

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

NANOTIV, 500 IU and 1000 IU, powder and solvent for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Nanotiv is supplied as a powder and solvent for solution for injection, containing nominally 500 or 1000 IU human coagulation factor IX (factor IX) per vial.

The product contains approximately 100 IU/ml (500 IU/5 ml and 1000 IU/10 ml, respectively) factor IX when reconstituted with 5 and 10 ml water for injection, respectively.

The potency (IU) is determined using the European Pharmacopoeia one stage clotting test. The specific activity of Nanotiv is approximately 190 IU/mg protein.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

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

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

There are insufficient data to recommend the use of the product in children less than 6 years of age (see section 5.1 and 5.2).

Posology

The dosage and duration of substitution therapy depend on the severity of the factor IX deficiency, on the location and extent of the bleeding 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 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. The calculation of the required dosage of factor IX is based on the empirical finding that one (1) International Unit factor IX per kg body weight raises the plasma factor IX activity by 1.2% of normal activity. The required dosage is determined using the following formula:

Required units (IU) = body weight (kg) x desired factor IX rise (IU/dl) x 0.8*

*reciprocal of observed recovery

Intermittent treatment

The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case. 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 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	Frequency of doses and Duration of therapy
Haemorrhage		
Early haemarthrosis, muscle bleeding or oral bleeding	20 – 40 IU/dl	Repeat infusion 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 IU/dl	Repeat infusion every 24 hours for 3 - 4 days or more until pain and acute symptoms are resolved
Life-threatening haemorrhage	60 –100 IU/dl	Repeat infusion every 8 -24 hours until threat is resolved
Surgery		
<i>Minor</i> Including tooth extraction	30 – 60 IU/dl	Once every 24 hours, at least 1 day, until healing is achieved
<i>Major</i>	80 –100 IU/dl (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 - 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 infusions. 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. 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 against bleeding in patients with severe haemophilia B, the usual doses are 20 to 40 IU of factor IX per kilogram 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.

Monitoring of factor IX inhibitor

Patients should be monitored for the development of factor IX inhibitor. 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 antibodies to factor IX have been developed. 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 care of patients with haemophilia (see 4.4. Special warnings and precautions for use).

Method of administration

Dissolve the preparation as described in 6.6 (Instructions for handling and use and disposal). Nanotiv should be administered via the intravenous route at a rate up to 100 IU of factor IX (up to 1.0 ml) per minute.

4.3 Contraindications

Hypersensitivity to factor IX or to any of the excipients.

4.4 Special warnings and precautions for use

As with any intravenous protein product, allergic type hypersensitivity reactions are possible. Patients should be informed of the early signs of hypersensitivity reactions including urticaria, tightness of the chest, wheezing, hypotension, and anaphylactic reactions. 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.

Virus safety

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 HIV, HBV and HCV, and for the non-enveloped 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 (foetal 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.

After repeated treatment with human coagulation factor IX products, patients should be monitored for 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 might be at an increased risk of anaphylactic reactions with subsequent challenge with factor IX.

Because of the risk of allergic reactions with factor IX concentrates, the initial administration 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.

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

It is strongly recommended that every time that Nanotiv 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.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions of human coagulation factor IX products with other medicinal products are known.

4.6 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 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

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

In patients treated with factor IX containing products the following reactions have rarely been observed:

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 chest, tingling, vomiting, wheezing). 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 4.4 Special warnings and precautions for use).

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

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.

There is a 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, DIC, venous thrombosis and pulmonary embolism. The use of high purity factor IX preparations, is rarely associated with such side effects.

Adverse reactions

The frequency is defined as follows: Rare (>1/10,000, <1/1,000); Very Rare (<1/10,000).

<u>System Organ Class</u>	<u>Rare</u>	<u>Very Rare</u>
Blood and lymphatic system disorders		Factor IX inhibition
Immune system disorders	Hypersensitivity	Anaphylactic shock
Vascular disorders		Thromboembolism
Renal and urinary disorders		Nephrotic syndrome
General disorders and administration site conditions	Pyrexia	

For information on virus safety see 4.4. Special warnings and special precautions for use

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Blood coagulation factor (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 level of factor IX is increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

Properties in children

Data on 15 children with hemophilia B treated with Nanotiv have been evaluated. Seven children started their therapy at 9 to 17 months of age, and they had not received any other factor IX concentrate previously. Eight children who had previously been treated with other factor IX concentrate, started Nanotiv therapy at 6 to 17 years of age.

