

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

NanoFIX 500 IU, 500 IU powder and solvent for solution for injection

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

- NanoFIX 500 IU is presented as a powder and solvent for solution for injection containing nominally 500 IU human coagulation factor IX per vial.

The product contains approximately 100 IU/ml human coagulation factor IX when reconstituted with 5 ml water for injections (Ph.Eur.).

NanoFIX is produced from plasma of human donors.

The potency (IU) is determined using the European Pharmacopoeia one stage clotting test, in comparison with an international standard from the World Health Organisation (WHO). The specific activity of NanoFIX is approximately 100 IU/mg protein.

### Excipients with known effect

This medicinal product contains up to 69 mg sodium for 1 vial NanoFIX 500 IU. For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

The powder is white or pale yellow also appearing as a friable solid.

## 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

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

### Previously untreated patients

The safety and efficacy of NanoFIX in previously untreated patients have not yet been established.

### 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.

### Posology

Dose and duration of the substitution therapy depend on the severity of the factor IX deficiency, on the location and extent of the bleeding and on 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 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 (IU) of factor IX activity is equivalent to that quantity of factor IX in one ml of normal human plasma.

### On demand treatment

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 % 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 0.8**

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) 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)
<b>Haemorrhage</b>		
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.
<b>Surgery</b>		
<i>Minor Surgery</i> including tooth extraction	30 - 60	Every 24 hours, at least 1 day, until healing is achieved.
<i>Major Surgery</i>	80 – 100 (pre-and /post-operative)	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).

#### Prophylaxis

For long term prophylaxis against bleeding in patients with severe haemophilia B, the usual doses are 20 to 40 IU of factor IX per kilogram of body weight at intervals of 3 to 4 days.

In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

#### Continuous infusion

There is not enough data available to recommend continuous infusion of NanoFIX in surgical procedures..

#### Paediatric population

In the study conducted in 25 children under 6 years of age, the median dose administered per exposure day was similar for prophylaxis and treatment of bleeding, i.e. 35 to 40 IU/kg BW.

#### Method of administration

Intravenous use.

It is recommended not to administer more than 2 - 3 ml per minute. For instructions on reconstitution of the medicinal product before administration, see section 6.

### 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Known allergy related reduction of thrombocytes during heparin treatment (heparin – induced thrombocytopenia [HIT] type II).

### 4.4 Special warnings and precautions for use

#### Hypersensitivity

Allergic type hypersensitivity reactions are possible with NanoFIX. The product contains traces of human proteins other than factor IX and heparin. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal

product immediately and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.

In case of shock, standard medical-treatment for shock should be implemented

#### Inhibitors

After repeated treatment with human coagulation factor IX products, 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 products, 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.

#### Thromboembolism

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 disseminated intravascular coagulation (DIC). In each of these situations, the benefit of treatment with NanoFIX should be weighed against the risk of these complications.

#### Cardiovascular events

In patients with existing cardiovascular risk factors, substitution therapy with FIX may increase the cardiovascular risk.

#### Catheter-related complications

If a central venous access device (CVAD) is required, risk of CVAD-related complications including local infections, bacteraemia and catheter site thrombosis should be considered.

#### Transmissible agents

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 viruses. Despite this, when medicinal products 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 and other pathogens.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) and for the non-enveloped hepatitis A virus (HAV). The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia). Appropriate vaccination (hepatitis A and B) should be considered for patients in regular / repeated receipt of human plasma-derived factor IX concentrates.

It is strongly recommended that every time that NanoFIX 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.

#### Patients on controlled sodium diet

This medicinal product contains up to 69 mg sodium for 1 vial NanoFIX 500 IU, equivalent to 3.45% of the WHO recommended maximum daily intake of 2 g sodium for an adult. To be taken into consideration by patients on a controlled sodium diet.

#### Paediatric population

The listed warnings and precautions apply both to adults and children.

### **4.5 Interaction with other medicinal products and other forms of interactions**

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

### **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

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

#### 4.8 Undesirable effects

##### Summary of the safety profile

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 rarely and may in some cases progress to severe anaphylaxis (including shock). 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 in haemophilia B patients with factor IX inhibitors and a history of allergic reaction.

On rare occasions, fever has been observed

Patients with haemophilia B may develop neutralising 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. A study in 25 children with Haemophilia B was conducted, thereof 6 patients were previously untreated and had a median no. of exposure days to NanoFIX of 38 (range 8-90). All patients had a factor IX inhibitor level of <0.4 BU at baseline. No inhibitor was observed during the study.

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 adverse reactions.

For safety information with respect to transmissible agents, see section 4.4.

##### Tabulated list of adverse reactions

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level). Frequencies have been evaluated according to the following convention: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data).

