GRIFOLS

AlphaNine® SD

Solvent Detergent Treated and Virus Filtered

COAGULATION FACTOR IX (HUMAN)

3052368

DESCRIPTION

Coagulation Factor IX (Human), AlphaNine® SD, is a purified, solvent detergent treated, virus filtered preparation of Factor IX derived from human plasma.[1] It contains a minimum of 150 IU Factor IX/mg protein; levels of Factor VII (proconvertin), Factor II (prothrombin) and Factor X (Stuart-Prower Factor) which are below the limit of detection (less than 0.04 Factor VII unit, less than 0.05 Factor II unit, and less than 0.05 Factor X unit per IU Factor IX). AlphaNine® SD is a sterile, lyophilized preparation intended for intravenous administration only. Each vial is a single dose container.
AlphaNine® SD contains not more than (NMT) 0.04 unit of heparin, NMT 0.2 mg of dextrose, NMT 1.0 µg polysorbate 80 and NMT 0.10 µg tri(n-butyl) phosphate/IU of Factor IX.

CLINICAL PHARMACOLOGY

AlphaNine® SD is a purified formulation of Factor IX containing not less than 150 IU Factor IX activity/mg of total protein.[2] AlphaNine® SD contains non-therapeutic levels of Factor II, Factor VII and Factor X.
Thrombogenicity of AlphaNine® SD in animals is markedly lower than that of Factor IX Complex, Profilnine® Heat-Treated. Five lots of AlphaNine® SD (three lots of non-virus filtered product and two lots of virus filtered product) failed to show any evidence of thrombogenicity when tested directly in the Wessler rabbit stasis model for thrombogenicity[3,4] at a dose of 200 IU Factor IX/kg body weight. When various lots of AlphaNine® SD were further tested at doses between 300 and 650 IU Factor IX/kg, only 5 out of 40 animals (12.5%) showed evidence of thrombus formation (Wessler scores of +1, +2, +1, +1, +1 out of +4 maximum). In comparison, Factor IX Complex concentrate, Profilnine®, was thrombogenic in 100% of the animals tested at a dose of 100 IU Factor IX/kg.
At a dose of 200 IU Factor IX/kg body weight in a porcine model, the heptane heat-treated formulation of this product (AlphaNine®) showed little evidence of disseminated intravascular coagulation (DIC) following infusion.[3] This model exhibited no depletion of coagulation factors, a minimal increase in fibrin monomer (+1 in protamine test), a slight temporary decrease in platelet counts, and no evidence of intravascular coagulation upon gross autopsy.[5] In contrast, Harrison, et al., report that all Factor IX Complex concentrates studied in the same porcine model were thrombogenic at doses between 50 and 100 IU of Factor IX/kg animal weight.[3]
A clinical evaluation of AlphaNine® SD half-life and recovery characteristics was performed. A total of 18 patients with severe to moderate hemophilia B each received a single infusion of 40 to 50 IU Factor IX/kg body weight of AlphaNine® SD. Following the administration of AlphaNine® SD, the mean half-life of Factor IX observed was approximately 21 hours.[2] This half-life value was computed using the biphasic linear regression model recommended by the International Society of Thrombosis and Haemostasis.[10] The half-life obtained for the solvent detergent treated product is comparable to that of AlphaNine® (approximately 19 hours) as well as the range of 18 to 36 hours reported for Factor IX Complex preparations.[11] The mean recovery observed in clinical trials was approximately 48% and was comparable to that of AlphaNine® (approximately 51%).[2]
A clinical trial was conducted using the heptane heat-treated product, AlphaNine®, to evaluate the efficacy of the product in providing hemostatic protection during and after surgery in 13 patients with hemophilia B. The types of surgical procedures performed included bilateral knee replacement (1), total knee replacement with synovectomy (2), hip replacement (1), below the knee amputation (1), herniorrhaphy (2), hemorrhoidectomy (1), rhinoplasty (2), oral surgery (2) and Hickman catheter insertion with temporalis muscle transfer (1). Presurgery doses ranged from 30.1 to 65.0 IU Factor IX/kg; postsurgery replacement therapy doses ranged from approximately 9.4 to 52.0 IU Factor IX/kg. The number of postsurgery days of treatment ranged from 1 to 23; the number of postsurgery infusions ranged from 2 to 26. No bleeding episodes were reported and hemostasis was maintained during the course of postsurgery therapy. None of the hematologic parameters examined (hematocrit, partial thromboplastin time, prothrombin time, fibrinogen/fibrin degradation products, fibrin monomers, D-dimers and platelet counts) provided any evidence that AlphaNine® possessed thrombogenic potential.[12]
A randomized crossover study with 11 hemophilia B patients was conducted with the heptane heat-treated version of the product, AlphaNine®, to determine whether an infusion of AlphaNine® caused less activation of the hemostatic system than the Factor IX Complex concentrate preparation, Profilnine® Heat-Treated. Each subject received a single infusion of either AlphaNine® or Profilnine® Heat-Treated for the treatment of a bleeding episode, at a dose of 50 IU Factor IX/kg body weight. Each subject received the other Factor IX concentrate for the treatment of a subsequent bleeding episode, separated by an interval of not less than 10 days. The level of prothrombin fragment 1+2 (F_{1+2}) is a sensitive index of the cleavage of prothrombin by activated Factor X. The level of fibrinopeptide A (FPA) released into the plasma measures the activity of thrombin on fibrinogen in the formation of fibrin. Following infusion of Factor IX Complex, statistically significant increases in F_{1+2} and in FPA were detected at all monitored time points (15, 60, 90, 120 and 240 minutes postinfusion). The statistically significant elevation in these two hemostatic parameters indicates increased activation of the coagulation cascade. Administration of AlphaNine® resulted in no increase in F_{1+2} at any monitored time points, and a statistically non-significant increase in FPA at 15, 60, and 90 minutes following infusion. Only at 120 and 240 minutes after infusion of AlphaNine® were statistically significant increases in FPA levels detected. These results suggest that the infusion of a high purity factor IX, such as AlphaNine®, may result in a lower level of activation of the coagulation cascade than does Factor IX Complex.[13]
The ability of the manufacturing process to inactivate and eliminate virus from the Coagulation Factor IX (Human) products was evaluated at key stages in the process (see Table 1). Known amounts of different viruses were added to samples obtained prior to those steps most likely to reduce virus load (DEAE Chromatography, Solvent Detergent, Dual Affinity Chromatography and nanofiltration) in the AlphaNine® and AlphaNine® SD processes to determine the level of viral inactivation/elimination of these specific steps in the process.

