

Medicinal product no longer authorised

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nonafact 100 IU/ml powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nonafact contains 100 IU/ml (500 IU/5ml or 1000 IU/10ml) human coagulation factor IX when reconstituted with 5 ml or 10 ml, respectively, of water for injections.

Each vial contains 500 IU or 1000 IU of human coagulation factor IX.

The potency (IU) is determined using a method equivalent to the test method described in the European Pharmacopoeia. The specific activity of Nonafact is at least 200 IU/mg protein.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection. White powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

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

The dose and the duration of substitution therapy depend on the severity of the factor IX deficiency. Other determining factors are the site and extent of the haemorrhage and the patient's clinical condition.

The number of units of factor IX administered is expressed in International Units (IU), which are related to the current International Standard for factor IX concentrate as approved by the WHO. 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 related to the quantity of factor IX in the International Standard for factor II, VII, IX and X in human plasma (approved by the WHO) which approximates to the quantity of factor IX in one ml of normal human plasma. The calculation of the required dosage 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 1.1 % of normal activity. The required dosage is determined using the following formula:

Required units = body weight (kg) x desired factor IX rise (%) (IU/dl) x 0.9

The amount to be administered and the frequency of treatment should always be determined on the basis of clinical effectiveness in the individual patient. Factor IX products rarely require to be administered more than once daily.

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 (%) (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		
<i>Minor</i> including tooth extraction	30-60	Every 24 hours, at least 1 day, until healing is achieved.
<i>Major</i>	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).

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 injections. In the case of major surgical interventions in particular, precise monitoring of substitution therapy by means of coagulation analysis (plasma factor IX activity) is indispensable. Individual patients may vary in their response to factor IX, achieving different levels of *in vivo* recovery and demonstrating different half-lives.

For long-term prophylaxis of haemorrhages in patients with severe haemophilia B, doses of 20 to 40 IU of factor IX per kilogram of body weight could be given at intervals of 3 to 4 days. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

Paediatric population

The safety and efficacy of Nonafact in children less than 6 years of age has not been established. There are insufficient data to recommend the use of Nonafact in children less than 6 years of age.

Patients should be monitored for the development of factor IX inhibitors. If the expected factor IX activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, an assay should be performed to determine if a factor IX inhibitor is present. In patients with high levels of inhibitor, factor IX therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of patients with haemophilia, see also 4.4.

Method of administration

The product should be administered via the intravenous route. It is recommended that the rate of administration should not exceed 2 ml/min. For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients;
- Hypersensitivity to mouse proteins.

4.4 Special warnings and precautions for use

As with any intravenous protein product, allergic type hypersensitivity reactions are possible. The product contains traces of mouse proteins. Patients should be informed of the early signs of hypersensitivity reactions including urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. If these symptoms occur, patients should be advised to discontinue use of the product immediately and contact their physician.

In case of shock, the current medical standards for shock-treatment should be observed.

Since the use of factor IX complex concentrates has historically been associated with the development of thromboembolic complications, the risk being higher in low purity preparations, 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 Nonafact should be weighed against the risk of these complications.

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of virus. Despite this, when medicines prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses or other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped viruses HAV and parvovirus B19.

Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of plasma-derived factor IX concentrates.

It is strongly recommended that every time that Nonafact 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 product.

After repeated treatment with Nonafact, patients should be monitored for the development of neutralising antibodies (inhibitors) that should be quantified in Bethesda Units (BU) 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.

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.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'.

4.5 Interactions with other medicinal products and other forms of interaction

No interactions of Nonafact with other medicinal products are known.

4.6 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 breast-feeding is not available. Therefore, factor IX should be used during pregnancy and lactation only if clearly indicated.

4.7 Effects on ability to drive and use machines

Nonafact has no influence on the ability to drive and use machines.

4.8 Undesirable effects

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 infrequently in patients treated with factor IX containing products. 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 4.4).

Nephrotic syndrome has been reported following attempted immune tolerance induction on haemophilia B patients with factor IX inhibitors and a history of allergic reaction.

On rare occasions, fever has been observed.

Haemophilia B patients may develop 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 haemophilia centre be contacted. During clinical trials with Nonafact conducted in previously treated patients development of inhibitors was not reported. There is no experience of the treatment of previously untreated patients with Nonafact.

