For the use only of a Registered Medical Practitioner (Hematologists) or a Hospital or a Laboratory.

Nonacog alfa (recombinant coagulation factor IX)
BeneFIX®

1. GENERIC NAME

Nonacog alfa (recombinant coagulation factor IX) 250 IU powder and solvent for solution for injection
Nonacog alfa (recombinant coagulation factor IX) 500 IU powder and solvent for solution for injection
Nonacog alfa (recombinant coagulation factor IX) 1000 IU powder and solvent for solution for injection
Nonacog alfa (recombinant coagulation factor IX) 2000 IU powder and solvent for solution for injection
Nonacog alfa (recombinant coagulation factor IX) 3000 IU powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nonacog alfa (recombinant coagulation factor IX) 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.

Nonacog alfa (recombinant coagulation factor IX) 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.

Nonacog alfa (recombinant coagulation factor IX) 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.

Nonacog alfa (recombinant coagulation factor IX) 2000 IU powder and solvent for solution for injection

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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.

Nonacog alfa (recombinant coagulation factor IX) 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 Nonacog alfa (recombinant coagulation factor IX) is not less than 200 IU/mg protein.

Nonacog alfa (recombinant coagulation factor IX) 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.

List of Excipients

Powder
Sucrose, Glycine, L-Histidine, Polysorbate 80

Solvent
Sodium chloride solution

3. DOSAGE FORM AND STRENGTH

Nonacog alfa (recombinant coagulation factor IX) 250 IU, 500 IU, 1000 IU, 2000 IU, 3000 IU powder and solvent for solution for injection

All strengths/presentations mentioned in this document might not be available in the market.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Nonacog alfa (recombinant coagulation factor IX), is a human blood coagulation factor indicated in adults and children with hemophilia 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

Limitation of Use

Nonacog alfa (recombinant coagulation factor IX) is not indicated for induction of immune tolerance in patients with hemophilia B (see sections 4.4).

4.2 Posology and method of administration

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

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 Nonacog alfa (recombinant coagulation factor IX) 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 5.3).

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

Nonacog alfa (recombinant coagulation factor IX) may be administered for long term prophylaxis against bleeding in patients with hemophilia 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.

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 dosing regimen (dose or frequency) based on the patient's clinical response.

Paediatric population

There is limited documentation of on-demand treatment and surgery in paediatric patients less than 6 years of age treated with Nonacog alfa (recombinant coagulation factor IX).

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 Nonacog alfa (recombinant coagulation factor IX) 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 Nonacog alfa (recombinant coagulation factor IX), dose selection for an elderly patient should be individualised.

Method of administration

Nonacog alfa (recombinant coagulation factor IX) is administered by intravenous infusion after reconstitution of the lyophilised powder for solution for injection with sterile 0.234% sodium chloride solution (see section 8.4).

Nonacog alfa (recombinant coagulation factor IX) 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 Nonacog alfa (recombinant coagulation factor IX), 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 Nonacog alfa (recombinant coagulation factor IX). 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 Nonacog alfa (recombinant coagulation factor IX) 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 8.4).

For instructions on reconstitution of the medicinal product before administration, see section 8.4.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 2.

Known allergic reaction to hamster proteins.

4.4 Special warnings and precautions for use

Hypersensitivity
Allergic-type hypersensitivity reactions are possible with Nonacog alfa (recombinant coagulation factor IX). The product contains traces of hamster proteins. Potentially life-threatening anaphylactic/anaphylactoid reactions have occurred with factor IX products, including Nonacog alfa (recombinant coagulation factor IX). 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 Nonacog alfa (recombinant coagulation factor IX) developed a clinically relevant low responding inhibitor during clinical studies and experience on antigenicity with recombinant factor IX is still limited, patients treated with Nonacog alfa (recombinant coagulation factor IX) 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 Nonacog alfa (recombinant coagulation factor IX) 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 Nonacog alfa (recombinant coagulation factor IX) should be weighed against the risk of these complications.

The safety and efficacy of Nonacog alfa (recombinant coagulation factor IX) 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 Nonacog alfa (recombinant coagulation factor IX) 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 hemophilia B patients with factor IX inhibitors and a history of allergic reaction. The safety and efficacy of using Nonacog alfa (recombinant coagulation factor IX) 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 Nonacog alfa (recombinant coagulation factor IX).

Record of use

It is strongly recommended that every time Nonacog alfa (recombinant coagulation factor IX) 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. 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.

4.5 Drugs interactions

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

4.6 Use in special populations

Animal reproduction studies have not been conducted with factor IX. Based on the rare occurrence of hemophilia 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 Nonacog alfa (recombinant coagulation factor IX) on fertility has not been established.

