B, 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 to 4 days. In younger patients, shorter dosage intervals or higher doses may be necessary.

Once-weekly 100 IU/kg Dosing Regimen

In PTPs with hemophilia B (FIX:C≤2%), BeneFIX had been administered as 100 IU/kg once weekly in clinical trials. There was limited data to demonstrate that the factor IX activity level could be maintained at >1% throughout the dosing interval (see section 5.1 **Pharmacodynamic properties**). Close monitoring of the trough concentrations and/or presence of breakthrough bleeds should be undertaken and the dosing regimen (dose or frequency) should be adjusted accordingly.

Use in Pediatric

There are insufficient data to recommend the use of BeneFIX in children less than 6 years of age. In clinical studies, 57% of the pediatric patients increased their doses due to lower than expected recovery or to obtain sufficient therapeutic response or both, some to an average dose of >50 IU/kg. Therefore, close monitoring of factor IX plasma activity should be performed, as well as calculation of pharmacokinetic parameters, such as recovery and half-life, as clinically indicated, in order to adjust doses as appropriate. If doses >100 IU/kg have been repeatedly needed during routine prophylaxis or treatment, a switch to another FIX product should be considered.

Patients should be monitored for the development of factor IX inhibitors. If the expected factor IX activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, biological testing should be performed to determine if a factor IX inhibitor is present.

In patients with high levels of inhibitor factor IX therapy may not be effective and other therapeutic options must be considered. Management of such patients should be directed by physicians with experience in the care of patients with hemophilia. See also section 4.4 **Special warnings and precautions for use**.

Use in Elderly

Clinical studies of BeneFIX did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. As with any patient receiving BeneFIX, dose selection for an elderly patient should be individualized.

Method of Administration

BeneFIX is administered intravenously after reconstitution of the lyophilized powder for solution for injection with the supplied diluent (see section 6.6 **Special precautions for disposal and other handling**). It should be injected over several minutes. The rate of administration should be determined by the patient's comfort level.

Reconstituted BeneFIX should not be administered in the same tubing or container with other medicinal products.

Following completion of BeneFIX treatment, remove the infusion set and discard. Dispose of all unused solution, empty vial(s), and used needles and syringes in an appropriate container for throwing away waste that might hurt others if not handled properly.

The safety and efficacy of administration by continuous infusion have not been established. See also section 4.4 **Special warnings and precautions for use** and section 4.8 **Undesirable effects**.

BeneFIX, when reconstituted, contains polysorbate-80, which is known to increase the rate of di-(2-ethylhexyl) phthalate (DEHP) extraction from polyvinyl chloride (PVC). This should be considered during the preparation and administration of BeneFIX, including storage time elapsed in a PVC container following reconstitution. It is important that the recommendations in section 4.2 **Posology and method of administration** be followed closely.

BeneFIX should be administered using the infusion set provided in the 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.

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

Note: Agglutination of red blood cells in the tubing/syringe has been reported with the administration of BeneFIX. No adverse events have been reported in association with this observation. To minimize the possibility of agglutination, it is important to limit the amount of blood entering the tubing. Blood should not enter the syringe. If red blood cell agglutination is observed in the tubing or syringe, discard all material (tubing, syringe and BeneFIX solution) and resume administration with a new package.

Reconstitution

Always wash your hands before performing the following procedures. Aseptic technique (meaning clean and germ-free) should be used during the reconstitution procedure. All components used in the reconstitution and administration of this product should be used as soon as possible after opening their sterile containers to minimize unnecessary exposure to the atmosphere.

BeneFIX is administered by IV infusion after reconstitution with the supplied diluent (0.234% sodium chloride diluent) in the pre-filled syringe.

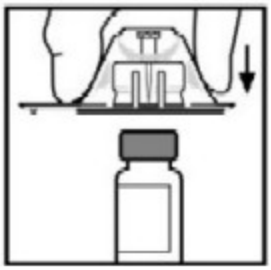
1. Allow the vial of lyophilized BeneFIX and the pre-filled diluent syringe to reach room temperature.

2. Remove the plastic flip-top cap from the BeneFIX vial to expose the central portions of the rubber stopper.

3. Wipe the top of the vial with the alcohol swab provided, or use another antiseptic solution, and allow to dry. After cleaning, do not touch the rubber stopper with your hand or allow it to touch any surface.

