ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

BeneFIX 250 IU powder and solvent for solution for injection
BeneFIX 500 IU powder and solvent for solution for injection
BeneFIX 1000 IU powder and solvent for solution for injection
BeneFIX 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 250 IU powder and solvent for solution for injection
Each vial contains nominally 250 IU nonacog alfa (recombinant coagulation factor IX). After reconstitution with the accompanying 5 mL (0.234%) sodium chloride solution for injection, each mL of the solution contains approximately 50 IU nonacog alfa.

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

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

BeneFIX 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 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

BeneFIX 250 IU, 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 bodyweight 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 patients' 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
Dose and duration of the substitution therapy depend on the severity of the factor IX deficiency, on 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 ≥ 12 years (further information in section 5.2).

The required dose is determined using the following formula:

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

Example: For a recovery of 0.8 IU/dL, the formula reads:

Number of factor IX IU required	=	body weight (in kg)	X	desired factor IX increase (%) or (IU/dL)	X	1.3 IU/kg

The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case.

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 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.

Elderly population
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.

Method of administration
BeneFIX is administered by intravenous infusion after reconstitution of the lyophilised powder for solution for injection with sterile 0.234% sodium chloride solution (see section 6.6).

BeneFIX should be administered at a slow infusion rate. In most of the cases, an infusion rate of up to 4 mL per minute has been used. The rate of administration should be determined by the patient's comfort level.

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 sections 4.4 and 4.8).

Agglutination of red blood cells in the tube/syringe
There have been reports of agglutination of red blood cells in the tube/syringe 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 agglutination of red blood cells in the tubing/syringe is observed, discard all this material (tubing, syringe and BeneFIX solution) and resume administration with a new package.

Continuous infusion
Administration by continuous infusion has not been approved and is not recommended (see also sections 4.4 and 6.6).

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

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.
Patients can affix one of the peel-off labels found on the vial to document the batch number in their diary or for reporting any side effects.

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.

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 human coagulation factor IX (rDNA) 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 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 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*
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 the national reporting system listed in Appendix V.

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 (≥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

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 container

BeneFIX 250 IU, 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 AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/047/004
EU/1/97/047/005
EU/1/97/047/006
EU/1/97/047/009
EU/1/97/047/007
EU/1/97/047/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 August 1997
Date of latest renewal: 20 July 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Wyeth BioPharma
Division of Wyeth Pharmaceuticals LLC
One Burtt Road
Andover MA 01810
USA

Name and address of the manufacturer responsible for batch release

Wyeth Farma S.A.
Autovia del Norte. A-1, Km. 23. Desvio Algete, Km. 1, 28700 San Sebastian de los Reyes, Madrid
Spain

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

BeneFIX 250 IU powder and solvent for solution for injection

BeneFIX 500 IU powder and solvent for solution for injection

BeneFIX 1000 IU powder and solvent for solution for injection

BeneFIX 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

Nonacog alfa (recombinant coagulation factor IX)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 250 IU nonacog alfa (approx. 50 IU/ml after reconstitution).

1 vial: 500 IU nonacog alfa (approx. 100 IU/ml after reconstitution).

1 vial: 1000 IU nonacog alfa (approx. 200 IU/ml after reconstitution).

1 vial: 1500 IU nonacog alfa (approx. 300 IU/ml after reconstitution).

1 vial: 2000 IU nonacog alfa (approx. 400 IU/ml after reconstitution).

1 vial: 3000 IU nonacog alfa (approx. 600 IU/ml after reconstitution).

3. LIST OF EXCIPIENTS

Sucrose, glycine, L-histidine, sodium chloride, polysorbate 80.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

1 vial with 250 IU nonacog alfa
1 vial with 500 IU nonacog alfa
1 vial with 1000 IU nonacog alfa
1 vial with 1500 IU nonacog alfa
1 vial with 2000 IU nonacog alfa
1 vial with 3000 IU nonacog alfa

1 pre-filled syringe with 5 ml solvent
1 sterile vial adapter reconstitution device
1 sterile infusion set
2 alcohol swabs

1 plaster
1 gauze pad

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use, single use administration only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only the pre-filled syringe of solvent provided in the box for reconstitution.