4.7 Effects on ability to drive and use machines

Nonacog alfa (recombinant coagulation factor IX) 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 hemophilia 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 hemophilia 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 hemophilia 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*
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];		Inadequate therapeutic response*

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)
		infusion-site pain[m]		
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 Nonacog alfa (recombinant coagulation factor IX) 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 Nonacog alfa (recombinant coagulation factor IX) 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 Nonacog alfa (recombinant coagulation factor IX) see sections 4.2 and 4.4.

Inhibitor development
A clinically relevant, low responding inhibitor was detected in 1 out of 65 Nonacog alfa (recombinant coagulation factor IX) 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 Nonacog alfa (recombinant coagulation factor IX) 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 5.2).

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.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action

Pharmacotherapeutic group: Antihaemorrhagics, blood coagulation factor IX; ATC code: B02BD04
Nonacog alfa (recombinant coagulation factor IX) 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 hemophilia B and substitution therapy may be required.

5.2 Pharmacodynamic properties

Hemophilia B is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor IX and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma levels of factor IX is increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

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 Nonacog alfa (recombinant coagulation factor IX) was reported from the only included PUP, who experienced hypersensitivity and inhibitor development.

Routine Prophylaxis

In an open-label trial of 25 patients (age range 12-54 years) comparing on-demand treatment versus prophylaxis when administered at a dose of 100 IU/kg once weekly, the annualized bleed rate (ABR) for the prophylaxis period was significantly lower ($p < 0.0001$) than the ABR for the on-demand period (mean ± standard deviation (SD): 3.6 ±

4.6, median: 2.0, min-max: 0-13.8 versus mean: 32.9 ± 17.4, median: 33.6, min-max: 6.1-69.0, respectively).

In an open-label crossover trial in patients aged 6-64 years, of 100 IU/kg once weekly (44 patients) and 50 IU/kg twice weekly (43 patients) with 4-month treatment periods, the ABR for the 100 IU/kg once-weekly prophylaxis period was mean 4.4 ± 10.0 episodes per year (median: 0.0, min-max: 0 – 50.5) and mean 2.8 ± 5.7 (median: 0.0, min-max: 0 – 24.1) for the 50 IU/kg twice-weekly period. Six patients aged <12 years had mean ABR of 1.6 ± 1.7 (median: 1.5, min-max: 0-3.3) in the 100 IU/kg weekly period, and mean ABR of 0 ± 0 (median: 0, min-max: 0-0) in the 50 IU/kg twice weekly period.

5.3 Pharmacokinetic properties

In a randomized, cross-over pharmacokinetic study, Nonacog alfa (recombinant coagulation factor IX) reconstituted in 0.234% sodium chloride diluent was shown to be pharmacokinetically equivalent to the previously marketed Nonacog alfa (recombinant coagulation factor IX) (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 Nonacog alfa (recombinant coagulation factor IX) 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 Nonacog alfa (recombinant coagulation factor IX) (75 IU/kg) at Baseline and Month 6 in Previously Treated Patients with Hemophilia B

Parameter	Baseline n = 24 Mean ± SD	Month 6 n = 23 Mean ± SD
C_{max} (IU/dL)	54.5 ± 15.0	57.3 ± 13.2
AUC_{∞} (IU·hr/dL)	940 ± 237	923 ± 205
$t_{1/2}$ (hr)	22.4 ± 5.3	23.8 ± 6.5
CL (mL/hr/kg)	8.47 ± 2.12	8.54 ± 2.04
Recovery (IU/dL 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

Table 2. Mean ± SD Pharmacokinetic Parameters Based on Individual Bayes Estimates from Population Pharmacokinetic Analysis					
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

6. NONCLINICAL PROPERTIES

6.1 Animal toxicology or pharmacology

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.

7. DESCRIPTION

Nonacog alfa (recombinant coagulation factor IX) is a sterile powder containing the inactive ingredients histidine, glycine, sucrose and polysorbate 80, pH 6.3 to 7.1. The powder is reconstituted with 0.234% (40 mM) sodium chloride (NaCl) in water for injection. All drug product dosage strengths are reconstituted with 5 mL of 0.234% NaCl provided in a pre-filled syringe. The drug product is contained in a Type I glass vial with an elastomeric closure. The drug product contains no preservative and is for single use only. The drug product is provided in single use vials containing 250, 500, 1000, 2000 or 3000 IU per vial.

8. PHARMACEUTICAL PARTICULARS

8.1 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.

8.2 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.

8.3 Packaging information

Nonacog alfa (recombinant coagulation factor IX) 250 IU, 500 IU, 1000 IU, 2000 IU, 3000 IU powder and solvent for solution for injection

Nonacog alfa (recombinant coagulation factor IX) 250 IU, 500 IU, 1000 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.

8.4 Storage and handling instructions

Store between 2 - 30°C. Do not freeze.