Table 1

Process Step	Virus Reduction (log_{10})							
	Sindbis	VSV	HIV-1	HIV-2	Parvo**†	EMC	Reo	HAV
DEAE Chromatography	1.4	NT	NT	NT	1.5*	NT	NT	NT
Solvent-Detergent	NLT 5.3	NLT 4.9	NLT 12.2	6.0	NT	NT	NT	NT
Dual Affinity Chromatography	4.7	NT	NT	NT	2.2*	NT	NT	NT
Nanofiltration	NT	NT	NT	NT	3.6	3.4	4.1	≥ 4.4

**Porcine NT=Not tested NLT=Not less than *Lower 95% confidence interval

The retrovirus known as human immunodeficiency virus (HIV) has been identified as a causative agent of Acquired Immunodeficiency Syndrome (AIDS) and has been shown to be transmissible via blood or blood products. The solvent detergent process used in the manufacture of AlphaNine® SD, was shown to inactivate greater than 12.2 logs of HIV-1 when the retrovirus was intentionally added to product samples under laboratory evaluation (as measured by virus antigen capture and reverse transcriptase assays). In addition, this process was shown to inactivate 6 logs of HIV-2 (as measured by reverse transcriptase assays) when the retrovirus was intentionally added to product samples.[2] In an ongoing efficacy and safety study of 26 patients, no subjects tested positive for HIV or viral hepatitis in relation to the investigation drug.[2]

