

BENEFIX® (NONACOG ALFA)

1. NAME OF THE MEDICINE

Nonacog alfa

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The potency (in international units, IU) is determined using an *in vitro* one-stage clotting assay against the World Health Organisation (WHO) International Standard for Factor IX concentrate. One IU is the amount of factor IX activity present in 1 mL of pooled, normal human plasma. The specific activity of BeneFIX is greater than or equal to 200 IU per milligram of protein. BeneFIX is not derived from human blood and contains no preservatives or added animal or human components. BeneFIX is inherently free from the risk of transmission of human blood-borne pathogens such as HIV, hepatitis viruses and parvovirus.

BeneFIX is formulated as a sterile, non-pyrogenic, lyophilised powder preparation. BeneFIX is intended for intravenous (IV) injection. It is available in single use vials containing the labelled amount of factor IX activity, expressed in IU. Each vial contains nominally 250, 500, 1000, 2000 IU of nonacog alfa.

For the full list of excipients, see **Section 6.1 List of excipients**.

3. PHARMACEUTICAL FORM

Sterile, lyophilised white powder for injection.

All dosage strengths yield a clear, colourless solution upon reconstitution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BeneFIX is indicated for the control and prevention of haemorrhagic episodes in patients with haemophilia B (congenital factor IX deficiency or Christmas disease), including control and prevention of bleeding in surgical settings.

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

4.2 Dose and method of administration

Dosage for Treatment

Treatment with BeneFIX should be initiated under the supervision of a physician

experienced in the treatment of haemophilia B. BeneFIX is for single use in one patient only.

If any suspected hypersensitivity 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 (see **Section 4.4 Special warnings and precautions for use**).

Treatment with all factor IX products, including BeneFIX, requires individualised 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, age and recovery of factor IX.

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 (see **Section 4.4 Special warnings and precautions for use**).

In an eleven patient crossover, randomised pharmacokinetic evaluation of BeneFIX and a single lot of high-purity plasma-derived factor IX, the recovery was lower for BeneFIX (see **Section 5.2 Pharmacokinetic properties**).

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 inhibitors, 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. The amount of BeneFIX to be infused, as well as the frequency of infusion, will vary with each patient and clinical situation.

BeneFIX may also be administered on a regular schedule (2-3 times per week). The initial treatment can be started with an approximate dose of 20-50 IU/kg. The required dose should be titrated for each patient taking the patient's pharmacokinetic data and clinical situation into consideration. For surgical interventions, precise monitoring of the factor IX replacement therapy using the factor IX activity assay is advised.

BeneFIX is administered by IV infusion over several minutes after reconstitution of the lyophilised powder with 0.234% sodium chloride solution.

Method of Calculating Dose

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

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

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

Patients ≥15 years

In patients ≥15 years, on average, one IU of BeneFIX per kilogram of body weight increased the circulating activity of factor IX by 0.8 ± 0.2 (ranged from 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:

$$\begin{array}{l} \text{Number of} \\ \text{factor IX IU} \\ \text{required} \\ \text{(IU)} \end{array} = \begin{array}{l} \text{Body weight} \\ \text{(kg)} \end{array} \times \begin{array}{l} \text{Desired factor IX} \\ \text{increase (\% or} \\ \text{IU/dL)} \end{array} \times 1.2 \text{ IU/kg per IU/dL}^*$$

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

Patients < 15 years

In patients < 15 years, on average, one IU of BeneFIX per kilogram of body weight increased the circulating activity of factor IX by 0.7 ± 0.3 (range 0.2 to 2.1) IU/dL. 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:

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

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

Dosage for Bleeding Episodes and Surgery

The following chart can be used to guide dosing in bleeding episodes and surgery. In the case of the haemorrhagic events listed in Table 1 below, the factor IX activity should not fall below the given plasma activity level (in % of normal or IU/dL) in the corresponding period.

Table 1: Dosing Guide for Control and Prevention of Bleeding Episodes and Surgery

Type of Haemorrhage	Circulating Factor IX activity required (%) [†]	Dosing Interval (hours)	Duration of Therapy (days)
Minor Uncomplicated haemarthroses, superficial muscular or soft tissue	20-30	12-24	1-2
Moderate Intramuscular or soft tissue with dissection, mucous membranes, dental extractions, haematuria	25-50	12-24	Treat until bleeding stops and healing begins: about 2-7 days
Major Pharynx, retropharynx, retroperitoneum, CNS, surgery	50-100	12-24	7-10

[†] (%=IU/dL) Source: Roberts HR, Eberst, ME. Current management of hemophilia B. *Hemat. Oncol. Clin. North Am.* 1993;7(6):1269-1280

Dosage for Prophylaxis

An appropriate dose for secondary prophylaxis has not been determined. In a clinical study of routine secondary prophylaxis in 19 previously treated patients (mean age 27.5 years, range 4 to 56 years) with moderate (1-5% FIX activity) or severe (<1% FIX activity) haemophilia B, the average dose was 40 IU/kg (range 13 to 78 IU/kg) twice weekly for an average of 18 months. Three patients did not experience haemorrhages, whereas the other 16 had an average of 13 haemorrhages each. In younger patients, shorter dosage intervals or higher doses may be necessary. See *Method of Calculating Dose* above.