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

5. Place the vial on a flat surface. While holding the adapter in the package, place the vial adapter over the vial. Press down firmly on the package until the adapter snaps into place on the top of the vial, with the adapter spike penetrating the vial stopper. Leave the adapter package in place.



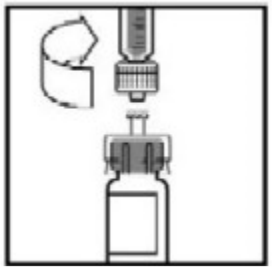
6. Grasp the plunger rod as shown in the diagram. Avoid contact with the shaft of the plunger rod. Attach the threaded end of the plunger rod to the diluent syringe plunger by pushing and turning firmly.

7. Remove the tamper-resistant, plastic-tip cap from the diluent syringe by bending the cap up and down to break the perforation. Do not touch the inside of the cap or the syringe tip.

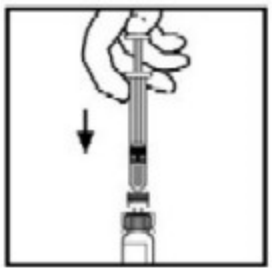
Place the cap on its side on a clean surface in a spot where it would be least likely to become environmentally contaminated.

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

9. Place the vial on a flat surface. Connect the diluent syringe to the vial adapter by inserting the tip into the adapter opening while firmly pushing and turning the syringe clockwise until the connection is secured.



10. Slowly depress the plunger rod to inject all the diluent into the BeneFIX vial.

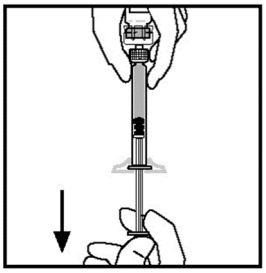


11. Without removing the syringe, gently swirl the contents of the vial until the powder is dissolved.

12. Inspect the final solution for specks before administration. The solution should appear clear and colorless.

    Note: If you use more than one vial of BeneFIX per infusion, reconstitute each vial by following the previous instructions.

13. Ensuring that the syringe plunger rod is still fully depressed, invert the vial. Slowly draw the solution into the syringe.



Note: If you prepared more than one vial of BeneFIX, remove the diluent syringe from the vial adapter, leaving the vial adapter attached to the vial. Quickly attach a separate large luer lock syringe and draw back the reconstituted contents as instructed above. Repeat this procedure with each vial in turn. Do not detach the diluent syringes or the large luer lock syringe until you are ready to attach the large luer lock syringe to the next vial adapter.

14. Detach the syringe from the vial adapter by gently pulling and turning the syringe counterclockwise. Discard the vial with the adapter attached.

    Note: If the solution is not to be used immediately, the syringe cap should be carefully replaced. Do not touch the syringe tip or the inside of the cap.

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

4.3 Contraindications

BeneFIX may be contraindicated in patients with a known history of hypersensitivity to any of the constituents of the preparation or in patients with a known history of hypersensitivity to hamster proteins.

4.4 Special warnings and precautions for use

Hypersensitivity

Allergic type hypersensitivity reactions, including anaphylaxis, have been reported for all factor IX products, including BeneFIX. Frequently, these events have occurred in close temporal association with the development of factor IX inhibitors. Patients should be informed of the early symptoms and signs of hypersensitivity reactions, including hives, generalized urticaria, 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 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 BeneFIX for immune tolerance induction have not been established.

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

Activity-neutralizing Antibodies (inhibitors)

Inhibitors have been detected in patients receiving factor IX-containing products. As with all factor IX products, patients using BeneFIX should be monitored for the development of factor IX inhibitors. Patients with factor IX inhibitors may be at an increased risk of anaphylaxis upon subsequent challenge with factor IX. 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 administrations (approximately 10-20) of factor IX should be performed under medical supervision where proper medical care for allergic reactions could be provided.

Thrombosis

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 BeneFIX contains no coagulation factor other than factor IX, the potential risk of thrombosis and DIC observed with other products containing factor IX should be recognized. Because of the potential risk of thromboembolic complications, caution should be exercised when administering this product to patients with liver disease, to patients post-operatively, to neonates, or to patients at risk of thromboembolic phenomena or DIC.

In each of these situations, the benefit of treatment with BeneFIX should be weighed against the risk of these complications.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

Drug/Laboratory Test Interactions

Temporary correction of abnormal partial thromboplastin time (PTT) was observed; no effect on normal PTT was seen.