In order to assess the ability of the solvent detergent treatment process to inactivate other viruses such as hepatitis B and C virus, the inactivation of the model viruses, Sindbis virus, a model virus for hepatitis C virus, and vesicular stomatitis virus (VSV), a model RNA virus for lipid enveloped viruses, by solvent detergent treatment was studied. Prior to solvent detergent treatment, samples were inoculated with a titer of either Sindbis or VSV. The results demonstrated that a minimum of 5.3 logs of Sindbis and a minimum of 4.9 logs of VSV were inactivated after 180 minutes of incubation with solvent detergent (when compared to an untreated control). It should be noted that the incubation time in the actual AlphaNine® SD process is twice (360 minutes total) that used in the model virus studies.
The ability of the AlphaNine® SD process to eliminate virus, by physically partitioning virus from product, was evaluated at key stages of the manufacturing process. Studies were performed using a lipid-enveloped model virus (Sindbis) and non-lipid model viruses (porcine parvovirus, encephalomyocarditis virus, and reovirus). Known amounts of these viruses were added to samples obtained from the AlphaNine® SD process. The amount of virus removed at each subsequent purification step was then determined by plaque assay.
Addition of Sindbis or porcine parvovirus prior to Factor IX Complex adsorption by DEAE chromatography showed this step to eliminate 1.4 logs of Sindbis and 1.5 logs (95% confidence interval: 1.51-2.33) of added porcine parvovirus. When Sindbis or parvovirus was introduced into the process after the barium citrate precipitation step of the AlphaNine® SD process, the subsequent dual affinity chromatography step was found to eliminate 4.7 logs of Sindbis and 2.2 logs (95% confidence interval: 2.25-2.75) of added parvovirus. When parvovirus, encephalomyocarditis virus (EMC), or Reovirus was introduced into the process after the dual affinity chromatography step, the subsequent nanofiltration step of the AlphaNine® SD process was found to eliminate 3.6 logs of parvovirus, 3.4 logs of EMC and 4.1 logs of added Reovirus. The studies mentioned above indicate that the manufacturing process of AlphaNine® SD is capable of reducing viruses by approximately 6 logs, in addition to virus reduction achieved by the solvent detergent process.[14] In another study, the nanofiltration step removed ≥ 4.4 logs of hepatitis A virus (HAV), a non-lipid enveloped virus. Table 1 summarizes the reduction factors obtained for each virus when individual steps in the manufacturing process for AlphaNine® SD were validated for virus removal/inactivation.

INDICATIONS AND USAGE

AlphaNine® SD is indicated for the prevention and control of bleeding in patients with Factor IX deficiency due to hemophilia B. AlphaNine® SD contains low, non-therapeutic levels of Factors II, VII, and X, and, therefore, is *not* indicated for the treatment of Factor II, VII or X deficiencies. This product is also *not* indicated for the reversal of coumarin anticoagulant-induced hemorrhage, nor in the treatment of hemophilia A patients with inhibitors to Factor VIII.

CONTRAINDICATIONS

None known.