Elderly Patients

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 individualised.

Patients with Inhibitors

The control of bleeding episodes in patients with high titre inhibitors, typically above 5 Bethesda Units may require an extensive factor IX infusion therapy, but might be impractical because of the very large dose needed to maintain adequate factor IX levels. If haemostasis cannot be achieved with factor IX in the presence of high titre inhibitors, the use of (activated) prothrombin complex concentrate (PCC) or activated factor VII preparation must be considered. These therapies should be directed by physicians with experience in the care of patients with haemophilia B.

Instructions for Use

Patients should follow the specific reconstitution and administration procedures provided by their physicians. Detailed instructions for preparation and administration of BeneFIX are contained in the patient insert provided in the pack.

Reconstitution

Reconstitute BeneFIX with the diluent supplied (0.234% sodium chloride solution) from the pre-filled syringe provided. Gently rotate the vial until all the powder is dissolved. After reconstitution, the solution is drawn back into the syringe. The solution should be clear and colourless. The solution should be discarded if visible particulate matter or discolouration is observed.

To reduce microbiological hazard, BeneFIX should be administered as soon as possible or within 3 hours after reconstitution. The reconstituted solution may be stored at room temperature prior to administration.

Administration (Intravenous injection)

BeneFIX, nonacog alfa, should be administered using the infusion set provided in the kit, and the pre-filled diluent syringe provided or a single sterile disposable plastic luer lock syringe. In addition, the solution should be withdrawn from the vial using the vial adapter. Attach the syringe to the luer end of the infusion set and perform venipuncture.

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 minimise the risk 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 this material (tubing, syringe and BeneFIX solution) and resume administration with a new package.

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

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 Dose and method of administration** be followed closely.

4.3

Contraindications

Because BeneFIX is produced in a Chinese hamster ovary cell line, it may be contraindicated in patients who have had a previous allergic reaction to hamster protein. BeneFIX may also be contraindicated in patients with a known history of hypersensitivity to any of the constituents of the preparation.

4.4 Special warnings and precautions for use

Use with caution in the following circumstances

Pharmacokinetic studies suggest that *in vivo* recovery with BeneFIX is significantly lower than that achieved with plasma derived factor IX products. Therefore, dosages are higher than those usually recommended with plasma derived products. Patients changing from a plasma derived product to BeneFIX should be aware of these differences when determining the recommended dose. Treatment should be commenced using the formulae outlined in the **4.2 Dose and method of administration** section and doses subsequently titrated using a factor IX activity assay.

In clinical trials with BeneFIX, the doses have been increased in several patients in order to achieve a therapeutic response, even in the absence of factor IX inhibitors. 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 (see **Section 4.2 Dose and method of administration**).

Thrombosis and disseminated intravascular coagulation

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 disseminated intravascular coagulation (DIC) observed with other products containing factor IX should be recognised. 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, to patients with signs of fibrinolysis, to patients at risk of thromboembolic phenomena or to patients with DIC.

The safety and efficacy of BeneFIX administration by continuous infusion have not been established (see **Section 4.8 Adverse effects (undesirable effects)**). 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.

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

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 (see **Section 5.1 Pharmacodynamic properties**). 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. The safety and efficacy of BeneFIX in patients with factor IX inhibitors has not been studied. However, BeneFIX may be considered in patients with factor IX inhibitor (neutralising antibody) less than 5 Bethesda Units, who continue to respond clinically with an increase in circulating factor IX provided that BeneFIX is given in a controlled medical setting with facility to manage anaphylactic reactions. BeneFIX should be given in the dosage regimen identified.

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

In a clinical study with the original formulation of BeneFIX, which is bioequivalent to the present formulation of BeneFIX, a low titre, transient inhibitor (maximum titre 1.5 BU) developed in 1 of 65 BeneFIX patients who had previously received plasma-derived products without a history of inhibitor development. This patient was able to continue treatment with BeneFIX with no anamnestic rise in inhibitor or anaphylaxis. Recovery and half-life returned to normal.