MedDRA Standard System Organ Class	Adverse reactions	
	Rare	Very rare
<i>Immune system disorders</i>	hypersensitivity	anaphylactic shock
<i>Vascular disorders</i>		thromboembolic event*
<i>Renal and urinary disorders</i>		nephrotic syndrome
<i>General disorders and administration site conditions</i>		heparin induced thrombocytopenia
		pyrexia
<i>Investigations</i>		anti factor IX antibody positive

\*MedDRA lowest level term (LLT)

##### Description of selected adverse reactions

Due to the amount of heparin contained in NanoFIX, a sudden, allergy-induced reduction of the blood platelet count below 100,000/ $\mu$ l or 50% of the starting count may be observed (thrombocytopenia type II) in rare cases. In patients not previously hypersensitive to heparin, this decrease in thrombocytes may occur 6–14 days after the start of treatment. In patients with a previous heparin hypersensitivity, this reduction may set in a few hours after treatment.

This severe form of blood platelet reduction may be accompanied by, or result in, arterial and venous thrombosis, thromboembolism, severe clotting disorder (consumptive coagulopathy), skin necrosis in the area of injection, flea bite-like bleeding (petechial haemorrhages), purpura and tarry stool. If the specified allergic reactions are observed, the injections with NanoFIX should be stopped immediately. The patient should be advised not to use any heparin-containing medicinal products in the future. Because of this rarely occurring heparin-induced effect on blood platelets, the patient's blood platelet count should be monitored closely, especially at the initiation of treatment.

Paediatric population

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRC Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: [www.hpra.ie](http://www.hpra.ie); e-mail: [medsafety@hpra.ie](mailto:medsafety@hpra.ie)

**4.9 Overdose**

No cases of overdose have been reported.

**5 PHARMACOLOGICAL PROPERTIES****5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: antihemorrhagics: blood coagulation factor IX.

ATC code: B02BD04

Factor IX is a single chain glycoprotein with a molecular mass of about 68,000 Dalton. It is a vitamin-K dependent coagulation factor and it 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 is increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

Paediatric population

A study in 25 children below 6 years of age was conducted. Thereof, 6 patients were previously untreated. The recovery after administration of >25 IU of NanoFIX/kg body weight was investigated during the first 3 months of treatment and after 12-24 months. The incremental recovery (geometric mean  $\pm$  s.d., one-stage assay, actual potency) was calculated to be  $0.8 \pm 1.4$  and  $0.9 \pm 1.3$  %/IU/kg at the 1<sup>st</sup> and the 2<sup>nd</sup> assessment, respectively.

**5.2 Pharmacokinetic properties**

For NanoFix the following results were achieved in one pharmacokinetic study with 13 Haemophilia B patients over 12 years of age (mean age 28 years, range 12-61 years):

N=13	Median	Mean	SD*	Minimum	Maximum
Incremental Recovery [IU/dl]/[IU/kg]	1.2	1.3	0.5	0.8	2.4
AUC* <sub>norm</sub> (IU x dl <sup>-1</sup> x h x IU <sup>-1</sup> x kg)	32.4	37.7	13.0	24.5	64.0
Half-life (h)	27.8	29.1	5.2	22.0	36.8
MRT* (h)	39.4	40.0	7.3	30.2	51.6
Clearance (ml x h <sup>-1</sup> x kg)	3.1	2.9	0.9	1.6	4.1

\*AUC= area under the curve

\*MRT = mean residence time

\*SD = standard deviation

The incremental recovery was also tested in a second study. The meta-analysis of all recovery assessments (n=19) resulted in a mean recovery of 1.1 [IU/dl]/[IU/kg].

### 5.3 Preclinical safety data

Human plasma coagulation factor IX (from the concentrate) is a normal constituent of the human plasma and acts like the endogenous factor IX.

Animal studies are limited and show no additional risks to those already mentioned in other sections of the SmPC.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Powder:

Heparin,

Sodium chloride,

Sodium citrate,

Arginine hydrochloride,

Lysine hydrochloride

Solvent:

Water for injections

### 6.2 Incompatibilities

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

Only the provided injection/infusion sets should be used because treatment failure can occur as a consequence of human coagulation factor IX adsorption to the internal surfaces of some injection/infusion equipment.

### 6.3 Shelf life

2 years

Biochemical and physical in-use stability has been demonstrated for 72 hours at 25°C. From a microbiological point of view, the reconstituted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the users and would not be recommended for longer than 8 hours stored at room temperature (25°C).

### 6.4 Special precautions for storage

Do not store above 25°C.

Do not freeze.

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

For storage conditions after reconstitution of the medicinal product, see section 6.3.

### 6.5 Nature and contents of container

NanoFIX comes as a combination package consisting of two cartons held together with a plastic film.

NanoFIX 500 IU:

Carton 1: powder in a 30 ml vial (type I glass), with a stopper (chlorobutyl or bromobutyl rubber) and a flip off cap (aluminium); package leaflet.

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Carton 2: 5 ml of solvent (water for injections) (type I or type II glass), with a stopper (chlorobutyl or bromobutyl rubber) and a flip off cap (aluminium).

