

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nanotiv 1000 IU, powder and solvent for solution for injection and infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Nanotiv is presented as a powder and solvent for solution for injection and infusion containing nominally 1000 IU human coagulation factor IX per vial.

The product contains approximately 100 IU/ml human coagulation factor IX when reconstituted with 10 ml Water for Injections.

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 excipients, see 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection and infusion.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

Nanotiv may be used in the management of acquired 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.

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 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 disability are resolved
Life-threatening haemorrhage	60 –100 IU/dl	Repeat infusion every 8 -24 hours until threat is resolved
Surgery		
Minor Including tooth extraction	30 – 60 IU/dl	Every 24 hours, at least 1 day, until healing is achieved
Major	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.

Continuous Infusion

Nanotiv is given within 1 hour after surgery as an IV bolus injection of 50 – 100 IU/kg depending on the extent and the severity of the surgery. Continuous infusion should be started immediately after the bolus injection. The initial infusion rate during **major** surgery should aim for a FIX:C level of 90 IU/dL. The posology in IU per 24 hours should be calculated according to the formula shown below.

Factor IX activity should be measured 10 – 20 min after the end of the bolus injection and postoperatively. As soon as the postoperative IX level is available, an appropriate correction of the infusion rate should be done whenever the observed level drops below the target level. The factor IX level for the 3 days following major surgery should be kept above 70 IU/dL. Thereafter, the target level may progressively be lowered to 40 IU/dL.

Similarly, the posology in connection with **minor** surgery should be calculated to reach a target level of 40 IU/dL during the day of surgery and 30 IU/dL the following days.

Additional Nanotiv may be given as bolus injections if the factor IX level drops below the therapeutic range.

Prior to surgery, a pharmacokinetic analysis in each individual should be performed to obtain an estimate of the clearance of factor IX. The required units needed per day should then be calculated on the clearance as follows:

Required units (IU/24h) = [body weight (kg) x clearance (ml/h/kg) x targeted steady state of FIX:C (IU/dL) x 24 (h)] 100

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 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 care of patients with haemophilia. (See also Section 4.4.).

Method of administration

Dissolve the preparation as described in Section 6.6.

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.

Nanotiv can be administered as continuous infusion by pump.

4.3 Contraindications

Hypersensitivity to the substance 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 hives, generalised 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.

Virus Safety

Standard measures to prevent infections resulting from the use of medicinal products prepared from 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.

The measures taken may be of limited value against non-enveloped viruses such as HAV and 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 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.

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 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 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.

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 factor IX 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 potentially 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.

In the interest of the patients, it is recommended that, whenever possible, every time that Nanotiv is administered, the name and batch number of the product is registered.

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 hemophilia 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

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) 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 Section 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.

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, DIC, venous thrombosis and pulmonary embolism.

The use of high purity factor IX preparations, as Nanotiv, is rarely associated with such side effects.

For information on virus safety see Section 4.4 Special warnings and precautions for use and Section 5.3 Preclinical safety data.

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Anti-haemorrhagics: blood coagulation factor IX.

ATC code: B02BD04

Factor IX is a single chain glycoprotein with a molecular mass of about 54 000 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 in 15 children with haemophilia 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 coagulation factor IX concentrate previously. Eight children, who had previously been treated with other coagulation 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.

Data showed that Nanotiv was efficacious, safe and well tolerated, except in 3 children who developed inhibitors. Since these children had a total factor IX gene deletion, this development of an inhibitor was not unexpected and has also been described with other coagulation factor IX concentrates.

Data from 8 surgical procedures in 6 patients showed that Nanotiv is an efficacious, safe and well tolerated treatment during and after surgery in children with haemophilia B.

5.2 Pharmacokinetic properties

In a pharmacokinetic study in twelve patients with haemophilia B the following mean values for pharmacokinetic parameters were shown:

Incremental recovery (k-value)	1.2 (IU /dl per IU /kg)
In vivo recovery	58 %
Area under the curve (AUC)	11.3 (IU x h /ml)
Plasma half-life of factor IX, T _{1/2} ,	22.6 hours
Mean residence time (MRT)	28.1 hours
Total clearance	4.8 (ml /h /kg)

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.

5.3 Preclinical safety data

Toxicological properties

The active constituent in Nanotiv is a normal constituent of the human plasma and acts like the endogenous factor IX.

Single dose toxicity testing is of no relevance since higher doses result in overloading.

Repeated dose toxicity testing in animals is impracticable and of no relevance due to interference with developing antibodies to heterologous human protein.

