Package leaflet: Information for the user

RIXUBIS 250 IU powder and solvent for solution for injection
RIXUBIS 500 IU powder and solvent for solution for injection
RIXUBIS 1000 IU powder and solvent for solution for injection
RIXUBIS 2000 IU powder and solvent for solution for injection
RIXUBIS 3000 IU powder and solvent for solution for injection

nonacog gamma (recombinant human coagulation factor IX)

Read all of this leaflet carefully before you start using 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 or pharmacist.
- 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, or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What RIXUBIS is and what it is used for

RIXUBIS contains the active substance nonacog gamma and is a coagulation factor IX product. Factor IX is a normal constituent of human blood necessary for effective blood clotting. RIXUBIS is used in patients with haemophilia B (Christmas disease, an inherited bleeding disorder caused by lack of factor IX). It works by replacing the missing factor IX to enable the patient's blood to clot.

RIXUBIS is used for the treatment and prevention of bleeding in patients with haemophilia B of all age groups.

2. What you need to know before you use RIXUBIS

Do not use RIXUBIS
- if you are allergic to nonacog gamma or any of the other ingredients of this medicine (listed in section 6)
- if you are allergic to hamster proteins

Warnings and precautions
Allergic-type hypersensitivity reactions are possible with RIXUBIS. Stop your infusion and contact your doctor immediately or seek emergency medical care if you experience early signs of hypersensitivity/allergic reactions like hives, rash, tightness of the chest, wheezing, low blood pressure or anaphylaxis (severe allergic reaction that can cause difficulty in swallowing and/or breathing, red or swollen face and/or hands). Your doctor may need to treat you promptly for these reactions. Your doctor may also do a blood test to check if you have developed activity-neutralising antibodies

(inhibitors) against your medicine, as inhibitors may develop together with allergies. Patients with factor IX inhibitors may be at an increased risk of anaphylaxis during future treatment with factor IX.

Talk to your doctor immediately if your bleeding does not stop as expected or if you experience a significant increase in your usage of RIXUBIS in order to control a bleed. Your doctor will do a blood test to check if you have developed activity-neutralising antibodies (inhibitors) against RIXUBIS. The risk for developing inhibitors is highest in patients who have not been treated with a factor IX replacement medicine before or in the early phases of treatment, i.e. for small children.

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 have factor IX inhibitors and an allergic reaction in the early period with any factor IX concentrate. Therefore if you are known to have such a mutation, your doctor will monitor you more closely for signs of an allergic reaction.

If you suffer from liver or cardiac disease or if you have recently had major surgery, please inform your doctor, as there is an increased risk for blood clotting (coagulation) complications.

Kidney disorders (nephrotic syndrome) have been reported following high doses of Factor IX in haemophilia B patients with factor IX inhibitors and a history of allergic reactions.

Whenever possible, please record the name of the product and the batch number every time you use RIXUBIS (e.g. in your diary) to keep track of the products and product batches you have used.

Other medicines and RIXUBIS
Tell your doctor if you are using or have recently used or might use any other medicines. No interactions of RIXUBIS with other medicines are known.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. Haemophilia B very rarely occurs in women.

Driving and using machines
RIXUBIS has no influence on the ability to drive and use machines.

RIXUBIS contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium-free’. However, depending on your body weight and your dose of RIXUBIS, you could receive more than one vial. This should be taken into consideration if you are on a controlled sodium diet.

3. How to use RIXUBIS

Treatment with RIXUBIS will be started by a doctor who is experienced in the care of patients with haemophilia B.

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

Your doctor will decide the dose of RIXUBIS you will receive. This dose and duration will depend on the severity of your factor IX deficiency, on the location and extent of the bleeding and on your clinical condition, age and how quickly your body uses up factor IX which will have to be checked regularly.

RIXUBIS is administered by intravenous infusion (IV) after reconstitution of the powder with the provided solvent by your doctor or nurse. You or somebody else might also administer RIXUBIS as an injection but only after receiving adequate training.

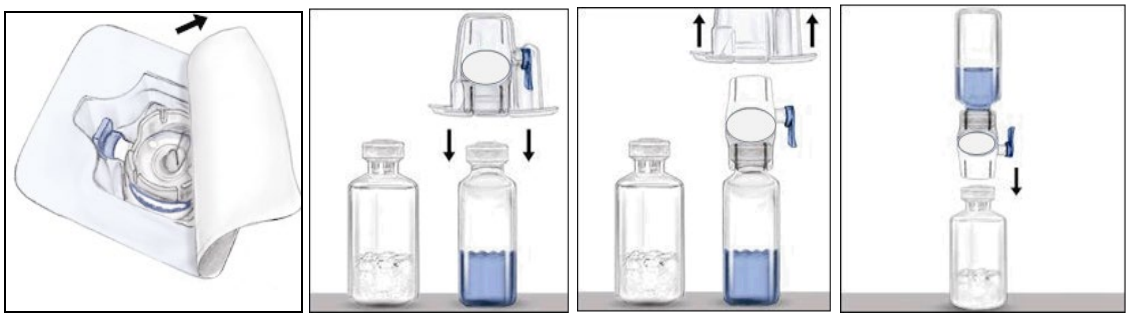
Reconstitution and administration

- For reconstitution use only the solvent and the reconstitution device (BAXJECT II) provided in the pack.
- For administration the use of a luer-lock syringe is required.
- Do not use if the BAXJECT II device, its sterile barrier system or its packaging is damaged or shows any sign of deterioration.

