BeneFIX™

1. Name of the Medicinal Product

1.1 Product name

BeneFIX

1.2 Strength

250 IU, 500 IU, 1,000 IU or 2,000 IU in single-use vials

1.3 Pharmaceutical dosage form

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 1,000 IU powder and solvent for solution for injection

Each vial contains nominally 1,000 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 2,000 IU powder and solvent for solution for injection

Each vial contains nominally 2,000 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.

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 Ala^{148} 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

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

4. Clinical Particulars

4.1 Therapeutic indications

BeneFIX is a human blood coagulation factor indicated in adults and children with haemophilia B (congenital factor IX deficiency or Christmas disease) for:

- On-demand treatment and control of bleeding episodes.
- Perioperative management of bleeding.
- Routine prophylaxis to reduce the frequency of bleeding episodes.

Limitations of Use

BeneFIX is not indicated for induction of immune tolerance in patients with haemophilia B.

4.2 Posology and method of administration

For intravenous use after reconstitution only.

- Each vial of BeneFIX has the recombinant coagulation factor IX potency in the International Units (IU) stated on the vial.
- Initiate treatment under the supervision of a physician experienced in the treatment of haemophilia B.
- Dosage and duration of treatment with BeneFIX 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 (see section 5). Subjects at the low end of the observed factor IX recovery may require upward dosage adjustment of BeneFIX to as much as two times (2X) the initial empirically calculated dose in order to achieve the intended rise in circulating factor IX activity.
- Monitor patients using a factor IX activity assay to ensure that the desired factor IX activity level has been achieved. Titrate the dose using the factor IX activity, pharmacokinetic parameters, such as half-life and recovery, as well as taking the clinical situation into consideration in order to adjust the dose as appropriate.

Dose

Calculating initial dose

- Use the following formula to calculate the initial dose of BeneFIX:

number of factor IX IU required (IU)	=	Body weight (kg)	X	Desired factor IX increase (% of normal or IU/dL)	X	reciprocal of observed recovery (IU/kg per IU/dL)

Average recovery

Adolescents/Adults (≥12 years)

In adults, on average, one International Unit (IU) of BeneFIX per kilogram of body weight increased the circulating activity of factor IX by 0.8 ± 0.2 IU/dL (range 0.4 to 1.2 IU/dL). Use the following formula to estimate the dose with 0.8 IU/dL average increase of factor IX per IU/kg body weight administered:

number of factor IX IU required (IU)	=	Body weight (kg)	X	Desired factor IX increase (% of normal or IU/dL)	X	1.3 (IU/kg per IU/dL)

Children (<12 years)

In children, on average, one international unit of BeneFIX per kilogram of body weight increased the circulating activity of factor IX by 0.7 ± 0.3 IU/dL (range 0.2 to 2.1 IU/dL; median of 0.6 IU/dL per IU/kg). Use the following formula to estimate the dose with 0.7 IU/dL average increase of factor IX per IU/kg body weight administered:

number of factor IX IU required (IU)	=	Body weight (kg)	X	Desired factor IX increase (% of normal or IU/dL)	X	1.4 (IU/kg per IU/dL)

Doses administered should be titrated to the patient's clinical response. Patients may vary in their pharmacokinetic (e.g., half-life, recovery) and clinical responses to BeneFIX. Although the dose can be estimated by the calculations above, it is highly recommended that, whenever possible, appropriate laboratory tests, including serial factor IX activity assays, be performed.

Dosing for on-demand treatment and control of bleeding episodes and perioperative management

Type of Hemorrhage	**Circulating Factor IX Activity Required (% of normal or IU/dL)**	**Dosing Interval (hours)**	**Duration of Therapy (days)**
Minor			
Uncomplicated hemarthroses, superficial muscle, or soft tissue	20-30	12-24	1-2
Moderate			
Intramuscular or soft tissue with dissection, mucous membranes, dental extractions, or hematuria	25-50	12-24	Treat until bleeding stops and healing begins; about 2 to 7 days
Major			
Pharynx, retropharynx, retroperitoneum, CNS, surgery	50-100	12-24	7-10
Adapted from: Roberts and Eberst			

Routine prophylaxis

For long-term prophylaxis against bleeding, the recommended regimen is 100 IU/kg once weekly. Children (<12 years) have lower recovery, shorter half-life and higher clearance (based on per kg body weight) as compared to adolescents and adults. Adjust the dosing regimen (dose or frequency) based on the patient's clinical response.

Preparation and reconstitution

The procedures below are provided as general guidelines for the preparation and reconstitution of BeneFIX.

Preparation

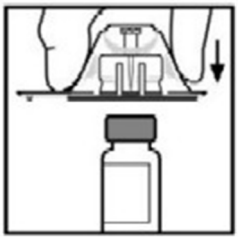
1. Always wash hands before performing the following procedures.
2. Use aseptic technique (meaning clean and germ-free) during the reconstitution procedure.
3. Use all components in the reconstitution and administration of this product as soon as possible after opening their sterile containers to minimize unnecessary exposure to the atmosphere.
4. Pooling: If needing more than one vial of BeneFIX per infusion, reconstitute each vial according to the following instructions. Remove the diluent syringe leaving the vial adapter in place, and use a separate large luer lock syringe to draw back the reconstituted contents of each vial. 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.

Reconstitution

1. If refrigerated, 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 and press down firmly on the package until the adapter spike penetrates the vial stopper.

