

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

BeneFIX 500 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 1500 IU powder and solvent for solution for injection
BeneFIX 2000 IU powder and solvent for solution for injection
BeneFIX 3000 IU powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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 1500 IU powder and solvent for solution for injection

Each vial contains nominally 1500 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 300 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.

BeneFIX 3000 IU powder and solvent for solution for injection

Each vial contains nominally 3000 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 600 IU nonacog alfa.

The potency (IU) is determined using the European Pharmacopoeia one-stage clotting assay. The specific activity of BeneFIX is not less than 200 IU/mg protein.

BeneFIX contains recombinant coagulation factor IX, (INN = nonacog alfa). Nonacog alfa is a purified protein that has 415 amino acids in a single chain. It has a primary amino acid sequence that is comparable to the Ala¹⁴⁸ allelic form of plasma-derived factor IX, and some post-translational modifications of the recombinant molecule are different from those of the plasma-derived

molecule.

Recombinant coagulation factor IX is a glycoprotein that is secreted by genetically engineered mammalian cells derived from a Chinese hamster ovary (CHO) cell line.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

BeneFIX 500 IU, 1000 IU, 1500 IU, 2000 IU, 3000 IU powder and solvent for solution for injection

Powder and solvent for solution for injection

White/almost white powder and clear and colourless solvent.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

BeneFIX can be used for all age groups.

4.2 Posology and method of administration

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

Treatment monitoring

During the course of treatment, appropriate determination of factor IX levels is advised to guide the dose to be administered and the frequency of repeated infusions. Individual patients may vary in their response to factor IX, demonstrating different half-lives and recoveries. Dose based on body weight may require adjustment in underweight or overweight patients. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor IX activity) is indispensable.

When using an in vitro thromboplastin time (aPTT)-based one-stage clotting assay for determining factor IX activity in a patient's blood samples, plasma factor IX activity results can be significantly affected by both the type of aPTT reagent and the reference standard used in the assay. This is of importance, particularly when changing the laboratory and/or reagents used in the assay.

Posology

The dose and duration of the substitution therapy depend on the severity of the factor IX deficiency, the location and extent of bleeding, and on the patient's clinical condition.

The number of units of factor IX administered is expressed in International Units (IU), which is 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.

On-demand treatment

The calculation 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 patients \geq 12 years (further information in section 5.2).

The required dose is determined using the following formula:

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

Example: For a recovery of 0.8 IU/dL, the formula reads:
 In the case of the following haemorrhagic events, the factor IX activity should not fall below the given plasma activity levels (in % of normal or in IU/dL) in the corresponding period. The following table can be used to guide dosing in bleeding episodes and surgery:

Degree of haemorrhage/Type of surgical procedure	Factor IX level required (%) or (IU/dL)	Frequency of doses (hours)/Duration of Therapy (days)
Haemorrhage		
Early haemarthrosis, 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 haemarthrosis, muscle bleeding or haematoma	30-60	Repeat infusion every 24 hours for 3-4 days or more until pain and acute disability are resolved.
Life-threatening haemorrhages	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 postoperative)	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)

Prophylaxis

BeneFIX may be administered for long term prophylaxis against bleeding in patients with severe haemophilia B. In a clinical study for routine secondary prophylaxis the average dose for previously treated patients (PTP) was 40 IU/kg (range 13 to 78 IU/kg) at intervals of 3 to 4 days.

In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

Paediatric population

There is limited documentation of on-demand treatment and surgery in paediatric patients less than 6 years of age treated with BeneFIX.

Mean dosage (□ standard deviation) for prophylaxis was 63.7 (□ 19.1) IU/kg at intervals of 3 to 7 days. In younger patients, shorter dosage intervals or higher doses may be necessary. FIX

consumption for routine prophylaxis in 22 evaluable patients was 4607 (□ 1849) IU/kg per year and 378 (□ 152) IU/kg per month.

Close monitoring of factor IX plasma activity should be performed as clinically indicated, as well as calculation of pharmacokinetic parameters such as recovery and half-life, in order to adjust doses as appropriate.

Hypersensitivity

Allergic-type hypersensitivity reactions are possible with BeneFIX. The product contains traces of hamster proteins. Potentially life-threatening anaphylactic/anaphylactoid reactions have occurred with factor IX products, including BeneFIX. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal product immediately and contact their physician. Patients should be informed of early signs of hypersensitivity reactions including difficult breathing, shortness of breath, swelling, hives, generalised urticaria, itching, tightness of the chest, bronchospasm, laryngospasm, wheezing, hypotension, blurred vision, and anaphylaxis.

In some cases, these reactions have progressed to severe anaphylaxis. In the case of shock, the current medical standards for treatment of shock should be observed. In case of severe allergic reactions, alternative haemostatic measures should be considered.