There is a potential risk of thromboembolic episodes following the administration of factor IX products, with a higher risk for low purity preparations. The use of low purity factor IX products has been associated with instances of myocardial infarction, disseminated intravascular coagulation, venous thrombosis and pulmonary embolism. The use of high purity factor IX is rarely associated with such side effects.

Nonafact contains trace amounts (< 0.1 ng mouse IgG/IU of factor IX) of the murine monoclonal antibody used in its purification. In theory, therefore, the use of Nonafact could generate antibodies to mouse protein. The clinical relevance of antibodies to mouse protein, if these do indeed arise, is not known.

For safety with respect to transmissible agents, see 4.4.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: antihæmorrhagics, blood coagulation factor IX. ATC code: B02BD04.

Factor IX is a single chain glycoprotein with a molecular weight of about 68,000 Dalton. It is a vitamin K-dependent coagulation factor and is synthesised in the liver. Factor IX is activated by factor XIa in the intrinsic coagulation pathway and by the factor VII/tissue factor complex in the extrinsic pathway. Activated factor IX, in combination with activated factor VIII, activates factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot is formed. Haemophilia 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 are increased, thereby enabling a temporary correction of the factor IX deficiency and correction of the bleeding tendencies.

There are insufficient data to recommend the use of Nonafact in children less than 6 years of age.

5.2 Pharmacokinetic properties

The *in vivo* increase in factor IX levels obtained with Nonafact is 1.1 IU/dl per IU administered per kg body weight, which corresponds to an *in vivo* recovery of 49 %. Nonafact has a half-life of approximately 19 (17 – 21) hours.

5.3 Preclinical safety data

Plasma coagulation factor IX is a normal constituent of human plasma. Factor IX in this product therefore behaves like endogenous factor IX. Conventional animal toxicity studies and mutagenicity studies with plasma coagulation factor IX were not carried out. In pharmacodynamic studies in rabbits and guinea pigs, the thrombogenicity of Nonafact was shown to be minimal.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Sodium chloride
Sucrose
Histidine.

Solvent:
Water for injections.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

After reconstitution:
Chemical and physical in-use stability has been demonstrated for 3 hours at a temperature of 21°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and

would normally not be longer than 24 hours at 2 to 8 °C, unless reconstitution/dilution (etc) has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (at 2°C – 8°C). Do not freeze. Keep the vials in the outer carton, in order to protect from light. For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

500 IU: one vial (glass type I) of powder + one vial (glass type I) of 5 ml solvent with stoppers (bromobutyl).

1000 IU: one vial (glass type I) of powder + one vial (glass type I) of 10 ml solvent with stoppers (bromobutyl).

6.6 Instructions for use/and handling, and disposal

Reconstitution

1. Bring the two vials to a temperature between 15°C and 25°C.
2. Remove the plastic cap from the vials.
3. Disinfect the surface of the stoppers of both vials with a gauze soaked in 70 % alcohol.
4. Remove the protective sheath from one end of a transfer needle and pierce the stopper of the vial containing water for injections. Remove the protective sheath from the other end of the transfer needle. Invert the solvent vial and pierce the stopper of the vial containing the powder.
5. Tilt the product vial when transferring the solvent to allow the solvent to flow down the side of the vial.
6. Remove the empty vial and the transfer needle.
7. Swirl the vial gently to completely dissolve the powder within 5 minutes. The resulting solution is clear, colourless to light yellow and has a neutral pH.

Reconstituted products should be inspected visually for particulate matter and discoloration prior to administration. The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits.

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

7. MARKETING AUTHORISATION HOLDER

Sanquin
Plesmanlaan 125
NL-1066 CX Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/186/001 (500 IU)
EU/1/01/186/002 (1000 IU)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 3 July 2001
Renewal of authorisation: 3 July 2006

10. DATE OF REVISION OF TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMA) <http://www.ema.europa.eu>.

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ANNEX II

- A. MANUFACTURER OF THE BIOLOGICAL ACTIVE
SUBSTANCE AND MANUFACTURING AUTHORISATION
HOLDER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**

**A MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND
MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH
RELEASE**

Name and address of the manufacturer of the biological active substance

Stichting Sanquin Bloedvoorziening,
Plesmanlaan 125
1066 CX Amsterdam
The Netherlands

Name and address of the manufacturers responsible for batch release

Stichting Sanquin Bloedvoorziening,
Plesmanlaan 125
1066 CX Amsterdam
The Netherlands

B CONDITIONS OF THE MARKETING AUTHORISATION

• **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE
IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, 4.2)

• **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND
EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not Applicable.