Special Precaution for Use/Handling/Disposal

Nonacog alfa (recombinant coagulation factor IX) 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.

Reconstitution and administration

The procedures below are provided as guidelines for the reconstitution and administration of Nonacog alfa (recombinant coagulation factor IX). Follow the specific venipuncture procedures provided by their doctor.

Nonacog alfa (recombinant coagulation factor IX) 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:

Nonacog alfa (recombinant coagulation factor IX) will be administered by intravenous infusion (IV) after reconstitution with sterile solvent for injection.

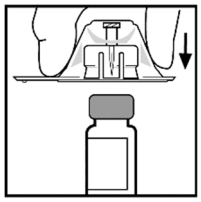
1. Allow the vial of lyophilised (freeze-dried) Nonacog alfa (recombinant coagulation factor IX) and the pre-filled syringe to reach room temperature.

2. Remove the plastic flip-top cap from the Nonacog alfa (recombinant coagulation factor IX) vial to expose the central portion of the rubber stopper.

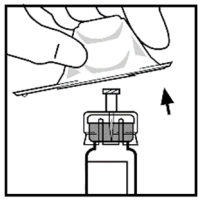
3. Wipe the top of the vial with an alcohol swab provided, or use another antiseptic solution and allow to dry. After cleaning do not touch the rubber stopper with your hand or allow it to touch any surface.

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.

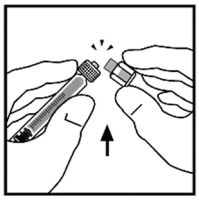


6. Lift the package away from the adapter and discard the package.

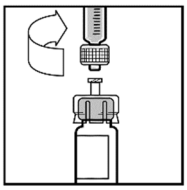


7. Attach the plunger rod to the solvent syringe by pushing and turning firmly.

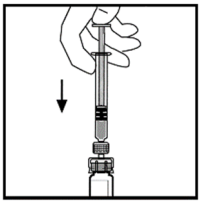
8. Break off the tamper-resistant plastic tip cap from the solvent syringe by snapping the perforation of the cap. This is done by bending the cap up and down until the perforation is broken. Do not touch the inside of the cap or the syringe tip. The cap may need to be replaced (if not administering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



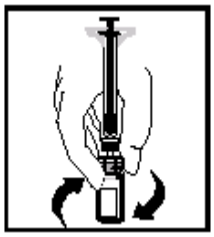
9. Place the vial on a flat surface. Connect the solvent syringe to the vial adapter by inserting the tip of the syringe into the adapter opening while firmly pushing and turning the syringe clockwise until the connection is secured.



10. Slowly depress the plunger rod to inject all the solvent into the Nonacog alfa (recombinant coagulation factor IX) vial.



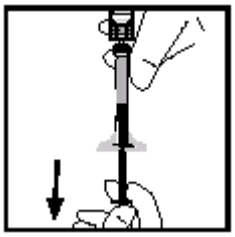
11. With the syringe still connected to the adapter, gently rotate the vial until the powder is dissolved.



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 Nonacog alfa (recombinant coagulation factor IX) 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.

Nonacog alfa (recombinant coagulation factor IX) should be administered immediately or within 3 hours after reconstitution. The reconstituted solution may be stored at room temperature prior to administration.

Nonacog alfa (recombinant coagulation factor IX), 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 Nonacog alfa (recombinant coagulation factor IX). 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 Nonacog alfa (recombinant coagulation factor IX) by continuous infusion has not been evaluated, Nonacog alfa (recombinant coagulation factor IX) should not be mixed with infusion solutions or be given in a drip.

9. PATIENT COUNSELLING INFORMATION

Advise patients comprehensively about the product including allergic-type hypersensitivity reactions are possible. Inform patients of the early signs of hypersensitivity reactions [including hives (rash with itching), generalized urticaria, tightness of the chest, wheezing, hypotension] and anaphylaxis. Advise patients to discontinue use of the product and contact their physicians if these symptoms occur.

Advise patients to contact their physician or treatment facility for further treatment and/or assessment if they experience a lack of a clinical response to factor IX replacement therapy, as in some cases this may be a manifestation of an inhibitor.

10. DETAILS OF MANUFACTURER

Manufactured by:
Wyeth Farma, S.A. Autovía del Norte A-1 Km 23.
Desvío Algete, Km 1, 28700 San Sebastian de los Reyes, Madrid, Spain

Imported and Marketed by:

Pfizer Products India Private Limited, The Capital- B Wing, 1802, 18th Floor,
Plot No. C-70, G Block, Bandra Kurla Complex, Bandra (East), Mumbai 400 051,
India.

11. DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

BIO/IMP/18/000004 dated 3 Oct 2018

12. DATE OF REVISION

June 2022