4.6 Pregnancy and lactation

Pregnancy

Animal reproduction and lactation studies have not been conducted with BeneFIX. There is insufficient experience with the use of factor IX products in pregnant women. Therefore, factor IX should be administered to pregnant women only if clearly indicated.

Lactation

There is insufficient experience with the use of factor IX products in lactating women. Therefore, factor IX should be administered to 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, BeneFIX has no or negligible influence on the ability to drive or use machines.

4.8 Undesirable effects

The table below lists adverse reactions reported in the clinical trials of previously treated patients and previously untreated patients and identified in post-marketing use. The frequencies are based on all causality treatment emergent events in pooled clinical trials with 287 subjects.

Table 1: Adverse Reactions Table

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1000 to <1/100	Frequency Not Known (cannot be estimated from available data)
Infections and infestations			Infusion-site cellulitis[k]	
Blood and lymphatic system disorders		Factor IX inhibition[c]		
Immune system disorders		Hypersensitivity[d]		Anaphylactic reaction[o]
Nervous system disorders	Headache[a]	Dizziness; dysgeusia	Somnolence; tremor	
Eye disorders			Visual impairment[l]	
Cardiac disorders			Tachycardia[m]	
Vascular disorders		Phlebitis; hypotension[e]; flushing[f]		Superior vena cava syndrome[o,p]; deep vein thrombosis[o;] thrombosis[o]; thrombophlebitis[o]
Respiratory, thoracic and mediastinal disorders	Cough[b]		Respiratory distress	
Gastrointestinal disorders	Vomiting	Nausea		
Skin and subcutaneous disorders		Rash[g]; urticaria		
Renal and urinary disorders			Renal infarct[n]	

Table 1: Adverse Reactions Table

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1000 to <1/100	Frequency Not Known (cannot be estimated from available data)
General disorders and administration site conditions	Pyrexia	Chest discomfort[h]; infusion-site reaction[j]; infusion-site pain[i]	Chills	Inadequate therapeutic response[o]
Investigations				Inadequate factor IX recovery[o,q]

[a] including migraine, sinus headache.
[b] including productive cough.
[c] low-titer transient inhibitor formation and high-titer inhibitor formation.
[d] including drug hypersensitivity, angioedema, bronchospasm, wheezing, dyspnea, and laryngospasm.
[e] including blood pressure decreased.
[f] including hot flush, feeling hot, skin warm.
[g] including rash macular, rash papular, rash maculopapular.
[h] including chest pain and chest tightness.
[i] including infusion-site pruritus, infusion-site erythema.
[j] including injection site pain, infusion-site discomfort.
[k] including cellulitis.
[l] including scintillating scotoma and blurred vision.
[m] including heart rate increased, sinus tachycardia.
[n] developed in a hepatitis C antibody-positive patient 12 days after a dose of BeneFIX for a bleeding episode.
[o] ADR identified in post-marketing.
[p] superior vena cava (SVC) syndrome in critically ill neonates, while receiving continuous-infusion of BeneFIX through a central venous catheter.
[q] This is a verbatim term. No MedDRA 17.1 PT was retrieved.

If any suspected hypersensitivity reaction takes place that is thought to be related to the administration of BeneFIX, see sections 4.2 **Posology and method of administration** and 4.4 **Special warnings and precautions for use**.

Inhibitor development

Patients with hemophilia B may develop neutralizing antibodies (inhibitors).

A clinically relevant, low-responding transient inhibitor (maximum titer 1.5 BU) was detected in 1 out of 65 BeneFIX patients (including 9 patients participating only in the surgery study) who had previously received plasma-derived products (PTPs). This patient was able to continue treatment with BeneFIX with no anamnestic rise in inhibitor or anaphylaxis.

From results of the PUP study, 2/63 patients developed inhibitors after 7 and 15 exposure days. Both were high-titer inhibitors. Both patients experienced allergic manifestations in temporal association with their inhibitor development.

4.9 Overdose

No symptoms of overdose have been reported with recombinant coagulation factor IX products.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihemorrhagic Blood Coagulation Factor IX;

ATC code: B02BD04

Mechanism of Action

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 activate factor IX. 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 is increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

Clinical Trials Data on Efficacy

In 4 clinical studies of BeneFIX, a total of 128 subjects (56 previously treated patients [PTPs], 9 subjects participating only in the surgical study, and 63 previously untreated patients [PUPs]) received more than 28 million IU administered over a period of up to 64 months. The studies included 121 HIV-negative and 7 HIV-positive subjects.