WARNINGS

Because Coagulation Factor IX (Human), AlphaNine® SD is made from pooled human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. Stringent procedures designed to reduce the risk of adventitious agent transmission have been employed in the manufacture of this product, from the screening of plasma donors and the collection and testing of plasma to the application of viral elimination/reduction steps such as column chromatography, solvent detergent treatment and nanofiltration in the manufacturing process. Despite these measures, such product can potentially transmit disease, therefore the risk of infectious agents cannot be totally eliminated. The physician should weigh the risks and benefits of the use of this product and should discuss these with the patient.
Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections. Scientific opinion encourages hepatitis B and hepatitis A vaccinations at birth or diagnosis for patients with hemophilia.
Incidences of thrombosis or disseminated intravascular coagulation (DIC), have been reported following administration of Factor IX Complex concentrates which contain high amounts of Factor II, VII and X.
Following administration of Coagulation Factor IX (Human), AlphaNine® SD in surgery patients and individuals with known liver disease, the physician should closely observe the patient for signs or symptoms of potential disseminated intravascular coagulation (DIC). Continued administration of the product should be left to the discretion of the physician.
Allergic type hypersensitivity reactions, including anaphylaxis, have been reported for all factor IX products. Frequently these events have occurred in close temporal association with the development of factor IX inhibitors. Patients should be informed of the early symptoms and signs of hypersensitivity reactions, including hives, generalized urticaria, angioedema, chest tightness, dyspnea, wheezing, faintness, hypotension, tachycardia and anaphylaxis. Patients should be advised to discontinue use of the product and contact physician and/or seek immediate emergency care, depending on the severity of the reactions, if any of these symptoms occur.
Nephrotic syndrome has been reported following attempted immune tolerance induction with factor IX products in Hemophilia B patients with factor IX inhibitors and a history of severe allergic reactions to Factor IX. The safety and efficacy of using AlphaNine® SD in attempted immune tolerance induction has not been established.
In Previously Untreated Patients (PUPs), it is possible that anaphylaxis may occur after a median exposure of eleven (11) days.[15] It is recommended that these patients are monitored closely between the tenth and twentieth exposure day.

PRECAUTIONS

General

In order to minimize the possibility of thrombogenic complications, dosing guidelines should be *strictly* followed. Refer to "Dosage and Administration" section for recommended amount of product to be administered.
AlphaNine® SD should *not* be administered at a rate exceeding 10 ml/minute. Rapid administration may result in vasomotor reactions.
Nursing personnel and others who administer this material should exercise appropriate caution in handling due to the risk of exposure to viral infection.
Discard any unused contents into the appropriate safety container. Discard administration equipment after single use into the appropriate safety container. Do not resterilize components.

Information for Patients

Patients should be informed of the early symptoms and signs of hypersensitivity reaction, including hives, generalized urticaria, chest tightness, dyspnea, wheezing, faintness, hypotension, and anaphylaxis. Patients should be advised to discontinue use of the product and contact their physician and/or seek immediate emergency care, depending on the severity of the reaction, if these symptoms occur.
Some viruses, such as parvovirus B19 or hepatitis A, are particularly difficult to remove or inactivate at this time. Parvovirus B19 may most seriously affect sero-negative pregnant women, or immunocompromised individuals. The majority of parvovirus B19 and hepatitis A infections are acquired by environmental (natural) sources.
Preliminary information suggests a relationship may exist between the presence of major deletion mutations in the Factor IX gene and an increased risk of inhibitor formation and of acute hypersensitivity reactions. Patients known to have major deletion mutations of the Factor IX gene should be observed closely for signs and symptoms of acute hypersensitivity reactions, particularly during the early phases of initial exposure to product.

Pregnancy Category C

Animal reproduction studies have not been conducted with AlphaNine® SD. It is also not known whether AlphaNine® SD can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. AlphaNine® SD should be given to a pregnant woman only if clearly indicated.

Pediatric Use

Clinical trials for safety and effectiveness in pediatric patients 16 years of age and younger have not been conducted. Across a well controlled half-life and recovery clinical trial in patients previously treated with Factor IX concentrates of Hemophilia B, the three pediatric patients receiving AlphaNine® SD (solvent detergent treated) responded similarly when compared with 15 adult patients.[2] In an ongoing safety and efficacy clinical trial in patients not previously treated with Factor IX concentrates for Hemophilia B, 21 pediatric patients received AlphaNine® SD (solvent detergent treated) responded similarly when compared with the five adult patients above the age of 16 years. Adverse events were similar in this group compared to the patients above the age of 16 years. Anecdotal evaluation of the results indicates no safety and efficacy differences between pediatric and adult populations.