• **OTHER CONDITIONS**

Official batch release: in accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

ANNEX III
LABELLING AND PACKAGE LEAFLET

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A. LABELLING

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PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND ON THE IMMEDIATE PACKAGING

BOX VIAL OF POWDER 500 IU
BOX VIAL OF POWDER 1000 IU

1. NAME OF THE MEDICINAL PRODUCT

Nonafact 100 IU/ml powder and solvent for solution for injection
Human coagulation factor IX

2. STATEMENT OF ACTIVE SUBSTANCE(S)

500 IU human coagulation factor IX (100 IU/ml after reconstitution).
1000 IU human coagulation factor IX (100 IU/ml after reconstitution).

3. LIST OF EXCIPIENTS

Contains: sodium chloride, histidine and sucrose.

Solvent: water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection.

Contents:

1 vial of powder for solution for injection

1 vial water for injections 5 ml

1 vial water for injections 10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Reconstitute with 5 ml of water for injections.

Reconstitute with 10 ml of water for injections.

The product should be used immediately.

Single dose administration only.

for intravenous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not use if the solution is not totally clear or if the powder is not totally reconstituted.

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (at 2°C – 8°C). Do not freeze.
Keep the container in the outer carton, in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Sanquin, Plesmanlaan 125, NL-1066 CX Amsterdam, the Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/186/001

EU/1/01/186/002

13. BATCH NUMBER

Lot: {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL OF POWDER 500 IU

VIAL OF POWDER 1000 IU

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Nonafact 100 IU/ml powder for solution for injection
Human coagulation factor IX
for intravenous use

2. METHOD OF ADMINISTRATION

Reconstitute with 5 ml of water for injections.
Reconstitute with 10 ml of water for injections.
Administer immediately.
Read the package leaflet before use.

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot: {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

500 IU (100 IU/ml after reconstitution)

1000 IU (100 IU/ml after reconstitution)

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL OF SOLVENT 5 ml
VIAL OF SOLVENT 10 ml

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Water for injections

2. METHOD OF ADMINISTRATION

For reconstitution of Nonafact.
Read the package leaflet before use.

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot: {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml
10 ml

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B. PACKAGE LEAFLET

Medicinal product no longer authorised

PACKAGE LEAFLET: INFORMATION FOR THE USER

Nonafact 100 IU/ml Powder and solvent for solution for injection Human coagulation factor IX

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Powder

The active substance is human coagulation factor IX.

The product contains 100 International Units (IU) per ml (500 IU/5 ml or 1000 IU/10 ml) human coagulation factor IX when reconstituted with 5 ml or 10 ml, respectively, of water for injections.

The other ingredients are sodium chloride, sucrose and histidine.

Solvent

Water for injections.

In this leaflet:

1. What Nonafact is and what it is used for
2. Before you use Nonafact
3. How to use Nonafact
4. Possible side effects
5. How to store Nonafact
6. Further information

1. WHAT NONAFACT IS AND WHAT IT IS USED FOR

Nonafact can be administered to prevent and treat bleeding in patients suffering from haemophilia B (a congenital lack of active factor IX). Factor IX is a normal constituent of human blood. A deficiency of factor IX causes blood coagulation problems, which may lead to bleeding in joints, muscles or internal organs. The administration of Nonafact can compensate for this deficiency.

2. BEFORE YOU USE NONAFACT

Do not use Nonafact:

- if you are hypersensitive (allergic) to the active substance, human coagulation factor IX.
- if you are hypersensitive (allergic) to any of the other ingredients or to mouse proteins.

Take special care with Nonafact:

See your doctor immediately, if bleeding does not stop as expected.

After it has been dissolved in the supplied water for injections, the product should be clear. Check this immediately prior to administration. The product must not be administered if any cloudiness, lumps or particulate matter are visible.

In rare cases, Nonafact can give rise to a severe allergic reaction (anaphylactic shock). If, after administration, you develop hypersensitive reactions like hives, itching and rash, chest tightness, wheezing and light headedness contact your physician immediately. If you have previously experienced hypersensitivity in response to the administration of blood or a blood product, Nonafact

should only be administered when absolutely necessary (in life-threatening situations). This must be carried out in hospital or under the careful supervision of a doctor.