Fifty-six PTPs received approximately 20.9 million IU of BeneFIX in two clinical studies. The median number of exposure days was 83.5. These PTPs who were treated for bleeding episodes on an on-demand basis or for the prevention of bleeds were followed over a median interval of 24 months (range 1 to 29 months; mean 23.4 ± 5.34 months). Fifty-five of these PTPs received a median of 42.8 IU/kg (range 6.5 to 224.6 IU/kg; mean 46.6 ± 23.5 IU/kg) per infusion for bleeding episodes. All subjects were evaluable for efficacy. One subject discontinued the study after one month of treatment due to bleeding episodes that were difficult to control; he did not have a detectable inhibitor. The subject's dose had not been adequately titrated. The remaining 55 subjects were treated successfully. Bleeding episodes that were managed successfully included hemarthrosis and bleeding in soft tissue and muscle. Data concerning the severity of bleeding episodes were not reported. Eighty-eight percent of the total infusions administered for bleeding episodes were rated as providing an “excellent” or “good” response. Eighty-one percent of all bleeding episodes were managed with a single infusion of BeneFIX. One subject developed a low-titer, transient inhibitor (maximum titer 1.5 BU). This subject had previously received plasma-derived products without a history of inhibitor development. He was able to continue treatment with BeneFIX with no anamnestic rise in inhibitor or anaphylaxis; however, increased frequency of BeneFIX administration was required; subsequently, the subject's factor IX inhibitor and its effect on the half-life of BeneFIX resolved.

Forty-one of the subjects had measurements of fibrinopeptide A and prothrombin fragment 1 + 2 prior to infusion, 4 to 8 hours and then 24 hours following the infusion. Twenty-nine of the subjects

had elevations in fibrinopeptide A with a maximum value of 35.3 nmol/L (22 of the 29 subjects had elevated baseline values). Ten of the subjects had elevated prothrombin fragment 1 + 2 with a maximum value of 1.82 nmol/L (3 of the 10 subjects had elevated baseline values).

Prophylaxis

A total of 20 PTPs were treated with BeneFIX for secondary prophylaxis (the regular administration of FIX replacement therapy to prevent bleeding in patients who may have already demonstrated clinical evidence of hemophilic arthropathy or joint disease) at some regular interval during the study with a mean of 2.0 infusions per week. Nineteen subjects were administered BeneFIX for routine secondary prophylaxis (at least twice weekly) for a total of 345 patient-months with a median follow-up period of 24 months per subject. The average dose used by these 19 subjects was 40.3 IU/kg, ranging from 13 to 78 IU/kg. One additional subject was treated weekly, using an average dose of 33.3 IU/kg, over a period of 21 months. Ninety-three percent of the responses were rated as "excellent" or "effective". These 20 PTPs received a total of 2,985 infusions of BeneFIX for routine prophylaxis. Seven of these PTPs experienced a total of 26 spontaneous bleeding episodes within 48 hours after an infusion.

Once-weekly 100 IU/kg Dosing Regimen

In an open-label, two-period study, 25 patients (aged 12-54 years) with FIX:C≤2% were given on-demand treatment with BeneFIX for 6 months followed by routine prophylaxis with BeneFIX 100 IU/kg once weekly for 12 months. 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). There were 21 (84%) subjects who experienced spontaneous bleeds during the on-demand period while 13 (52%) subjects experienced spontaneous bleeds during the prophylaxis period. A total of 64 spontaneous bleeds occurred in the 13 subjects during the prophylaxis period and the majority (47 of 64 bleeds, 73.4%) occurred >72 hours from the previous prophylaxis infusion.

In an open-label, four-period, crossover study, patients aged 6-64 years were given BeneFIX in an on-demand manner for 4 months followed by random assignment to either prophylaxis with 50 IU/kg twice weekly, or 100 IU/kg once weekly. This was followed by a 2-month on-demand period, after which the patients crossed over to the alternate prophylaxis treatment for 4 months. Forty-three patients had ABR data for 50 IU/kg twice weekly and 44 patients had data for 100 IU/kg once weekly. The ABRs for both prophylaxis periods were significantly lower ($p<0.0001$) than the ABR for the on-demand period (adjusted mean 35.1). There were 35 bleeding episodes reported during the 50 IU/kg twice-weekly treatment period and the adjusted mean ABR was 2.6. Of the 35 observed bleeds, 29 occurred in the first 72 hours after a prophylaxis dose. In contrast, 52 bleeding episodes were reported during the 100 IU/kg once-weekly treatment period and the adjusted mean ABR was 4.6. Of the 52 observed bleeds, 12 occurred in the first 72 hours and 40 occurred during 72-168 hours after BeneFIX administration.