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

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, generalised urticaria, chills (rigors), flushing, angioedema, chest tightness,

laryngospasm, bronchospasm, dyspnoea, wheezing, faintness, hypotension, tachycardia, blurred vision and anaphylaxis. Patients should be advised to discontinue use of the product immediately and contact their physician and/or seek immediate emergency care, depending on the type/severity of the reaction if any of these symptoms occur. Patients experiencing allergic reactions should be evaluated for the presence of inhibitor.

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. If any suspected hypersensitivity 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, as dictated by the response of the patient.

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

Use in the elderly

See **Section 4.2 Dose and method of administration.**

Paediatric use

Safety and efficacy have been demonstrated in previously treated and previously untreated children (see **Section 4.2 Dose and method of administration, 4.8 Adverse effects (undesirable effects), 5 Pharmacological properties**).

Effects on laboratory tests

Temporary correction of partial thromboplastin time (PTT) was observed. No effect on normal prothrombin time was seen. In seven patients for whom fibrinopeptide A or prothrombin fragment 1+2 were measured pre-infusion, at 4 to 8 hours and then daily up to 96 hours, there was no significant increase in coagulation activation.

4.5 Interactions with other medicines and other forms of interactions

No formal drug interaction studies have been conducted with BeneFIX. No interactions of BeneFIX with other medicinal products are known.

For information regarding physiochemical incompatibilities see **Section 4.2 Dose and method of administration** and **Section 6.2 Incompatibilities**.

4.6 Fertility, pregnancy and lactation

Effects on fertility

No investigations on impairment of fertility have been conducted.

Use in pregnancy – Pregnancy Category B2

Animal reproduction studies have not been conducted with BeneFIX. It is not known whether BeneFIX can affect the course of pregnancy or cause foetal harm when given to pregnant women. BeneFIX should be administered to pregnant women only if clearly indicated.

Use in lactation

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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. On the basis of the pharmacodynamic and pharmacokinetic profile and reported adverse reactions BeneFIX is unlikely to influence the ability to drive or use machines.

4.8 Adverse effects (undesirable effects)

The following adverse events, reported from clinical trials, with current BeneFIX and the original formulation, directly related or possibly related to therapy, are presented below by system organ class and frequency of occurrence per infusion and were recorded with a frequency less than 1%.

Uncommon $\geq 1/1,000$ and $< 1/100$ ($\geq 0.1\%$ and $< 1\%$)

Rare $\geq 1/10,000$ and $< 1/1,000$ ($\geq 0.01\%$ and $< 0.1\%$)

Immune System Disorders - *Rare*: hypersensitivity/allergic reactions (including, but not limited to hives, generalised urticaria, chills, flushing, angioedema, chest tightness, laryngospasm, bronchospasm, dyspnoea, wheezing, faintness, hypotension, tachycardia, blurred vision, anaphylaxis), anaphylaxis.

Gastrointestinal Disorders - *Uncommon*: nausea, dysgeusia. *Rare*: diarrhoea, vomiting.

Cardiac Disorders - Rare: tachycardia.

Vascular Disorders – Rare: phlebitis, hypotension, flushing.

Nervous System Disorders - Uncommon: dizziness, headache. *Rare:* burning sensation in jaw and skull, dizziness, drowsiness, teichopsia.

Respiratory, Thoracic and Mediastinal Disorders - Uncommon: cough with hypoxaemia. *Rare:* dry cough/sneeze, respiratory distress, chest tightness.

Skin and Subcutaneous Tissue Disorders - Rare: hives, rash, infusion site cellulitis, angioedema.

General Disorders and Administration Site Conditions - Uncommon: infusion site discomfort. *Rare:* allergic rhinitis, lethargy, pyrexia.

Post-marketing experience

The following post-marketing adverse reactions have been reported for BeneFIX: inadequate factor IX recovery, inadequate therapeutic response, inhibitor development (see **Section 4.4 Special warnings and precautions for use**), anaphylaxis, dyspnoea, hypotension, thrombosis, tremor, somnolence, injection site reaction (including infusion site pruritis, infusion site erythema), infusion site pain (including infusion site irritation) and renal infarct.

The renal infarct developed in a hepatitis C antibody-positive patient 12 days after a dose of BeneFIX for a bleeding episode. The relationship of the infarct to the prior administration of BeneFIX is uncertain.

The safety and efficacy of BeneFIX administration by continuous infusion have not been established (see **Section 4.4 Special warnings and precautions for use**). 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. Cases of peripheral thrombophlebitis, thrombosis and deep vein thrombosis (DVT) have also been reported. In some, BeneFIX was administered via continuous infusion, which is not an approved method of administration.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product.