8. EXPIRY DATE

EXP
Use immediately or within 3 hours of reconstitution.

9. SPECIAL STORAGE CONDITIONS

Store below 30°C. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/047/004
EU/1/97/047/005
EU/1/97/047/006
EU/1/97/047/009
EU/1/97/047/007
EU/1/97/047/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

BeneFIX 250
BeneFIX 500
BeneFIX 1000
BeneFIX 1500
BeneFIX 2000
BeneFIX 3000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

BeneFIX 250 IU powder for solution for injection

BeneFIX 500 IU powder for solution for injection

BeneFIX 1000 IU powder for solution for injection

BeneFIX 1500 IU powder for solution for injection

BeneFIX 2000 IU powder for solution for injection

BeneFIX 3000 IU powder for solution for injection

Nonacog alfa (recombinant coagulation factor IX)
Intravenous use

2. METHOD OF ADMINISTRATION

Single use injection.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

See front label (Lot, Exp.)

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

250 IU

500 IU

1000 IU

1500 IU

2000 IU

3000 IU

6. OTHER

Store below 30 ºC. Do not freeze.

Use only the pre-filled syringe provided in the box for reconstitution.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SOLVENT SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for BeneFIX

For intravenous use.

2. METHOD OF ADMINISTRATION

Use the entire contents.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

Pfizer Europe MA EEIG

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Contains 5 ml of 0.234% sodium chloride solution for injection

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

BeneFIX 250 IU powder and solvent for solution for injection
BeneFIX 500 IU powder and solvent for solution for injection
BeneFIX 1000 IU powder and solvent for solution for injection
BeneFIX 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
nonacog alfa (recombinant coagulation factor IX)

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What BeneFIX is and what it is used for

BeneFIX is an injectable clotting (coagulation) factor IX product that is produced by recombinant DNA technology. The active ingredient in BeneFIX is nonacog alfa. People who are born with haemophilia B (Christmas disease) lack sufficient factor IX to control bleeding. BeneFIX works by replacing factor IX in haemophilia B patients to enable their blood to clot.

BeneFIX is used for the treatment and prevention of bleeding in patients with haemophilia B (congenital factor IX deficiency) in all age groups.

2. What you need to know before you take BeneFIX

Do not take BeneFIX

- if you are allergic to nonacog alfa or any of the other ingredients of this medicine (listed in section 6).
- if you are allergic to hamster proteins.

Warnings and precautions

- Talk to your doctor or pharmacist before using BeneFIX.

- See your doctor immediately if your bleeding does not stop as expected.

- Allergic reactions are possible. The product may contain traces of hamster proteins (see Do not take BeneFIX). Potentially life-threatening anaphylactic reactions (severe allergic reactions) have occurred with factor IX products, including BeneFIX. Early signs of allergic reactions

include difficulty breathing, shortness of breath, swelling, hives, itching, generalised urticaria, tightness of the chest, wheezing, low blood pressure, blurred vision and anaphylaxis (severe allergic reaction that can cause difficulty in swallowing and/or breathing, red or swollen face and/or hands).

- If allergic or anaphylactic-type reactions occur, **stop the infusion immediately and contact a doctor or seek emergency medical care immediately**. In case of severe allergic reactions, alternative therapy should be considered.

- Activity-neutralizing antibodies (inhibitors) are an uncommon event in patients who have received previous treatment with factor IX-containing products. However, as with all factor IX products you should be carefully monitored for the development of factor IX inhibitors while being treated with BeneFIX.

- Research has shown a link between the occurrence of a factor IX inhibitor and allergic reactions. Therefore, if you experience allergic reactions such as those described above, you should be tested for the presence of an inhibitor. It should be noted that patients with a factor IX inhibitor may be at an increased risk of anaphylaxis during future treatment with BeneFIX.