ADVERSE REACTIONS

The administration of plasma preparations may cause allergic reactions, mild chills, nausea or stinging at the infusion site. For most reactive individuals, slowing the infusion rate relieves the symptoms. For those highly reactive individuals, a different lot may be satisfactory.
Adverse reactions, characterized by either thrombosis or disseminated intravascular coagulation (DIC), have been reported following administration of Factor IX Complex concentrates. Patients who receive Coagulation Factor IX (Human), AlphaNine® SD, following operation, or those with known liver disease, should be kept under close observation for potential signs or symptoms of intravascular coagulation. Continued administration should be left to the discretion of the physician.
In the clinical study that compared the *in vivo* half-life and recovery of AlphaNine® SD and HT products, no adverse events were associated with 18 infusions of AlphaNine® SD administered to 18 individuals with severe to moderate hemophilia B.[2] Short term safety of the earlier version of this product, AlphaNine®, was demonstrated by an absence of adverse events after 225 infusions of this product were received by 31 patients participating in three clinical trials. In the clinical trial to evaluate efficacy of AlphaNine® in providing hemostatic protection during and after surgery, 13 patients, received a total of 370,655 IU of AlphaNine®. In 208 total infusions, each patient received approximately 15,000 IU (range 3,295 to 52,200 IU Factor IX) in an average of 16 infusions (range 2 to 26 infusions). Results from this study showed no bleeding episodes during the course of postsurgery therapy. There was no hematological evidence (measured by hematocrit, partial thromboplastin time, prothrombin time, fibrinogen/fibrin degradation products, fibrin monomers, D-dimers and platelet counts) of thrombogenicity.[12]
To report SUSPECTED ADVERSE REACTIONS, contact Grifols at 1-323-225-2221.

DOSAGE AND ADMINISTRATION

For adult usage:
AlphaNine® SD should be administered intravenously promptly following reconstitution. Administration of AlphaNine® SD within three hours after reconstitution is recommended to avoid the potential ill effect of any inadvertent bacterial contamination occurring during reconstitution. Discard any unused contents into the appropriate safety container.
The amount of AlphaNine® SD required to establish hemostasis will vary with each patient and depend upon the circumstances. The following formula may be used as a guide in determining the number of units to be administered.[16]

Body weight (in kg) X Desired increase in Plasma Factor IX (Percent) X 1.0 IU/kg = Number of Factor IX IU Required

Example:

70 kg X 40 (% increase) X 1.0 IU/kg = 2,800 IU AlphaNine® SD

In clinical practice there is variability between patients and their clinical response. Therefore, the Factor IX level of each patient should be monitored frequently during replacement therapy.

Treatment Guidelines for Hemorrhagic Events and Surgery in Patients Diagnosed with Hemophilia B

Type of Hemorrhage or Surgical Procedure	Examples	Treatment Guidelines
Minor Hemorrhages	Bruises, cuts or scrapes, uncomplicated joint hemorrhage	FIX levels should be brought to at least 20-30% (20-30 IU FIX/kg/twice daily) until hemorrhage stops and healing has been achieved (1-2 days).[17,18,19]
Moderate Hemorrhages	Nose bleeds, mouth and gum bleeds, dental extractions, hematuria	FIX levels should be brought to 25-50% (25-50 IU FIX/kg/twice daily) until healing has been achieved (2-7 days, on average).[17,18,19,20,21]
Major Hemorrhages	Joint and muscle hemorrhages (especially in the large muscles), major trauma, hematuria, intracranial and intraperitoneal bleeding	FIX levels should be brought to 50% for at least 3-5 days (30-50 IU FIX/kg/twice daily). Following this treatment period, FIX levels should be maintained at 20% (20 IU FIX/kg/twice daily) until healing has been achieved. Major hemorrhages may require treatment for up to 10 days.[17,18,19,20,21]
Surgery		Prior to surgery, FIX should be brought to 50-100% of normal (50-100 IU FIX/kg/twice daily). For the next 7 to 10 days, or until healing has been achieved, the patient should be maintained at 50-100% FIX levels (50-100 IU FIX/kg/twice daily).[17,18,19,20,21]