Individuals with haemophilia B who receive factor IX preparations, should be monitored for the development of neutralising antibodies against factor IX (inhibitors) (see Possible side effects). Your doctor will check your blood regularly for the presence of these antibodies, especially if you experienced a severe allergic reaction with the previous use of a factor IX product.

The occurrence of activity-neutralising antibodies (inhibitors) is a very rare event in previously treated patients receiving factor IX-containing products.

There is a slight risk that higher doses of Nonafact will cause clots to form in blood vessels, resulting in thrombosis. If you suffer from a liver or cardiac disease or if you have recently had surgery, there is an increased risk for coagulation complications. This also applies to newborn babies and patients with an increased risk of thrombosis or “DIC”, disseminated intravascular coagulation, a disease in which the blood coagulation system is disturbed. Your doctor will consider whether administration of Nonafact imposes a risk for coagulation complications.

When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and the testing of each donation and pools of plasma for signs of virus/infections. Manufacturers of these products also include steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus, and for the non-enveloped hepatitis A and parvovirus B19 viruses.

Your doctor may recommend that you consider vaccination against hepatitis A and B if you regularly/repeatedly receive human plasma-derived coagulation factor IX.

It is strongly recommended that every time you receive a dose of Nonafact the name and batch number of the product are recorded in order to maintain a record of the batches used.

There is no experience of the treatment of previously untreated patients with Nonafact.

Use in children

There are insufficient data to recommend the use of Nonafact in children less than 6 years of age.

Using other medicines:

There are no known interactions between Nonafact and other medicinal products.

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

Pregnancy and breast-feeding:

Based on the rare occurrence of haemophilia B in women, experience regarding the use of factor IX during pregnancy and breast-feeding is not available. Therefore, factor IX should be used by pregnant or breast-feeding women only if clearly indicated.

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

Driving and using machines:

Nonafact has no known effects on the ability to drive and to use machines.

Information about some of the ingredients of Nonafact:

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'.

3. HOW TO USE NONAFAC

Dosage:

Your doctor will decide how much Nonafact you require. The exact dose will depend on the seriousness of the clinical situation, your body weight and the amount of factor IX in your blood. If you have to undergo surgery or have a tooth extracted, inform your doctor or dentist that you have factor IX deficiency. They will then ensure that factor IX is administered to you, should this prove necessary.

Nonafact is given to you by your doctor or nurse. Nonafact may be self administered if it is an approved practice in your country and when you have been trained sufficiently. Always use Nonafact exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

It is important that the concentration of factor IX in your blood is checked regularly. If you are administered 1 IU per kilogram of body weight, the concentration of factor IX in your blood will increase by 1.1 % of normal activity.

The required dosage is determined using the following formula:

Required units = body weight (kg) x desired factor IX rise (%) (IU/dl) x 0.9

Your doctor will determine the dose of Nonafact you need and how frequently you should use it depending on the situation. The following table can be used to guide dosing in bleeding episodes and surgery:

Degree of bleeding / Type of surgical procedure	Factor IX level required (%) (IU/dl)	Frequency of doses (hours)/Duration of therapy (days)
Bleeding		
Early signs of bleeding in joints, 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 bleeding in joints, 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 bleeding	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.

<i>Major</i>	80-100 (pre- and postoperative)	Repeat infusion every 8-24 hours until adequate wound healing, then therapy for at least another 7 days.
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During the course of treatment it is advised that the concentrations of factor IX in your blood are checked regularly. Particularly with major surgery, it is important that the concentrations of factor IX in your blood are checked carefully before and after the operation.

For long-term prevention of bleeding in individuals with severe haemophilia B, doses of 20 IU to 40 IU of factor IX per kilogram body weight should be given at intervals of 3 to 4 days. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

If you have the impression that the effect of Nonafact is too strong or too weak, talk to your doctor. Individuals with haemophilia B may develop antibodies (inhibitors) against factor IX. As a result, the factor IX product used becomes inactivated (see Possible side effects). It is advised that the treatment of this serious condition be taken care of in a haemophilia treating centre where an appropriate dose will be determined. The administration of factor IX can repress these inhibitors.