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

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

Total BeneFIX coverage during the surgical period for the major procedures ranged from 4,230 to 385,800 IU. The pre-operative dose for the major procedures ranged from 75 to 155 IU/kg. Nine of the major surgical procedures were performed in 8 subjects using a continuous infusion regimen. Following pre-operative bolus doses (94.1-144.5 IU/kg), continuous infusion of BeneFIX was administered at a median rate of 6.7 IU/kg/hr (range of average rates: 4.3-8.6 IU/kg/hr; mean 6.4 ± 1.5 IU/kg/hr) for a median duration of 5 days (range 1-11 days; mean 4.9 ± 3.1). Six of the 8 subjects who had received continuous infusion of BeneFIX in conjunction with major surgeries were switched over to intermittent pulse regimens at a median dose of 56.3 IU/kg (range 33.6-89.1 IU/kg; mean 57.8 ± 18.1 IU/kg SD) for a median of 3.5 exposure days (range 1-5 days, mean 3.3 ± 1.4 SD) during the post-operative period. Although circulating factor IX levels targeted to restore and maintain hemostasis were achieved with both pulse replacement and continuous infusion regimens, clinical trial experience with continuous infusion of BeneFIX for surgical prophylaxis in hemophilia B has been too limited to establish the safety and clinical efficacy of administration of the product by continuous infusion. Subjects administered BeneFIX by continuous infusion for surgical prophylaxis also received intermittent bolus infusions of the product.

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

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

Sixty-three PUPs received approximately 6.2 million IU of BeneFIX in an open-label safety and efficacy study over 89 median exposure days. These PUPs were followed over a median interval of 37 months (range 4 to 64 months; mean 38.1 ± 16.4 months). Fifty-four of these PUPs received a median dose of 62.7 IU/kg (range 8.2 to 292.0 IU/kg; mean 75.6 ± 42.5 IU/kg) per infusion for bleeding episodes. Data concerning the severity of bleeding episodes were not reported. Ninety-four percent of the infusions administered to initiate treatment of bleeding were rated as providing "excellent" or "good" response.

Seventy-five percent of all bleeding episodes were managed with a single infusion of BeneFIX. Three of these 54 subjects were not successfully treated, including one episode in a subject due to delayed time to infusion and insufficient dosing, and in 2 subjects due to inhibitor formation. One subject developed a high-titer inhibitor (maximum titer 42 BU) on exposure day 7. A second subject developed a high-titer inhibitor (maximum titer 18 BU) after 15 exposure days. Both subjects experienced allergic manifestations in temporal association with their inhibitor development.

Thirty-two PUPs administered BeneFIX for routine prophylaxis. Twenty-four PUPs administered BeneFIX at least twice weekly for a total of 2,587 infusions. The mean dose per infusion was 72.5 ± 37.1 IU/kg, and the mean duration of prophylaxis was 13.4 ± 8.2 months. Eight PUPs administered BeneFIX once weekly for a total of 571 infusions. The mean dose per infusion was 75.9 ± 17.9 IU/kg, and the mean duration of prophylaxis was 17.6 ± 7.4 months. Five PUPs experienced a total of 6 spontaneous bleeding episodes within 48 hours after an infusion.

Twenty-three PUPs received BeneFIX for surgical prophylaxis in 30 surgical procedures. All surgical procedures were minor, except 2 hernia repairs. The preoperative bolus dose ranged from 32.3 IU/kg to 247.2 IU/kg. The perioperative total dose ranged from 385 to 23,280 IU. Five of the surgical procedures were performed using a continuous infusion regimen over 3 to 5 days. Clinical

trial experience with continuous infusion of BeneFIX for surgical prophylaxis in hemophilia B has been too limited to establish the safety and clinical efficacy of administration of the product by continuous infusion.

5.2 Pharmacokinetic properties

A single infusion of BeneFIX in 56 PTP patients (baseline data) with hemophilia B has shown mean ± SD recovery values, determined by age, 0.78 ± 0.19 IU/dL/IU/kg (range 0.39 to 1.2 IU/dL per IU/kg) for those >15 years old (n=16), and 0.66 ± 0.16 IU/dL per IU/kg (range 0.44 to 0.92 IU/dL per IU/kg) for those ≤15 years old (n=7).

