Your doctor is the best resource for medical advice and information. The health information contained herein is provided for educational / awareness purposes only and is not intended to replace discussions with a medical practitioner and/or medical advice or be construed as a promotional information.

Package Leaflet: Information for the user Nonacog alfa (recombinant coagulation factor IX) BeneFIX®

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- If you have any further questions, ask your doctor.
- 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. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What BeneFIX (Nonacog alfa (recombinant coagulation factor IX)) 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 (Nonacog alfa (recombinant coagulation factor IX)) works by replacing factor IX in haemophilia B patients to enable their blood to clot.

BeneFIX (Nonacog alfa (recombinant coagulation factor IX)) is used 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

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Limitation of Use

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

2. What you need to know before you take BeneFIX (Nonacog alfa (recombinant coagulation factor IX))

Do not take BeneFIX (Nonacog alfa (recombinant coagulation factor IX))

- 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 (Nonacog alfa (recombinant coagulation factor IX)).
- 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 (Nonacog alfa (recombinant coagulation factor IX)).
- 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 (Nonacog alfa (recombinant coagulation factor IX)).
- 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 (Nonacog alfa (recombinant coagulation factor IX)).
- Because of the risk of allergic reactions with factor IX, your initial administrations of BeneFIX (Nonacog alfa (recombinant coagulation factor IX)) 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 (Nonacog alfa (recombinant coagulation factor IX)) 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 (Nonacog alfa (recombinant coagulation factor IX)).
- It is recommended that every time you use BeneFIX (Nonacog alfa (recombinant coagulation factor IX)), 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 (Nonacog alfa (recombinant coagulation factor IX))

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

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 (Nonacog alfa (recombinant coagulation factor IX)) upon specific instructions from your doctor. It is not known whether BeneFIX (Nonacog alfa (recombinant coagulation factor IX)) can cause harm to an unborn baby when given to pregnant women. Your doctor may advise you to stop treatment with BeneFIX (Nonacog alfa (recombinant coagulation factor IX)) if you are breast-feeding or become pregnant.

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

Driving and using machines

BeneFIX (Nonacog alfa (recombinant coagulation factor IX)) has no influence on the ability to drive or use machines.

3. How to take BeneFIX (Nonacog alfa (recombinant coagulation factor IX))

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

Your doctor may decide to change the dose of BeneFIX (Nonacog alfa (recombinant coagulation factor IX)) you receive during your treatment.

Reconstitution and administration

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

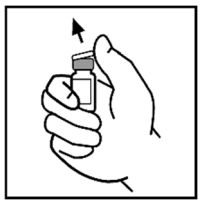
BeneFIX (Nonacog alfa (recombinant coagulation factor IX)) is administered by intravenous (IV) infusion after reconstitution of the powder for injection with the supplied solvent (a sodium chloride (salt) solution) in the pre-filled syringe.

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

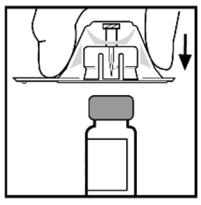
Reconstitution:

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

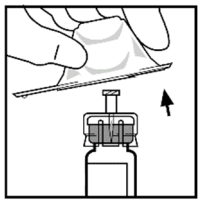
1. Allow the vial of lyophilised (freeze-dried) BeneFIX (Nonacog alfa (recombinant coagulation factor IX)) and the pre-filled syringe to reach room temperature.
2. Remove the plastic flip-top cap from the BeneFIX (Nonacog alfa (recombinant coagulation factor IX)) vial to expose the central portion of the rubber stopper.



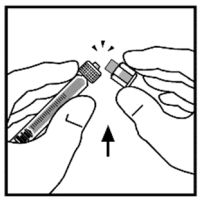
3. Wipe the top of the vial with an alcohol swab provided, or use another antiseptic solution and allow to dry. After cleaning do not touch the rubber stopper with your hand or allow it to touch any surface.
4. Peel back the lid from the clear plastic vial adapter package. Do not remove the adapter from 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.



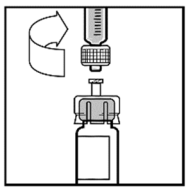
6. Lift the package away from the adapter and discard the package.



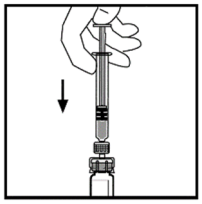
7. Attach the plunger rod to the solvent syringe by pushing and turning firmly.
8. Break off the tamper-resistant plastic tip cap from the solvent syringe by snapping the perforation of the cap. This is done by bending the cap up and down until the perforation is broken. Do not touch the inside of the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



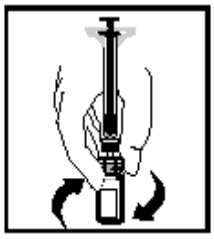
9. Place the vial on a flat surface. Connect the solvent syringe to the vial adapter by inserting the tip of the syringe into the adapter opening while firmly pushing and turning the syringe clockwise until the connection is secured.



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

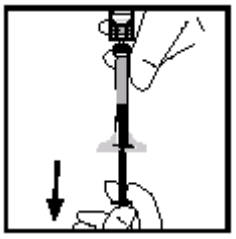


12. The final solution should be inspected visually for fine particles before administration. The solution should appear clear and colourless.

Note: If you use more than one vial of BeneFIX (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.

BeneFIX (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.

Administration (Intravenous Injection):

BeneFIX (Nonacog alfa (recombinant coagulation factor IX)) 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 (Nonacog alfa (recombinant coagulation factor IX)) 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 (Nonacog alfa (recombinant coagulation factor IX)). 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 (Nonacog alfa (recombinant coagulation factor IX)) solution) and resume administration with a new package.

Because the use of BeneFIX (Nonacog alfa (recombinant coagulation factor IX)) by continuous infusion (drip) has not been evaluated, BeneFIX (Nonacog alfa (recombinant coagulation factor IX)) 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 (Nonacog alfa (recombinant coagulation factor IX)) than you should

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

If you stop taking BeneFIX (Nonacog alfa (recombinant coagulation factor IX))

Do not stop taking BeneFIX (Nonacog alfa (recombinant coagulation factor IX)) 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 (Nonacog alfa (recombinant coagulation factor IX)). 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 (Nonacog alfa (recombinant coagulation factor IX)) 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 administration 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 (Nonacog alfa (recombinant coagulation factor IX)) 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 (Nonacog alfa (recombinant coagulation factor IX)) 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 (Nonacog alfa (recombinant coagulation factor IX)) 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 1 in 100 to 1 in 10)

- 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 1 in 1000 to 1 in 100)

- 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)

5. How to store BeneFIX (Nonacog alfa (recombinant coagulation factor IX))

BeneFIX (Nonacog alfa (recombinant coagulation factor IX)) must be stored Store between 2 - 30ºC.

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.

Any unused product or waste material should be disposed of in accordance with local requirements.

6. Contents of the pack and other information

What BeneFIX (Nonacog alfa (recombinant coagulation factor IX)) contains

- The active substance is Nonacog alfa (recombinant coagulation factor IX). Each vial of BeneFIX (Nonacog alfa (recombinant coagulation factor IX)) 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 (Nonacog alfa (recombinant coagulation factor IX)) per ml prepared solution

Amount of BeneFIX (Nonacog alfa (recombinant coagulation factor IX)) per Vial	Amount of BeneFIX (Nonacog alfa (recombinant coagulation factor IX)) 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 (Nonacog alfa (recombinant coagulation factor IX)) looks like and contents of the pack

BeneFIX (Nonacog alfa (recombinant coagulation factor IX)) 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:

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.

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