Instructions for use:

Dissolving the powder

The powder should be dissolved in the supplied amount of water for injections. The solution should not be too cold when it is administered. In addition, the powder will dissolve more readily if both vials are first allowed to reach room temperature (15°C – 25°C).

1. Remove from the refrigerator and allow the two vials to reach room temperature (15°C – 25°C).
2. Remove the plastic cap from the vials.
3. Disinfect the surface of the stoppers of both vials with a gauze soaked in 70 % alcohol.
4. Remove the protective sheath from one end of a transfer needle and pierce the stopper of the vial containing water for injections. Remove the protective sheath from the other end of the transfer needle. Invert the solvent vial and pierce the stopper of the vial containing the powder.
5. Tilt the product vial when transferring the solvent to allow the solvent to flow down the side of the vial.
6. Remove the empty vial and the transfer needle.
7. Swirl the vial gently to completely dissolve the powder. Do not shake! The powder dissolves within 5 minutes to produce a clear, colourless to light-yellow solution.

Immediately before administration, the solution should be inspected: the solution should be clear and must be free of lumps. Once dissolved, the product should be used immediately (at least within 3 hours).

Nonafact should never be mixed with other medicinal products.

Administration

1. Using a hypodermic needle and syringe, draw the dissolved product out of the vial.
2. Nonafact should be injected into a vein (intravenous administration).
3. Inject the dissolved product very gradually (approx. 2 ml per minute).

Disposal

Any unused product or waste material must be discarded as instructed by your doctor or pharmacist.

Duration of treatment:

Haemophilia B is a chronic disease, therefore lifelong treatment with a factor IX product may be necessary.

If you use more Nonafact than you should:

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

4. POSSIBLE SIDE EFFECTS

As with all medicinal products derived from human blood, the use of Nonafact can cause allergic reactions which may include swelling of the larynx, burning and stinging at the infusion site, chills, flushing, hives, itching and rash, headache, tiredness, nausea, restlessness, fast heart beat, chest tightness, tingling, vomiting, wheezing.

You should discuss the possible side effects with your doctor in order to know how to recognise them and what to do if they occur. Where necessary, mild allergic reactions, such as hives, can be treated with antihistamines (medicinal products which counteract allergies). In the case of a severe allergic reaction (anaphylactic shock), immediately stop the administration of the product and contact your doctor immediately.

There is a very slight risk that Nonafact will cause clots to form in blood vessels, resulting in thrombosis. The use of Nonafact may also produce an increase in body temperature in rare cases.

Your body may develop antibodies (inhibitors) against factor IX, which will inactivate Nonafact. Your doctor will check your blood regularly for the presence of these antibodies. Contact your doctor immediately if you suspect that the product is becoming progressively less effective. This will show itself as an increased tendency to bleed.

If you need therapy for repressing antibodies (inhibitors) this should be taken care of in a haemophilia treating centre. You will be closely monitored for any possible side effect during this treatment.

If you should experience one of these side effects, you are advised to contact your doctor. If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. HOW TO STORE NONAFAC

Keep out of the reach and sight of children.

Do not use after the expiry date stated on the label and carton.

Store in a refrigerator (at 2°C – 8°C).

Keep the vial in the outer carton in order to protect from light.

From a microbiological point of view the product, once dissolved, should be used immediately, but no longer than 3 hours after reconstitution.

Before administration, check that the solution is clear. The product must not be used if any cloudiness, lumps or particulate matter are visible.

6. FURTHER INFORMATION

Nonafact 100 IU/ml human coagulation factor IX

What Nonafact contains:

- The active substance is human coagulation factor IX. Each vial contains 500 IU or 1000 IU of human coagulation factor IX.
- The other ingredients are sodium chloride, sucrose, histidine and water for injections.

What Nonafact looks like and contents of the pack:

Nonafact is presented as a powder and a solvent for solution for injection (vial of 5 ml or 10 ml)

Nonafact consists of a carton containing:

- A vial of Nonafact containing 500 IU or 1000 IU of factor IX
- A vial water for injections containing 5 ml or 10 ml

Marketing Authorisation Holder and Manufacturer

Sanquin, Plesmanlaan 125 NL, 1066 CX Amsterdam, the Netherlands

This leaflet was last approved

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

Medicinal product no longer authorised