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 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 every 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.

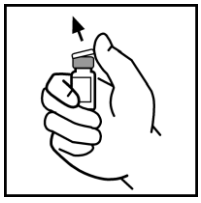
Always wash your hands prior to performing the following procedures. Aseptic technique (meaning clean and germ free) should be used during the reconstitution procedure.

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.

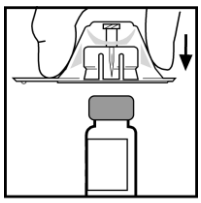
2. Remove the plastic flip-top cap from the BeneFIX vial to expose the central portion of the rubber stopper.



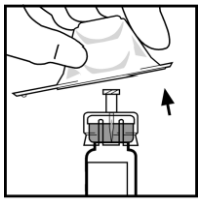
3. Wipe the top of the vial with an alcohol swab provided, or use another antiseptic solution and allow to dry. After cleaning do not touch the rubber stopper with your hand or allow it to touch any surface.

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.

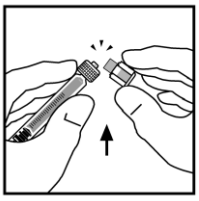


6. Lift the package away from the adapter and discard the package.

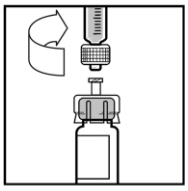


7. Attach the plunger rod to the solvent syringe by pushing and turning firmly.

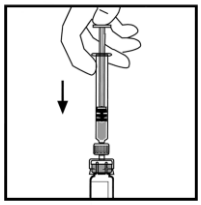
8. Break off the tamper-resistant plastic tip cap from the solvent syringe by snapping the perforation of the cap. This is done by bending the cap up and down until the perforation is broken. Do not touch the inside of the cap or the syringe tip. The cap may need to be replaced (if not administering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



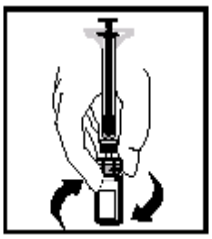
9. Place the vial on a flat surface. Connect the solvent syringe to the vial adapter by inserting the tip of the syringe into the adapter opening while firmly pushing and turning the syringe clockwise until the connection is secured.



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



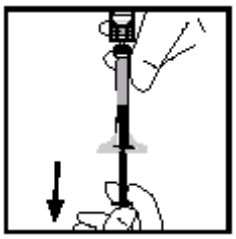
11. With the syringe still connected to the adapter, gently rotate the vial until the powder is dissolved.



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 Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. 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, 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, 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
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, 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

Marketing Authorisation Holder

Pfizer Limited
Ramsgate Road, Sandwich, Kent, CT13 9NJ, United Kingdom

Manufacturer

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

For any information about this medicine, please contact:
Medical Information, Pfizer Ltd, Walton Oaks, Dorking Road, Tadworth, Surrey, KT20 7NS.
Tel: 01304 616161

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