Reconstitution
Use Aseptic Technique

1. If the product is stored in a refrigerator, take both the RIXUBIS powder and solvent vials from the refrigerator and let them reach room temperature (between 15°C and 30°C).
2. Wash your hands thoroughly using soap and warm water.
3. Remove caps from powder and solvent vials.
4. Cleanse stoppers with alcohol swabs. Place the vials on a flat clean surface.
5. Open the package of BAXJECT II device by peeling away the paper lid without touching the inside (Fig. a). Do not remove the device from the package.
6. Turn the package over and insert the clear plastic spike through the solvent stopper. Grip the package at its edge and pull the package off BAXJECT II (Fig. b). Do not remove the blue cap from the BAXJECT II device.
7. With BAXJECT II attached to the solvent vial, invert the system so that the solvent vial is on top of the device. Insert the white plastic spike through the RIXUBIS stopper. The vacuum will draw the solvent into the RIXUBIS vial (Fig. c).
8. Swirl gently until all material is dissolved. The product dissolves rapidly (within 2 minutes). Be sure that RIXUBIS is completely dissolved, otherwise not all reconstituted solution will pass through the device filter. Reconstituted medicinal products should be inspected visually for particulate matter and discoloration prior to administration. The solution should be clear or slightly opalescent. Do not use solution that are cloudy or have deposits.

Fig. a **Fig. b** **Fig. c**



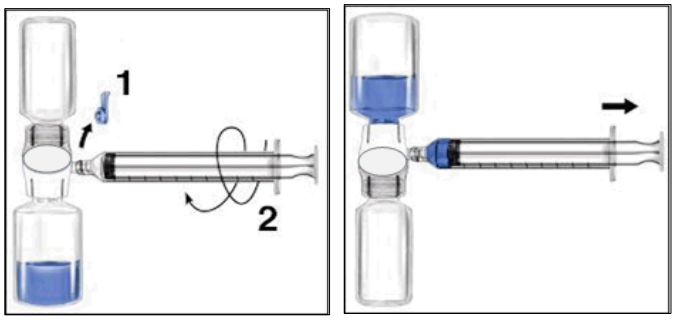
Do not refrigerate the preparation after reconstitution.
Use immediately.

Administration
Use Aseptic Technique

1. Remove the blue cap from BAXJECT II. **Do not draw air into the syringe**. Connect the syringe to BAXJECT II (Fig. d).
2. Invert the system (the vial with the reconstituted solution has to be on top). Draw the reconstituted solution into the syringe by pulling the plunger back slowly (Fig. e).
3. Disconnect the syringe.

4. Attach a butterfly needle to the syringe. Inject intravenously. The solution should be administered slowly, at a rate as determined by the patient's comfort level, not to exceed 10 ml per minute.

Fig. d **Fig. e**



Whenever possible, please record the name of the product and the batch number every time you use RIXUBIS (e.g. in your diary) to keep track of the products and product batches you have used.

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

If you use more RIXUBIS than you should
Always use RIXUBIS exactly as your doctor has told you. If you are not sure check with your doctor. If you injected more RIXUBIS than recommended, tell your doctor as soon as possible.

If you forget to use RIXUBIS
Do not inject a double dose to make up for a forgotten dose. Proceed with the next injection as scheduled and continue as advised by your doctor.

If you stop using RIXUBIS
Do not stop using RIXUBIS without consulting your doctor.

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

4. Possible side effects

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

Allergic-type hypersensitivity reactions are possible with RIXUBIS. Such reactions may include burning sensations and stinging at the infusion site, chills, flushing, lethargy, restlessness, tingling, hives, itching and rash, low blood pressure, fast heart rate, tightness of the chest, wheezing, swelling of the throat, anaphylaxis (severe allergic reaction), headache, nausea and vomiting. Please, contact your doctor immediately if you experience such signs. Your doctor may need to treat you promptly for these reactions (see section 2 'Warnings and precautions').

The following side effects have been observed with RIXUBIS:

Common side effects (may affect up to 1 in 10 patients)
- altered taste
- pain in limbs.

Side effects with unknown frequency (frequency cannot be estimated from the available data)
- allergic reactions (hypersensitivity).

Problems from exaggerated blood clotting (thromboembolic episodes) have not been observed with this product, but may occur with any factor IX products. These may include heart attack, blood clots in the veins or blood clots in the lung.

Reporting of side effects
If you get any side effects, talk to your doctor or, pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via Yellow Card Scheme at 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 RIXUBIS

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 after EXP. The expiry date refers to the last day of that month.