In a randomized, cross-over pharmacokinetic study, BeneFIX reconstituted in 0.234% sodium chloride diluent was shown to be pharmacokinetically equivalent to the previously marketed 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 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 2:

Table 2: Pharmacokinetic Parameter Estimates for 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.

A single-dose pharmacokinetic study reported a longer estimate of $t_{1/2}$ when sample collection to measure factor IX activity (FIX) was extended to 96 hours. A summary of pharmacokinetic data is presented in Table 3.

Table 3: Summary of Plasma FIX Activity Pharmacokinetic Parameter Values after Administration of Nonacog Alfa 50 IU/kg.

Parameter	Age group	
	<18 years (6 to <12 years) (n = 4)	⩾18 years (n = 8)
C_{max}, IU/dL	38.8 (26)	42.3 (16)
T_{max}, h	0.5 (0.25–3.0)	0.375 (0.25–3.0)
k_{el}, h^{-1}	0.02509 (16)	0.01781 (20)
$t_{½}$, h	27.9 ± 4.5	39.6 ± 7.4
AUC_{last}, IUh/dL	693 (18)	971 (15)
AUC_{inf}, IUh/dL	784 (16)	1166 (15)
MRT, h	35.8 (14)	51.0 (16)
CL, ml/h/kg	6.38 (16)	4.29 (15)
V_{ss}, ml/kg	228 (20)	219 (19)
Incremental recovery, (IU/dL)/(IU/kg)	0.78 (26)	0.82 (17)

Geometric mean (geometric percent coefficient of variation) applies to all results, except: median (range) for T_{max} and arithmetic mean ± SD for $t_{½}$. AUC_{last}, area under the plasma FIX activity–time profile from time 0 to the time of the last quantifiable FIX activity; AUC_{inf}, area under the plasma FIX activity– time

profile from time 0 extrapolated to infinity; CL, clearance; C_{max}, maximum observed FIX activity; FIX, factor IX; k_{el}, terminal phase rate constant; MRT, mean residence time; SD, standard deviation; $t_{½}$, terminal half-life; T_{max}, time to C_{max}; V_{ss}, steady-state volume of distribution.

5.3 Preclinical safety data

BeneFIX has been shown to be non-mutagenic in the Ames assay and non-clastogenic in a chromosomal aberrations assay. No investigations on carcinogenesis or impairment of fertility have been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Sucrose
Glycine
L-Histidine
Polysorbate 80

Solvent
Sodium chloride solution

6.2 Incompatibilities

In the absence of incompatibility studies, reconstituted BeneFIX must not be administered in the same tubing or container with other medicinal products. Only the provided infusion set should be used. Treatment failure can occur as a consequence of human coagulation factor IX adsorption to the internal surfaces of some infusion equipment.

6.3 Shelf-life

3 years

The reconstituted product should be used immediately, but no longer than 3 hours after reconstitution. Chemical and physical in-use stability has been demonstrated for 3 hours at temperatures up to 25°C.

6.4 Special precautions for storage

Store and transport refrigerated (2°C – 8°C). Freezing should be avoided to prevent damage to the prefilled diluent syringe.

For the purpose of ambulatory use, the product may be removed from refrigerated storage for one single period of storage at or below 30°C for up to 6 months within 36 months. At the end of this period, the product should not be put back in the refrigerator, but should be used or discarded.

6.5 Nature and contents of container

Powder in a 10 ml vial (type 1 glass) with a stopper (chlorobutyl) and a flip-off seal (aluminium) and 5 ml of solvent in a prefilled syringe (type 1 glass) with a plunger stopper (bromobutyl), a tip-cap (bromobutyl) and a sterile vial adapter reconstitution device, a sterile infusion set, two alcohol swabs, a plaster, and a gauze pad.

6.6 Special precautions for disposal and other handling

Reconstitute lyophilized BeneFIX powder for injection with the supplied diluent (0.234% sodium chloride solution) from the pre-filled syringe provided. Once the diluent has been injected into the vial, gently rotate the vial until all powder is dissolved. After reconstitution, the solution is drawn back into the syringe and infused.

The solution should be clear and colorless. The solution should be discarded if visible particulate matter or discoloration is observed. The product does not contain a preservative, and the reconstituted solution should be used within 3 hours after reconstitution.

All unused solution, empty vials and used needles and syringes must be discarded in accordance with local requirements.

7. PRODUCT OWNER

Pfizer Inc
New York,
United States

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