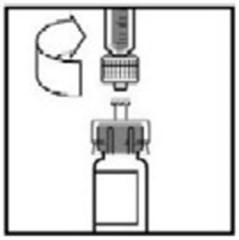


6. Grasp the plunger rod as shown in the diagram. Avoid contact with the shaft of the plunger rod. Attach the threaded end of the plunger rod to the diluent syringe plunger by pushing and turning firmly.

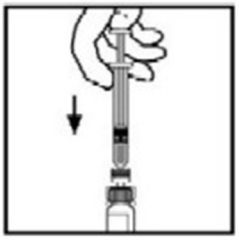
7. Break off the tamper-resistant plastic-tip cap from the diluent syringe by snapping the perforation of the cap. Do not touch the inside of the cap or the syringe tip. The diluent syringe may need to be recapped (if not administering reconstituted BeneFIX immediately), so place the cap on its top on 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.

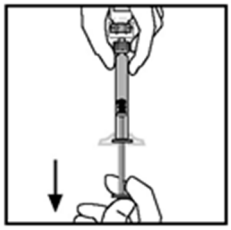
9. Place the vial on a flat surface. Connect the diluent syringe to the vial adapter by inserting the tip into the adapter opening while firmly pushing and turning the syringe clockwise until the connection is secured.



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. Invert the vial and slowly draw the solution into the syringe.



13. Detach the syringe from the vial adapter by gently pulling and turning the syringe counter-clockwise. Discard the vial with the adapter attached.
14. The reconstituted solution should be clear and colorless. If it is not, discard and use a new kit. If the solution is not to be used immediately, recap the syringe. Do not touch the syringe tip or the inside of the cap.
15. Store the reconstituted solution at room temperature and use it within 3 hours.
    Note: 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 for dosage and administration be followed closely, see section 4.2.
    Note: The tubing of the infusion set included with this kit does not contain DEHP.

Administration

For intravenous use after reconstitution only.

The safety and efficacy of administration by continuous infusion have not been established, see section 4.4.

- Inspect BeneFIX solution for particulate matter and discoloration prior to administration, whenever solution and container permit.
- Administer BeneFIX using the tubing provided in this kit, and the pre-filled diluent syringe provided, or a single sterile disposable plastic syringe.
- Do not mix or administer BeneFIX in the same tubing or container with other medicinal products.

Administration

1. Attach the syringe to the luer end of the infusion set tubing provided.
2. Apply a tourniquet and prepare the injections site by wiping the skin well with an alcohol swab provided in the kit.

3. Perform venipuncture. Insert the needle on the infusion set tubing into the vein, and remove the tourniquet. Inject the reconstituted BeneFIX intravenously over several minutes. Adjust the rate of administration based on the patient's comfort level.

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.

4. Following completion of BeneFIX treatment, remove and discard the infusion set. Dispose of all unused solution, empty vial(s), and used needles and syringes in an appropriate container.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Known allergic reaction to hamster proteins.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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 BeneFIX 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.

Sodium content

After reconstitution, BeneFIX contains 0.2 mmol sodium (4.6 mg) per vial, that is to say essentially 'sodium-free'. Depending on body weight of the patient and posology of BeneFIX, patients could receive multiple vials. This should be taken into consideration if the patient is on a low salt diet.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions of recombinant coagulation factor IX products with other medicinal products have been reported.

4.6 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.

4.7 Effects on ability to drive and use machines

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

4.8 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 (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 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 post-marketing 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 organ class	**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*

System organ class	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)
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; infusion-site reaction[n]; infusion-site pain[m]		Inadequate therapeutic response*
Investigations				Inadequate factor IX recovery[p,*]

* ADR identified post-marketing

System organ class	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)

[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).

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: 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 prophylaxis regimen including 4 on-demand patients who shortly changed to prophylaxis. Two 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 ($\geq$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.

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 ± 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 per 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 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.

Table 2. Mean ± SD 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 ± 2.1	13.1 ± 2.9	15.5	9.2 ± 2.3	8.0 ± 0.6
Vss (mL/kg)	252 ± 35	257 ± 25	303	234 ± 49	225 ± 59
Elimination half-life (h)	15.6 ± 1.2	16.7 ± 1.9	16.3	21.5 ± 5.0	23.9 ± 4.5
Recovery (IU/dL per IU/kg)	0.61 ± 0.10	0.60 ± 0.08	0.47	0.69 ± 0.16	0.74 ± 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

Hydrochloric acid

Nitrogen gas

Solvent

Sodium chloride solution

Water for injection

6.2 Incompatibilities

In the absence of incompatibility studies, reconstituted BeneFIX should 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

Refer to carton for expiry date.

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

Stored at 2°C to 8°C (Refrigerate) and protect from light for 3 years. Prior to the expiration date, BeneFIX may be stored at or below 30°C, for up to 6 months.

Do not freeze to prevent damage to the diluent syringe

6.5 Nature and contents of container

The drug product is contained in a Type I glass vial with an elastomeric closure.

6.6 Special precautions for disposal and other handling

Freezing should be avoided to prevent damage to the pre-filled diluent syringe.

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 be followed closely.

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. Marketing Authorization Holder

Pfizer (Thailand) Limited

8. Marketing Authorization Numbers

9. Date of Authorization

10. Date of Revision of the Text

26 April 2022