- The production of factor IX in the body is controlled by the factor IX gene. Patients who have specific mutations of their factor IX gene such as major deletion may be more likely to develop an inhibitor to factor IX and/or experience allergic reactions. Therefore if you are known to have such a mutation your doctor may monitor you more closely for signs of an allergic reaction particularly when you first start to take BeneFIX.

- Because of the risk of allergic reactions with factor IX, your initial administrations of BeneFIX should be performed under medical observation where proper medical care for allergic reactions can be provided.

- Even in the absence of factor IX inhibitor, higher doses of BeneFIX may be needed than required for other plasma-derived factor IX products that you may have taken previously. Therefore, close monitoring of factor IX plasma activity (which measures the ability of your blood to form clots) has to be performed to adjust doses as appropriate. If bleeding is not controlled with the recommended dose, contact your doctor.

- If you suffer from liver or heart disease or if you have recently had surgery, there is an increased risk for blood clotting (coagulation) complications.

- A kidney disorder (nephrotic syndrome) has been reported following high doses of plasma-derived factor IX in haemophilia B patients with factor IX inhibitors and a history of allergic reactions.

- Sufficient data have not been obtained from clinical studies on the treatment of previously untreated patients (patients who have never received a previous infusion of factor IX), with BeneFIX.

- It is recommended that evey time you use BeneFIX, you record the name and batch number of the product. You can use one of the peel-off labels found on the vial to document the batch number in your diary or for reporting any side effects.

Other medicines and BeneFIX

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, you should only take BeneFIX upon specific instructions from your doctor. It is not known whether BeneFIX can cause harm to an unborn baby when given to pregnant women. Your doctor may advise you to stop treatment with BeneFIX if you are breast-feeding or become pregnant.

Ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

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

BeneFIX contains sodium

After reconstitution, BeneFIX contains 0.2 mmol sodium (4.6 mg) per vial, that is to say essentially 'sodium-free'. However, depending on your body weight and your dose of BeneFIX, you could receive multiple vials. This should be taken into consideration if you are on a low salt diet.

3. How to take BeneFIX

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor will decide the dose of BeneFIX you will receive. This dose and duration will depend upon your individual needs for replacement factor IX therapy and how quickly your body uses up factor IX, which will be checked regularly. You may notice a difference in the dose you receive if you are changing from a plasma-derived factor IX product to BeneFIX.

Your doctor may decide to change the dose of BeneFIX you receive during your treatment.

Reconstitution and administration

The procedures below are provided as guidelines for the reconstitution and administration of BeneFIX. Patients should follow the specific venipuncture procedures provided by their doctor.

BeneFIX is administered by intravenous (IV) infusion after reconstitution of the powder for injection with the supplied solvent (a sodium chloride (salt) solution) in the pre-filled syringe.

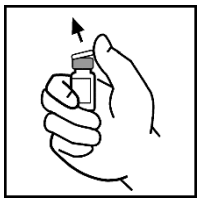
Always wash your hands prior to performing the following procedures. Aseptic technique (meaning clean and germ free) should be used during the reconstitution procedure.

Reconstitution:

BeneFIX will be administered by intravenous infusion (IV) after reconstitution with sterile solvent for injection.

1. Allow the vial of lyophilised (freeze-dried) BeneFIX and the pre-filled syringe to reach room temperature.

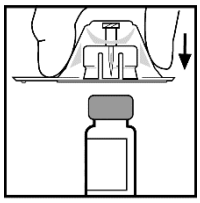
2. Remove the plastic flip-top cap from the BeneFIX vial to expose the central portion of the rubber stopper.



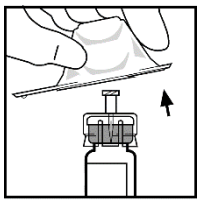
3. Wipe the top of the vial with an alcohol swab provided, or use another antiseptic solution and allow to dry. After cleaning do not touch the rubber stopper with your hand or allow it to touch any surface.