Carton 2 also contains the following medical devices:

- 1 equipment pack for intravenous injection (1 transfer set, 1 infusion set, 1 disposable syringe)
- 2 alcohol swabs

## 6.6 Special precautions for disposal and other handling

**Please read all the instructions and follow them carefully!**

**During the procedure described below, sterility must be maintained!**

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

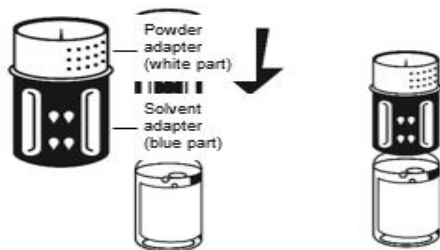
Reconstituted medicinal product should be inspected visually for particulate matter and discoloration prior to administration. The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits.

Use the prepared solution immediately, to prevent microbial contamination.

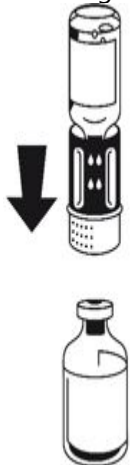
Only use the infusion set provided. The use of other injection/infusion equipment can cause additional risks and treatment failure.

### Instructions for preparing the solution:

1. Do not use the product directly from the refrigerator. Allow the solvent and the powder in the closed vials to reach room temperature.
2. Remove the flip off caps from both vials and clean the rubber stoppers with one of the provided alcohol swabs
3. The transfer set is depicted in Fig. 1. Place the solvent vial on an even surface and hold it firmly. Take the transfer set and turn it upside down. Place the blue part of the transfer set on top of the solvent vial and press firmly down until it snaps (Fig. 2 + 3). Do not twist while attaching.

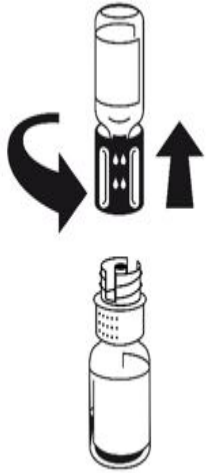


4. Place the powder vial on an even surface and hold it firmly. Take the solvent vial with the attached transfer set and turn it upside down. Place the white part on top of the powder vial and press firmly down until it snaps (Fig. 4). Do not twist while attaching. The solvent flows automatically into the powder vial.



5. With both vials still attached, gently swirl the powder vial until the product is dissolved.

The dissolving is completed in less than 10 minutes at room temperature. Slight foaming might occur during preparation. Unscrew the transfer set into two parts (Fig. 5). Foaming will disappear.



Dispose the empty solvent vial together with the blue part of the transfer set.

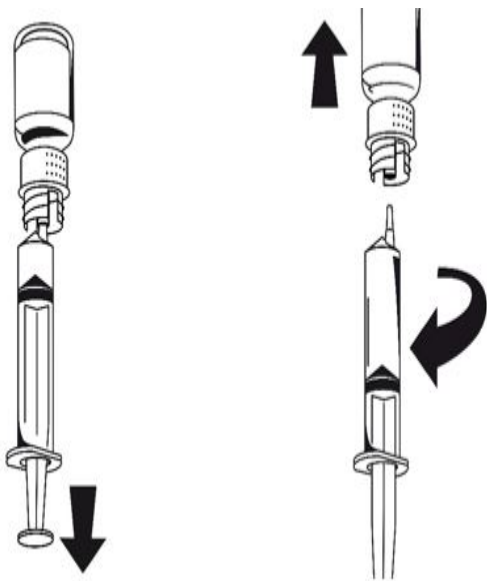
**Instructions for injection:**

As a precaution, your pulse rate should be taken before and during the injection. If a marked increase in your pulse rate occurs, reduce the injection speed or interrupt the administration for a short time.

1. Attach the syringe to the white part of the transfer set. Turn the vial upside down and draw the solution into the syringe (Fig. 6).

The solution in the syringe should be clear or slightly opalescent.

Once the solution has been transferred, firmly hold the plunger of the syringe (keeping it facing down) and remove the syringe from the transfer set (Fig. 7). Dispose the transfer set and the empty vial together with the white part of the transfer set.



2. Clean the chosen injection site with one of the provided alcohol swabs.
3. Attach the provided infusion set to the syringe.
4. Insert the injection needle into the chosen vein. If you have used a tourniquet to make the vein easier to see, this tourniquet should be released before you start injecting NanoFIX. No blood must flow into the syringe due to the risk of formation of fibrin clots.
5. Inject the solution into the vein at a slow speed, not faster than 2-3 ml per minute.

If you use more than one vial of NanoFIX powder for one treatment, you may use the same injection needle and syringe again. The transfer set is for single use only.

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

**7 MARKETING AUTHORISATION HOLDER**



1070 Anderlecht  
Belgium

**8 MARKETING AUTHORISATION NUMBER**

PA2219/009/001

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 15<sup>th</sup> October 2010

Date of last renewal: 16<sup>th</sup> March 2015

**10 DATE OF REVISION OF THE TEXT**

March 2021