Inhibitors

Inhibitors are an uncommon event in previously treated patients (PTPs) receiving factor IX-containing products. As one PTP treated with BeneFIX developed a clinically relevant low responding inhibitor during clinical studies and experience on antigenicity with recombinant factor IX is still limited, patients treated with BeneFIX should be carefully monitored for the development of factor IX inhibitors that should be titrated in Bethesda Units using appropriate biological testing.

There have been reports in the literature showing a correlation between the occurrence of a factor IX inhibitor and allergic reactions. Therefore, patients experiencing allergic reactions should be evaluated for the presence of an inhibitor. It should be noted that patients with factor IX inhibitors may be at an increased risk of anaphylaxis with subsequent challenge with factor IX. 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.

Because of the risk of allergic reactions with factor IX concentrates, the initial administrations of factor IX should, according to the treating physician's judgement, be performed under medical observation where proper medical care for allergic reactions could be provided.

Thrombosis

Although BeneFIX contains only factor IX, the risk of thrombosis and disseminated intravascular coagulation (DIC) should be recognised. Since

the use of factor IX complex concentrates has historically been associated with the development of thromboembolic complications, the use of factor IX-containing products may be potentially hazardous in patients with signs of fibrinolysis and in patients with disseminated intravascular coagulation (DIC). Because of the potential risk of thrombotic complications, clinical surveillance for early signs of thrombotic and consumptive coagulopathy should be initiated with appropriate biological testing when administering this product to patients with liver disease, to patients post-operatively, to new-born infants, or to patients at risk of thrombotic 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 (see also sections 4.2 and 4.8). 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 (see also section 4.8).

Cardiovascular events

In patients with existing cardiovascular risk factors, substitution therapy with FIX may increase the cardiovascular risk.

Nephrotic syndrome

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

Special populations

Sufficient data have not been obtained from clinical studies on the treatment of previously untreated patients (PUPs) with BeneFIX.

Record of use

It is strongly recommended that every time BeneFIX is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the medicinal product. Patients can affix one of the peel-off labels found on the vial to document the batch number in their diary or to report any side effects.

4.3 Interaction with other medicinal products and other forms of interaction

No interactions of human coagulation factor IX (rDNA) products with other medicinal products have been reported.

4.4 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with factor IX. Based on the rare occurrence of haemophilia B in women, experience regarding the use of factor IX during pregnancy and breastfeeding is not available. Therefore, factor IX should be used during pregnancy and breast-feeding only if clearly indicated

The effect of BeneFIX on fertility has not been established.

4.5 Effects on the ability to drive and use machines

BeneFIX has no influence on the ability to drive or use machines.

4.6 Undesirable effects

Summary of the safety profile

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed and may in some cases progress to severe anaphylaxis (including shock). In some cases, these reactions have progressed to severe anaphylaxis, and they have occurred in close temporal association with development of factor IX inhibitors (see also section 4.4). Nephrotic syndrome has been reported following attempted immune tolerance induction in haemophilia B patients with factor IX inhibitors and a history of allergic reaction.

Very rarely development of antibodies to hamster protein with related hypersensitivity reactions has been observed.

Patients with haemophilia B may develop neutralising antibodies (inhibitors) to factor IX. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted.

There is a potential risk of thromboembolic episodes following the administration of factor IX products, see section 4.4.

Tabulated list of adverse reactions

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level). Frequencies have been evaluated according to the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$), not known (cannot be estimated from the available data). The table lists adverse reactions reported in the clinical trials of previously treated patients and identified in postmarketing use. The frequencies are based on all causality treatment-emergent adverse events in pooled clinical trials with 224 subjects.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System class	organ	Very common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Frequency not known (cannot be estimated from the available data)
Infections and infestations				Infusion-site cellulitis ^a	
Blood and lymphatic system disorders				Factor IX inhibition ^b	
Immune system disorders			Hypersensitivity ^c		Anaphylactic reaction*
Nervous system disorders	Headache ^d		Dizziness; Dysgeusia	Somnolence; tremor	
Eye disorders				Visual impairment ^e	
Cardiac disorders				Tachycardia ^f	
Vascular disorders			Phlebitis; flushing ^g	Hypotension ^h	Superior vena cava syndrome ^{i,*} ; deep vein thrombosis*; thrombosis*; thrombophlebitis*
Respiratory, thoracic and mediastinal disorders	Cough ^j				
Gastrointestinal disorders			Vomiting; nausea		
Skin and subcutaneous tissue disorders			Rash ^k ; urticaria		
Renal and urinary disorders				Renal infarct ^l	
General disorders and administration site conditions	Pyrexia		Chest discomfort ^o ; infusion-site reaction ⁿ ; infusion-site pain ^m		Inadequate therapeutic response*
Investigations					Inadequate factor IX recovery ^{p, *}

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

Description of selected adverse reactions

Hypersensitivity/allergic reactions

If any suspected hypersensitivity reaction takes place that is thought to be related to the administration of BeneFIX see sections 4.2 and 4.4.

Inhibitor development

A clinically relevant, low responding inhibitor 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. This patient was able to continue treatment with BeneFIX with no anamnestic rise in inhibitor or anaphylaxis (see section 4.4).