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

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

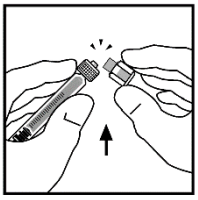


6. Lift the package away from the adapter and discard the package.

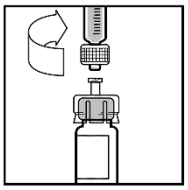


7. Attach the plunger rod to the solvent syringe by pushing and turning firmly.

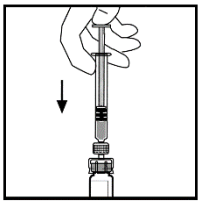
8. Break off the tamper-resistant plastic tip cap from the solvent syringe by snapping the perforation of the cap. This is done by bending the cap up and down until the perforation is broken. Do not touch the inside of the cap or the syringe tip. The cap may need to be replaced (if not administering reconstituted BeneFIX immediately), so set it aside by placing it on its top.



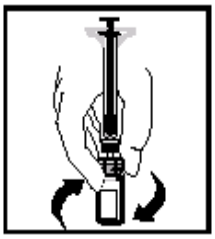
9. Place the vial on a flat surface. Connect the solvent syringe to the vial adapter by inserting the tip of the syringe into the adapter opening while firmly pushing and turning the syringe clockwise until the connection is secured.



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



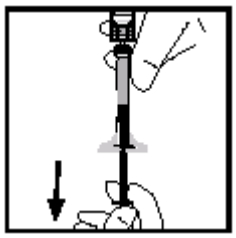
11. With the syringe still connected to the adapter, gently rotate the vial until the powder is dissolved.



12. The final solution should be inspected visually for fine particles before administration. The solution should appear clear and colourless.

    Note: If you use more than one vial of BeneFIX per infusion, each vial should be reconstituted as per the previous instructions. The solvent syringe should be removed, leaving the vial adapter in place, and a separate large luer lock (a device that connects the syringe to the vial) syringe may be used to draw back the reconstituted contents of each individual vial.

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



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

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

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

Administration (Intravenous Injection):

BeneFIX should be administered using the pre-filled solvent 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.

BeneFIX should be injected intravenously over several minutes. Your doctor may change your recommended infusion rate to make the infusion more comfortable.

There have been reports of clumping (agglutination) of red blood cells in the tube/syringe with the administration of BeneFIX. No side effects 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 clumping of red blood cells in the tubing/syringe is observed, discard all this material (tubing, syringe and BeneFIX solution) and resume administration with a new package.

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

Please dispose of all unused solution, empty vials and used needles and syringes in an appropriate container for throwing away waste as it may hurt others if not handled properly.

If you take more BeneFIX than you should

Please contact your doctor immediately if you inject more BeneFIX than your doctor recommends.

If you stop taking BeneFIX

Do not stop taking BeneFIX without consulting your doctor.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Hypersensitivity/allergic reactions

Allergic-type hypersensitivity reactions are possible with BeneFIX. Such reactions may include swelling of the face or throat, burning and stinging at the infusion site, chills, flushing, itching, headache, hives, low blood pressure, lethargy, nausea, restlessness, fast heart rate, tightness of the chest, tingling, vomiting, wheezing). In some cases, these reactions have progressed to severe anaphylaxis. Allergic reactions may occur together with the development of factor IX inhibitor (see also “Warnings and precautions”).

These reactions are potentially life-threatening. If allergic/anaphylactic reactions occur, **stop the infusion immediately and contact your doctor or seek emergency medical care immediately.** The

treatment required depends on the nature and severity of side-effects (see also “Warnings and precautions”).