Since clinical experience provides no hint for tumourogenic and mutagenic effects of human coagulation factor IX, experimental studies, particularly in heterologous species, are not considered imperative.

During production Nanotiv is treated with tri(n-butyl)-phosphate (TNBP) and Triton X-100, in order to inactivate viruses. The residual levels of these two chemicals in the finished product are below the limits of detection and do not constitute any health hazard in the patients.

L-lysine monohydrochloride is added as a stabiliser. The concentration in the finished product is not considered to be of any health hazard.

Human 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 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 injections

6.2 Incompatibilities

Nanotiv 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 absorption to the internal surface of some injection/infusion equipment.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Store the freeze-dried powder in a refrigerator at +2 to +8°C. However within the shelf-life of 36 months it can be stored below 25°C for 1 month without effects on the stability of the product. After one month's storage the powder should be returned to the refrigerator (+2°C to +8°C).

Chemical and physical in-use stability had 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 take longer than 24 hours at 2-8°C, unless reconstitution/dilution (etc.) has taken place in controlled and validated aseptic conditions.

Do not freeze.

Water for injections and administration devices can be stored below 30 °C.

Keep the vial with the powder for injection in the outer container to protect from light.

Do not use after the expiry date.

6.5 Nature and contents of container

The Nanotiv pack contains two cartons. One carton contains one injection bottle of freeze-dried Nanotiv powder and the package insert. The other carton contains one injection bottle of water for injections, and the following devices for administration: Transfer set, syringe, filter needle, injection needle, swabs, pressure bandage and adhesive plaster.

Powder for injections

Injection bottles glass type I (Ph.Eur.), 20 ml stoppered with a bromobutyl rubber stopper, type I (Ph. Eur.) and sealed with a flip off seal.

Water for injections

Injection bottles glass type I (Ph.Eur.), 8 ml stoppered with a bromobutyl rubber stopper, type I (Ph.Eur.) and sealed with a flip off seal.

Injection device

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

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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

The freeze-dried solution is reconstituted in 5 ml Water for Injections. Time for reconstitution is less than 1 minute.

The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits.

Reconstituted products should be inspected visually for particulate matter and discolouration prior to administration.

If continuous infusion is used, strict aseptic handling should be applied for reconstitution and for transfer to the infusion pump container.

When used in home treatment Nanotiv solution should be used immediately after reconstitution.

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

The use of the injection/infusion set enclosed in the package is highly recommended.

The compatibility of Nanotiv and the provided injection/infusion sets is validated. No adsorption could be determined.

Preparations of the solution

The vials with lyophilised substance and with water for injections must be at room temperature not exceeding 30°C.

The dissolution time is less than 5 minutes.

The reconstituted solution should be used within 1 hour.

1. Remove the plastic caps from the substance and water vials and put them on a firm surface.
2. Disinfect the stoppers of the two vials.
3. Remove the plastic cap from one of the ends of the transfer set. Insert the exposed end of the transfer set through the stopper of the standing water vial.
4. Remove the plastic cap from the other end of the transfer set. Invert the water vial and push the exposed end of the transfer set through the stopper of the substance vial. The water (5ml for 500 IU and 10ml for 1000 IU) is transferred by means of vacuum. **N.B. A small amount of water (about 1ml) remains in the water vial and not be transferred.**
5. Quickly remove the empty water vial and the transfer set.

6. The substance dissolves immediately. If necessary swirl the vial very gently until the substance is dissolved. Do not shake the vial. Formation of foam should be avoided as this can cause denaturation of factor IX.
7. Check that the substance is completely dissolved.
8. Disinfect the stopper of the Nanotiv vial.
9. Insert the filter needle through the stopper of the Nanotiv vial. Any foam present will disappear.
10. Draw up a few mls of air in the syringe and inject the air into the standing Nanotiv vial.
11. Turn the Nanotiv vial upside-down and draw the solution into the syringe.
12. Remove the syringe from the filter needle.
13. Insert the injection needle into an appropriate blood-vessel. The plastic tubing must be filled with blood before the syringe is connected to the tubing.
14. Inject the concentrate, by means of the injection needle. Hold the syringe in an upright position in order to ensure that air bubbles will not be injected.

Use immediately after reconstitution.

7 MARKETING AUTHORISATION HOLDER

Octapharma Limited UK
6 Elm Court
Copse Drive
Meriden Green
Conventry CV5 9RG
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 0521/010/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th December 1995

Date of last renewal: 19th December 2005

10 DATE OF REVISION OF THE TEXT

March 2007