Dosing requirements and frequency of dosing is calculated on the basis of an initial response of 1% FIX increase achieved per IU of FIX infused per kg body weight and an average half-life for FIX of 18 hours. If dosing studies have revealed that a particular patient exhibits a lower response, the dose should be adjusted accordingly.
For pediatric usage: See PRECAUTIONS.

INSTRUCTIONS FOR USE AND HANDLING

Do not use after the expiry date shown on the vial label.
Check assay value on label carefully before use.
Use aseptic technique during reconstitution and administration.
Left-over product must never be stored for later use, nor stored in a refrigerator.

Solution preparation:
1. Warm the vial and syringe but not above 30 °C.
2. Attach the plastic plunger to the syringe containing diluent.
3. Remove the filter from its packaging. Remove the grey rubber cap from the syringe tip and then attach the syringe to the filter.
4. Remove the vial adaptor from its packaging. Attach the vial adaptor to the syringe-filter assembly.
5. Remove the plastic flip-top cap from the concentrate vial and wipe the exposed rubber with the antiseptic wipe provided.
6. Place the syringe/filter/adaptor assembly over the top of the concentrate vial and pierce the stopper with the adaptor needle.
7. Transfer all the Water for Injections into the concentrate vial by depressing the syringe plunger.
8. Gently swirl the vial until all the concentrate has dissolved. As with other parenteral solutions, do not use the solution if it is not properly dissolved or particles are visible.
9. Briefly separate the syringe/filter and vial/adaptor assemblies to release any vacuum.
10. Invert the concentrate vial and draw-up the solution through the filter into the syringe.
11. Prepare the injection site, separate the filter/vial adaptor from the syringe. Inject the solution intravenously using the butterfly needle provided or a sterile needle.

Administer slowly at a rate not exceeding 10 ml/minute.
After reconstitution with the Water for Injections solvent provided, the product should be used immediately.
Do not re-use the administration sets.
Any unused product or waste material should be disposed of in accordance with local requirements.
The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits.
Reconstituted product should be inspected visually for particulate matter and discoloration prior to administration.

HOW SUPPLIED

AlphaNine® SD is supplied in sterile, lyophilized form in single dose vials accompanied by 10 mL diluent (sterile water for injections). AlphaNine® SD is packaged with a prefilled syringe with diluent (sterile water for injections) and accessories for injection.

STORAGE

AlphaNine® SD is stable for three years, up to the expiration date printed on its label, provided that the storage temperature is between 2 and 8 °C. Do not freeze diluent. May be stored at room temperature not to exceed 30 °C for one month.

Rx only

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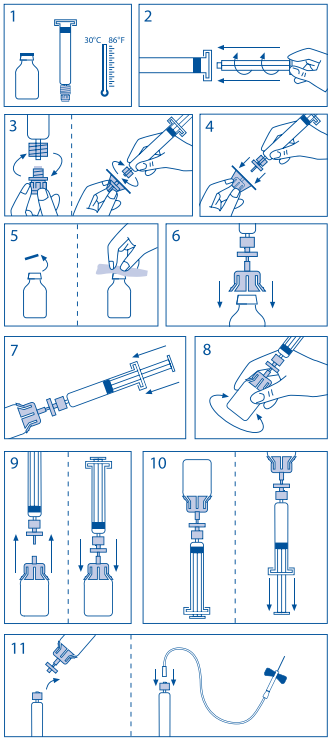
Manufactured by:
Grifols Biologicals LLC
5555 Valley Boulevard
Los Angeles, CA 90032 - U.S.A.



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