Store below 30°C.
Do not freeze.

Use the reconstituted solution immediately.

Do not use RIXUBIS if the solution is not clear and colourless.

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

6. Contents of the pack and other information

What RIXUBIS contains
- The active substance is nonacog gamma (recombinant human coagulation Factor IX). Each powder vials contains nominally 250, 500, 1000, 2000 or 3000 IU, corresponding to a concentration of 50, 100, 200, 400 or 600 IU/ml after reconstitution with 5 ml solvent.
- The other ingredients in the powder are sucrose, mannitol, sodium chloride, calcium chloride, L-histidine, polysorbate 80.

Solvent vial: 5 ml sterilised water for injections.

What RIXUBIS looks like and contents of the pack

RIXUBIS is provided as a powder and solvent for solution for injection.

The contents of the pack are:

- one vial of RIXUBIS 250, 500, 1000, 2000 or 3000 IU powder in a glass vial with a rubber stopper
- one vial of 5 ml sterilised water for injections in a glass vial with a rubber stopper
- one BAXJECT II (needle-less reconstitution device)

Marketing Authorisation Holder

Baxalta Innovations GmbH
Industriestrasse 67
A-1221 Vienna
Austria

Tel.: +800 66838470
E-mail: medinfoEMEA@shire.com

Manufacturer

Baxalta Belgium Manufacturing SA
Boulevard René Branquart 80
B-7860 Lessines
Belgium

This leaflet was last revised in 01/2020.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

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.

To ensure that the desired factor IX activity plasma level has been attained, careful monitoring using an appropriate factor IX activity assay is advised and, if necessary, appropriate adjustments to the dose and the frequency of repeated infusions should be performed. 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 depends on the severity of the factor IX deficiency, on the location and extent of the bleeding, and on the patient's clinical condition, age and pharmacokinetic parameters of factor IX, such as incremental recovery and half-life.

The number of units of factor IX administered is expressed in International Units (IU), which are 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 of factor IX activity is equivalent to that quantity of factor IX in one ml of normal human plasma.

Adult population
On demand treatment:
The calculation of the required dose of factor IX is based on the empirical finding that 1 International Unit factor IX per kg body weight raises the plasma factor IX activity by 0.9 IU/dL (range from 0.5 to 1.4 IU/dL) or 0.9% of normal activity in patients 12 years and older (further information see section 5.2).

The required dose is determined using the following formula:

Required units	=	body weight (kg)	x	desired factor IX rise (%) or (IU/dL)	x	reciprocal of observed recovery (dL/kg)

For an incremental recovery of 0.9 IU/dL per IU/kg, the dose is calculated as follows:

Required units	=	body weight (kg)	x	desired factor IX rise (%) or (IU/dL)	x	1.1 dL/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 level (in % of normal or 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)**
<u>Haemorrhage</u> 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.
<u>Surgery</u> Minor surgery including tooth extraction	30 – 60	Every 24 hours, at least 1 day, until healing is achieved.
<u>Major surgery</u>	80 – 100 (pre- and postoperative)	Repeat infusion every 8 to 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).

Careful monitoring of replacement therapy is especially important in cases of major surgery or life-threatening haemorrhages.

Prophylaxis
For long-term prophylaxis against bleeding in patients with severe haemophilia B, the usual doses are 40 to 60 IU of factor IX per kilogram of body weight at intervals of 3 to 4 days for patients 12 years and older. In some cases, depending upon the individual patient´s pharmacokinetics, age, bleeding phenotype and physical activity, shorter dosage intervals or higher doses may be necessary.

Continuous infusion
Do not administer RIXUBIS by continuous infusion.

Paediatric population
Patients aged 12 to 17 years of age:
Posology is the same in adults and paediatric population from 12 to 17.

Patients less than 12 years:
On demand treatment
The calculation of the required dose of factor IX is based on the empirical finding that 1 International Unit (IU) factor IX per kg body weight raises the plasma factor IX activity by 0.7 IU/dL (range from 0.31 to 1.0 IU/dL) or 0.7% of normal activity in patients less than 12 years of age (further information see section 5.2).

The required dosage is determined using the following formula:

Patients less than 12 years:

Required units	=	body weight (kg)	x	desired factor IX rise (%) or (IU/dL)	x	reciprocal of observed recovery (dL/kg)

For an incremental recovery of 0.7 IU/dL per IU/kg, the dose is calculated as follows:

Required units	=	body weight (kg)	x	desired factor IX rise (%) or (IU/dL)	x	1.4 dL/kg

The same table as for adults can be used to guide dosing in bleeding episodes and surgery (see above).

Prophylaxis:
The recommended dose range for paediatric patients less than 12 years is 40 to 80 IU/kg at intervals of 3 to 4 days. In some cases, depending upon the individual patient´s pharmacokinetics, age, bleeding phenotype and physical activity, shorter dosage intervals or higher doses may be necessary.