PRESCRIBING INFORMATION

Before prescribing BeneFIX please refer to full Summary of Product Characteristics.

BeneFIX powder and solvent for solution for injection, nonacog alfa (recombinant coagulation factor IX). Available in strengths 250, 500, 1000, 2000 and 3000 IU

UK
Prescribing Information:
Presentation: Each vial of powder for solution for injection contains nominally 250, 500, 1000, 2000 or 3000 IU nonacog alfa. When reconstituted with the accompanying 5 ml 0.234% sodium chloride solution, each ml of the product contains approximately the following amounts of nonacog alfa (IU/ml):

Strength (IU)	Amount nonacog alfa (IU/ml)
250	50
500	100
1000	200
2000	400
3000	600

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

BeneFIX can be used for all age groups.

Dosage and Administration: Treatment should be under the supervision of a physician experienced in the treatment of haemophilia.
Dosage and duration of the substitution therapy depend on the severity of the factor IX deficiency, on the location and extent of bleeding, and the patient's clinical condition.
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.
In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.
There is limited documentation of on-demand treatment and surgery in paediatric patients less than 6 years of age treated with BeneFIX.
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.
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.
BeneFIX is administered by IV infusion after reconstitution of the lyophilised powder for solution for injection with 0.234% sodium chloride.
The reconstituted solution does not contain a preservative and should be used immediately, but no longer than 3 hours after reconstitution.
Only the provided infusion set should be used.
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. Administration by continuous infusion has not been approved and is not recommended.
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.
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.
Any unused product or waste material should be disposed of in accordance with local requirements.

Contra-indications: Hypersensitivity to the active substance or to any of the excipients. Known allergic reaction to hamster proteins.

Special Warnings and Precautions:
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.
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.

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.

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 DIC. Clinical surveillance for early signs of thrombotic and consumptive coagulopathy, with appropriate biological testing should be initiated when administering BeneFIX to post-operative patients, new-born infants, patients at risk of thrombotic phenomena or DIC, or with liver disease.
The safety and efficacy of BeneFIX administration by continuous infusion have not been established. There have been post-marketing reports of thrombotic events, including life-threatening superior vena cava (SVC) syndrome in critically ill new born infants, while receiving continuous-infusion BeneFIX through a central venous catheter.

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

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.

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

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 lactation only if clearly indicated.
The effect of BeneFIX on fertility has not been established.

Side Effects: Adverse events are presented 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 adverse reactions listed below were reported in 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.

Infections and infestations
Uncommon: Infusion-site cellulitis
Blood and lymphatic system disorders
Uncommon: Factor IX inhibition
Immune system disorders
Common: Hypersensitivity; Frequency unknown: Anaphylactic reaction
Nervous system disorders
Very common: Headache; Common: Dizziness; Dysgeusia; Uncommon: Somnolence; tremor
Eye disorders
Uncommon: Visual impairment
Cardiac disorders
Uncommon: Tachycardia
Vascular disorders
Common: Phlebitis; flushing, Uncommon: Hypotension, Frequency unknown: Superior vena cava syndrome; deep vein thrombosis; thrombosis; thrombophlebitis
Respiratory, thoracic and mediastinal disorders:
Very common: Cough
Gastrointestinal disorders:
Common: Vomiting; nausea
Skin and subcutaneous tissue disorders:
Common: Rash; urticaria
Renal and urinary disorders:
Uncommon: Renal infarct
General disorders and administration site conditions:
Very common: Pyrexia, Common: Chest discomfort; infusion site reaction; infusion site pain, Frequency unknown: Inadequate therapeutic response
Investigations
Frequency unknown Inadequate factor IX recovery

If any suspected hypersensitivity reaction takes place that is thought to be related to the administration of BeneFIX see posology and warnings and precautions.

Paediatric population
Allergic reactions might be experienced more frequently in children than in adults. There is insufficient data to provide information on inhibitor incidence in PUPs (see pharmacodynamics properties).

Legal Category: POM.

Package Quantities: The 250 IU, 500 IU, 1000 IU, 2000 & 3000 IU packs consist of a vial of BeneFIX, a pre-filled syringe of solvent, a sterile vial adapter reconstitution device, a sterile infusion set, two alcohol swabs, a plaster and a gauze pad.

Product Licence Number:
PLGB 00057/1543 – 250 IU
PLGB 00057/1545 – 500 IU
PLGB 00057/1540 – 1000 IU
PLGB 00057/1542 – 2000 IU
PLGB 00057/1544 – 3000IU
Basic NHS Cost: 60.7p per IU.
250 IU: £151.80, 500 IU: £303.60, 1000 IU: £607.20, 2000 IU: £1214.40, 3000IU: £1821.60

For further information and details of other side effects see Summary of Product Characteristics

Further information is available on request from Medical Information Department at Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey, KT20 7NS, UK.

Marketing Authorisation Holder:
Pfizer Limited, Ramsgate Road, Sandwich, Kent, CT13 9NJ, United Kingdom.

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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Pfizer Medical Information on 01304 616161

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