4.9 Overdose

No symptoms of overdose have been reported with recombinant coagulation factor IX products. In case of accidental overdosage, the development of thrombotic complications or DIC is enhanced in patients at risk for these complications. Therefore, surveillance should be carried out to detect the first signs of thrombosis and consumptive coagulopathy complications.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

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 haemophilia B and in patients with acquired factor IX deficiencies. The administration of BeneFIX increases plasma levels of factor IX and can temporarily correct the coagulation defect in these patients.

Clinical trials

The efficacy of BeneFIX was assessed in 20 patients with moderately severe to severe haemophilia B (FIX:C 2% of normal) previously treated with FIX. All patients were male and their median age was 22 years (range 12-61 years). Patients were without FIX inhibitor (<0.6 Bethesda Units) and not actively bleeding.

Fifteen patients received BeneFIX on-demand, 11 whilst also receiving routine prophylactic BeneFIX. The median dose per infusion was 87 IU/kg (range 30-147 IU/kg) and the median number of infusions per patient was 5 (range 1-27). Six of the 15 followed an on-demand regimen (2 later switching to routine prophylaxis). The 6 on-demand patients were observed for a median of 18 weeks (range 0.1-51 weeks) and had 69 bleeds. The bleeding rate was 21.8 bleeds per year, made up of 11.4 injury-related bleeds and 10.4 spontaneous bleeds per year.

Overall 17 patients received routine BeneFIX prophylaxis and 3 received intermittent prophylaxis. The median dose per infusion was 52 IU/kg (range 14-184 IU/kg) and the median number of infusions per patient 38 (range 15-67). Of those on routine prophylaxis, three patients received BeneFIX once weekly, 10 patients twice weekly and four patients more than twice weekly. The median duration of prophylaxis was 25 weeks (range 9-40 weeks). Eleven of the 17 patients (65%) did not have a spontaneous bleed whilst on prophylaxis. The other six patients had 26 bleeds. The bleeding rate for the 17 patients was 3.1 bleeds per year, made up of 2.3 injury-related bleeds and 0.8 spontaneous (plus one uncategorised) bleeds per year.

Of the 95 bleeds in the 20 patients, 81% resolved with one infusion of BeneFIX and 93% with one to two infusions. Response was rated excellent or good for 85% of infusions. The majority of bleeds were in joints (51%) or muscle/soft tissue (38%).

After one month's BeneFIX treatment, efficacy was rated very useful in 15 of 20 patients (75%), useful in 4 (20%) and slightly useful in 1 (5%). After 6 months, it was rated very useful in 80% and useful in 20%.

One patient, with a history of septic arthritis, had a surgical procedure, left knee wash.

This patient had 37 infusions of BeneFIX and no bleeding episodes. The median dose per infusion was 35 IU/kg (range 25-58 IU/kg). The efficacy of BeneFIX was rated as useful in this patient.

In clinical studies of the original formulation of BeneFIX, which is bioequivalent to the current formulation, involving a total of 128 patients (56 previously treated patients [PTPs], 63 previously untreated patients [PUPs], and the 9 patients participating only in the surgical study), more than 20 million IU were administered over a period of up to 24 months. This includes 121 HIV-negative and 7 HIV-positive patients. Fifty five previously treated 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 include haemarthroses and bleeding in soft tissue and muscle.

In a study of 28 haemophilia B patients undergoing 36 surgical procedures including liver transplantation, splenectomy, inguinal hernia repair, orthopaedic procedures, calf debridement and complicated dental extraction, the original formulation of BeneFIX, which is bioequivalent to the current formulation, was successful in maintaining haemostasis without clinical evidence of thrombotic complications.

The previous formulation was also studied in 63 previously untreated children aged 0-14 years with haemophilia B. Fifty four children received BeneFIX on demand for haemorrhage, mostly soft tissue and muscle haemorrhage and haemarthrosis. The median dose per infusion was 63 IU/kg and median exposure 19 days. Response was excellent or good in 94% of subjects. Seventy five percent of bleeding episodes resolved with one BeneFIX infusion. Thirty two children received BeneFIX for prophylaxis of bleeding at a mean dose per infusion of 73 IU/kg for a mean duration of 14 months and 98% had an excellent or effective response. The majority of patients (75%) received more than one infusion per week. Twenty three children received BeneFIX for prophylaxis of surgical bleeding, at a median dose of 70 IU/kg for 4 days and 97% had an excellent or good response.