Eight patients had primary prophylaxis and were given a total of >2135 injections of Nanotiv during 2-10 years of treatment, mean 3.4 years. The total amount of Nanotiv given to each of these patients varied between 50,000 and 1,245,000 IU.

Seven patients who got treatment in case of bleeding symptoms had a total of 57 injections of Nanotiv, with a total amount varying between 1,000 and 23,000 IU.

Three children developed inhibitors. This can be related to a total Factor IX gene deletion.

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

5.2 Pharmacokinetic properties

In a pharmacokinetic study in twelve patients with haemophilia B the following mean values and deviation values (SD) for pharmacokinetic parameters were shown:

- incremental recovery (k-value)	1.2 (IU /dl per IU /kg)	0.3
- <i>in vivo</i> recovery	58 %	17.5
- area under the curve (AUC)	11.3 (IU x h /ml)	3.2
- plasma half-life of factor IX, T _{1/2} ,	22.6 hours	7.1
- mean residence time (MRT)	28.1 hours	5.8
- total clearance	4.8 (ml /h /kg)	1.6
- distribution volume (V _{dss})	133.7 (ml/kg)	43.4

Properties in children

The incremental recovery has been measured in 10 children at 1-7 occasions. The mean incremental recovery varied between the children from 0.86 to 1.50 IU/dL per IU/kg, and the mean of these means (mean recovery for all children) was 1.06 IU/dL per IU/kg.

The clearance has been calculated repeatedly in a single child during two surgical episodes. The child had values between 4.9 and 7.8 mL/h/kg, indicating a somewhat higher clearance than for adults.

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

5.3 Preclinical safety data

Plasma coagulation factor IX is a normal constituent of the human plasma and acts like the endogenous factor IX. In rabbit studies the thrombogenicity of Nanotiv was shown to be minimal. No conventional preclinical safety studies have been conducted with the product.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:

Sodium chloride

L-lysine monohydrochloride

Sodium citrate

Solvent:
Water for injection

6.2 Incompatibilities

Nanotiv must not be mixed with other medicinal products.
The use of the injection/infusion set enclosed in the package is highly recommended.

6.3 Shelf life

3 years

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°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 2-8°C, unless reconstitution / dilution (etc) has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C- 8°C)...
Do not freeze.
Keep the vials in outer carton in order to protect from light..
Can be stored at maximum 25°C in one month.

Sterilised Water for Injections and administration devices can be stored at maximum 30°C.
For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder:

Glass vials type I (Ph.Eur.), with a bromobutyl rubber stopper, type I (Ph.Eur) and sealed with a flip off seal.

Solvent:

Glass vials type I (Ph.Eur.), with a bromobutyl rubber stopper, type I (Ph.Eur.) and sealed with a flip off seal.

Nanotiv 500 IU: 5 ml water for injection
Nanotiv 1000 IU: 10 ml water for injection

Injection device

Transfer set, syringe, filter needle, injection needle, alcohol-swabs, compress pad, and adhesive plaster.

6.6 Special precautions for disposal and other handling

Do not use after the expiry date given on the label.

The freeze-dried substance is reconstituted in 5 ml or 10 ml, respectively of water for injections. Time for reconstitution is less than 1 minute.
The product dissolves quickly at room temperature to a clear or slightly opalescent solution.
Do not use solutions that are cloudy or have particles.

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

7 MARKETING AUTHORISATION HOLDER

Octapharma AB
SE 112 75 Stockholm
Sweden

8 MARKETING AUTHORISATION NUMBER(S)

11562
11563

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Nanotiv, 500 IU powder and solvent for solution for injection:
1992-04-24 / 2007-04-24

Nanotiv, 1000 IU powder and solvent for solution for injection:
1992-04-24 / 2007-04-24

10 DATE OF REVISION OF THE TEXT

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