Paediatric population

Allergic reactions might be experienced more frequently in children than in adults.

There are insufficient data to provide information on inhibitor incidence in PUPs (see also section 5.1).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) <https://pv.pharmacyboardkenya.org>

4.7 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihaemorrhagics, 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. 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 haemophilia B and substitution therapy may be required.

Pharmacodynamic effects

Haemophilia 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.

Paediatric population

Efficacy analysis in study 3090A1-301-WW was based on 22 evaluable paediatric subjects on a prophylaxis regimen including 4 on-demand patients who shortly changed to prophylaxis.

patients underwent surgical procedures (circumcision and port-a-catheter insertion). Safety analysis of 25 evaluable patients reflected a safety profile as expected. The only documented serious adverse event related with BeneFIX was reported from the only included PUP, who experienced hypersensitivity and inhibitor development.

In two open-label studies BeneFIX was found to be safely administered at 100 IU/kg once-weekly. However, the half-life of the product (see section 5.2) and the limited pharmacokinetic study data for the once-weekly regimen do not allow recommending this regimen in general for long-term prophylaxis in severe haemophilia B patients.

5.2 Pharmacokinetic properties

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) in 24 previously treated patients (≥ 12 years) at a dose of 75 IU/kg. In addition, pharmacokinetic parameters were followed up in 23 of the same patients 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 is presented in Table 1.

Pharmacokinetic Parameter Estimates for BeneFIX (75 IU/kg) at Baseline and Month 6 in Previously Treated Patients with Haemophilia B		
Parameter	Baseline n = 24 Mean \pm SD	Month 6 n = 23 Mean \pm SD
C_{max} (IU/dL)	54.5 \pm 15.0	57.3 \pm 13.2
AUC_{∞} (IU·hr/dL)	940 \pm 237	923 \pm 205
$t_{1/2}$ (hr)	22.4 \pm 5.3	23.8 \pm 6.5
CL (mL/hr/kg)	8.47 \pm 2.12	8.54 \pm 2.04
Recovery (IU/dL per IU/kg)	0.73 \pm 0.20	0.76 \pm 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 population pharmacokinetic model was developed using data collected in 73 patients aged 7 months to 60 years. The parameters estimated using the final 2-compartment model are shown in Table 2.

Infants and children had higher clearance, larger volume of distribution, shorter half-life and lower recovery than adolescents and adults. The terminal phase has not been covered unambiguously due to lack of data beyond 24 hours in paediatric subjects < 6 years of age.

Pharmacokinetic Parameters Based on Individual Bayes Estimates from Population Pharmacokinetic Analysis					
Age Group (years)	Infants <2	Children 2 to <6	Children 6 to <12	Adolescents 12 to <18	Adults 18 to 60
Number of subjects	7	16	1	19	30
Clearance (mL/h/kg)	13.1 \pm 2.1	13.1 \pm 2.9	15.5	9.2 \pm 2.3	8.0 \pm 0.6
V_{ss} (mL/kg)	252 \pm 35	257 \pm 25	303	234 \pm 49	225 \pm 59
Elimination half-life (h)	15.6 \pm 1.2	16.7 \pm 1.9	16.3	21.5 \pm 5.0	23.9 \pm 4.5
Recovery (IU/dL per IU/kg)	0.61 \pm 0.10	0.60 \pm 0.08	0.47	0.69 \pm 0.16	0.74 \pm 0.20

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of genotoxicity.

No investigations on carcinogenicity, fertility impairment and foetal development 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 compatibility studies, this medicinal product must not be mixed 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

2 years

The reconstituted product does not contain a preservative and 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 below 30°C. Do not freeze.

6.5 Nature and contents of the container

BeneFIX 500 IU, 1000 IU, 1500 IU, 2000 IU, 3000 IU powder and solvent for solution for injection

BeneFIX 250 IU, 500 IU, 1000 IU, 1500 IU, 2000 IU, 3000 IU of powder in a 10 mL vial (type 1 glass) with a stopper (chlorobutyl) and a flip-off seal (aluminium) and 5 mL of clear, colourless 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

BeneFIX is administered by intravenous infusion after reconstitution of the lyophilised powder for injection with the supplied solvent (0.234% w/v sodium chloride solution) in the pre-filled syringe (see also section 3 of the package leaflet for reconstitution instructions).

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. It is important that the recommendations in section 4.2 be followed closely.

Any unused product or waste material should be disposed of in accordance with local requirements.

Because the use of BeneFIX by continuous infusion has not been evaluated, BeneFIX should not be mixed with infusion solutions or be given in a drip.

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:

Pfizer laboratories limited

Manufacturing site address:

Spain

8. Marketing authorization number

CTD10075

9. Date of first registration

22/03/2023

10. Date of revision of the text

15/09/2023

11. Dosimetry

Not Applicable

12. Instructions for preparation of radiopharmaceuticals

Not applicable.