5.2 Pharmacokinetic properties

A randomised cross-over study was performed using a single 75 IU/kg intravenous infusion over 10 minutes in 24 patients with moderately severe to severe haemophilia B (FIX:C 2% of normal) previously treated with coagulation factor IX (FIX) to compare the current formulation of BeneFIX to the original formulation. All patients were male and their median age was 21 years (range 12-61 years). Patients were without FIX inhibitor (<0.6 Bethesda Units) and not actively bleeding. The pharmacokinetic results demonstrated the bioequivalence of the current formulation to the original formulation. The pharmacokinetic characteristics of BeneFIX were also assessed in 23 of these patients. The mean increase in circulating FIX activity was 0.72 IU/dL per IU/kg infused (range 0.39, 1.24) and the mean plasma FIX half-life 22 h (range 13, 35). With repeated dosing over 6 months, the mean increase in circulating FIX activity after a single 75 IU/kg intravenous infusion was 0.76 IU/dL per IU/kg infused (range 0.44, 1.09) and the mean plasma FIX half-life 24 h (range 15, 48).

In a study of 19 children aged 4 to 15 years with the original formulation of BeneFIX, the mean increase in circulating FIX activity was 0.7 IU/dL per IU/kg infused (range

0.2, 2.1) and the mean plasma FIX half-life 20 h (range 14, 28).

In another randomised, cross-over study with the original formulation, the *in vivo* recovery of FIX using BeneFIX was statistically significantly lower by 28% than the recovery using a highly purified plasma-derived FIX product (pdFIX). There was no significant difference in plasma FIX half-life. Structural differences in the recombinant FIX molecule compared with pdFIX contribute to lower recovery of FIX from BeneFIX compared to pdFIX.

5.3 Preclinical safety data

Genotoxicity

BeneFIX has been shown to be nonmutagenic in the Ames assay and nonclastogenic in a chromosomal aberrations assay.

Carcinogenicity

No investigations on carcinogenicity have been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

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 (See **Section 4.2 Dose and method of administration**).

6.3 Shelf life

Please refer to carton for shelf life.

6.4 Special precautions for storage

Product as packaged for sale

BeneFIX should be stored under refrigeration at a temperature of 2°C to 8°C. Prior to the expiration date, BeneFIX may also be stored at room temperature not to exceed 30°C for up to 6 months. The patient should make note of the date the product was placed at room temperature in the space provided on the outer carton. Freezing should be avoided to prevent damage to the diluent syringe. Do not use BeneFIX after the expiry date on the label.

Product after reconstitution

BeneFIX does not contain a preservative. To reduce the possibility of microbiological hazard from environmental contamination, the reconstituted solution should be used as soon as possible after reconstitution or within 3 hours after reconstitution.

6.5 Nature and contents of container

BeneFIX 250 IU/vial, 500 IU/vial, 1000 IU/vial, 2000 IU/vial.

BeneFIX, nonacog alfa, is supplied in single use vials which contain nominally 250, 500, 1000 or 2000 IU per vial and a pre-filled diluent syringe containing 0.234% sodium chloride solution. The BeneFIX kit also contains a sterile infusion set, a sterile vial adapter, a sticking plaster, a sterile gauze pad and two (2) alcohol swabs. Actual factor IX activity in IU is stated on the label of each vial.

The container-closure system consists of a 10 mL USP Type I glass vial, a 20 mm OD rubber closure and a 20 mm diameter flip-off crimp seal.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Dispose of all unused solution, empty vials, used needles and syringes in a sharps bin. Any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure

BeneFIX, nonacog alfa is a purified protein produced by recombinant DNA technology for use in therapy of factor IX deficiency, known as haemophilia B or Christmas disease. Nonacog alfa is a glycoprotein with an approximate molecular mass of 55,000 Da consisting of 415 amino acids in a single chain. It has a primary amino acid sequence that is identical to the Ala 148 allelic form of plasma-derived factor IX, and has structural and functional characteristics similar to those of endogenous factor IX.

BeneFIX is produced by a genetically engineered Chinese hamster ovary (CHO) cell line that is extensively characterised and shown to be free of infectious agents. The stored cell banks are free of blood or plasma products. The CHO cell line secretes recombinant factor IX into a defined cell culture medium that does not contain any proteins derived from animal or human sources and the recombinant factor IX is purified by a chromatography purification process that does not require a monoclonal antibody step and yields a high-purity, active product. A membrane filtration step that has the ability to retain molecules with apparent molecular weights >70,000 (such as large proteins and viral particles) is included for additional viral safety. BeneFIX is predominantly a single component by SDS-polyacrylamide gel electrophoresis evaluation.

Pfizer Corporation Hong Kong Limited
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