Inhibitor development

Patients with haemophilia B may develop neutralising antibodies (inhibitors) to factor IX. If such inhibitors occur, a sign may be an increase in the amount of BeneFIX typically required to treat a bleed and or continued bleeding after treatment. In such cases, it is recommended that a specialised haemophilia centre be contacted. Your doctor may want to monitor you for inhibitor development (see “Warnings and precautions”).

A kidney disorder has been reported following high doses of plasma-derived factor IX to induce immune tolerance in haemophilia B patients with factor IX inhibitors and a history of allergic reactions (see also “Warnings and precautions”).

Thrombotic events

BeneFIX may increase the risk of thrombosis (abnormal blood clots) in your body if you have risk factors for developing blood clots, including an indwelling venous catheter. There have been reports of severe blood clotting events, including life-threatening blood clots in critically ill babies, while receiving continuous-infusion BeneFIX through a central venous catheter. Cases of peripheral thrombophlebitis (pain and redness of the veins) and deep venous thrombosis (blood clots in the extremities) have also been reported; in most of these cases, BeneFIX was administered via continuous infusion, which is not an approved method of administration.

Very common side effects (may affect more than 1 in 10 people)
- Headache
- Cough
- Fever

Common side effects (may affect up to 1 in 10 people)
- Hypersensitivity/allergic reactions
- Dizziness, altered taste
- Phlebitis (pain and redness of veins), flushing
- Vomiting, nausea
- Rash, hives
- Chest discomfort (including chest pain)
- Infusion-site reaction (including itching and redness at the infusion site), infusion-site pain and discomfort

Uncommon side effects (may affect up to 1 in 100 people)
- Development of neutralising antibodies (inhibitors)
- Infusion site cellulitis (pain and redness of the skin)
- Sleepiness, shaking
- Vision impairment (including blurred vision, appearance of spots/lights)
- Fast heart rate, low blood pressure
- Renal infarct (interruption to the blood supply to the kidney)

Side effects with unknown frequency (frequency cannot be estimated from the available data)
- Anaphylactic reaction
- Thrombotic events (abnormal blood clots)
- Lack of response to treatment (failure to stop or prevent bleeding episodes)

Reporting of side effects

If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effect not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store BeneFIX

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer box and vial label. The expiry date refers to the last day of that month.

BeneFIX must be stored below 30°C and must be used by the expiry date on the label.

Do not freeze in order to prevent damage to the pre-filled syringe.

Use the reconstituted solution immediately or within 3 hours.

Do not use this medicine if you notice the solution is not clear or colourless.

Use only the pre-filled syringe provided in the box for reconstitution. Other sterile disposable syringes may be used for administration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What BeneFIX contains

- The active substance is nonacog alfa (recombinant coagulation factor IX). Each vial of BeneFIX contains nominally 250, 500, 1000, 1500, 2000 or 3000 IU of nonacog alfa.
- The other ingredients are sucrose, glycine, L-histidine, polysorbate 80. A solvent (0.234% sodium chloride solution) is also supplied for reconstitution.
- After reconstitution with the supplied solvent (0.234% sodium chloride solution), each vial contains 50, 100, 200, 300, 400 or 600 IU/ml (see Table 1).

Table 1. Strength of BeneFIX per ml prepared solution

Amount of BeneFIX per Vial	Amount of BeneFIX per 1 ml of prepared solution for injection
250 IU	50 IU
500 IU	100 IU
1000 IU	200 IU
1500 IU	300 IU
2000 IU	400 IU
3000 IU	600 IU

What BeneFIX looks like and contents of the pack

BeneFIX is provided as a powder for injection in a glass vial and a solvent provided in pre-filled syringe.

The contents of the pack are:

- one vial of BeneFIX 250, 500, 1000, 1500, 2000 or 3000 IU powder
- one pre-filled syringe of solvent, 5 ml sterile 0.234% sodium chloride solution for injection for reconstitution, with one plunger rod
- one sterile vial adapter reconstitution device
- one sterile infusion set
- two alcohol swabs
- one plaster
- one gauze pad

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.