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GRIFOLS

Profilnine®

Solvent Detergent Treated/Nanofiltered

FACTOR IX COMPLEX

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DESCRIPTION

Factor IX complex, Profilnine®, is a solvent detergent treated, nanofiltered, sterile, lyophilized concentrate of coagulation factors IX, II, X, and low levels of factor VII. The factor II content is not more than (NMT) 150 units* per 100 factor IX units, the factor X content is NMT 100 units per 100 factor IX units, and the factor VII content is NMT 35 units per 100 factor IX units. Profilnine® is intended for intravenous administration only. Each vial is a single dose container and is labeled with the factor IX potency expressed in international units. Profilnine® does not contain heparin and contains no preservatives. Profilnine® contains few, if any, activated factors based on results from the non-activated partial thromboplastin time (NAPTT) test.[1, 2]

Profilnine® is prepared from pooled human plasma and purified by diethylaminoethyl (DEAE) cellulose adsorption. The risk of transmission of infective agents by Profilnine® has been substantially reduced by donor selection procedures and virus screening of individual donations and plasma pools by serological and nucleic acid testing. In addition, specific, effective virus elimination steps such as nanofiltration[3] and solvent/detergent (tri-n-butyl phosphate/TNBP) treatment[4] have been incorporated into the Profilnine® manufacturing process. Additional removal of some viruses occurs during the DEAE cellulose product purification step.

The ability of the manufacturing process to eliminate virus from Profilnine® was evaluated in the laboratory by intentionally adding virus to product just prior to the elimination step and monitoring virus removal. Table 1 shows the amounts of virus that can be removed by solvent detergent treatment, nanofiltration and purification by DEAE chromatography when vesicular stomatitis virus (VSV), human immunodeficiency virus-1 and 2 (HIV-1, HIV-2), parvo virus, West Nile virus (WNV), bovine viral diarrhea virus (BVDV), hepatitis A virus (HAV) and pseudorabies virus (PRV) were evaluated in these virus spiking studies. The results indicate that the solvent detergent treatment step effectively inactivates enveloped viruses and the nanofiltration step effectively removes both enveloped and non-enveloped viruses.

* Unit refers to International Unit in the labeling of Profilnine®.

Table 1

			Virus Reduction (log_{10}) Process Step		
Virus	**Virus Type**	**Model For:**	1st DEAE Chromatography	Solvent-Detergent	Nanofiltration
Sindbis	Env	Hepatitis C	1.4	≥ 5.3	NT
VSV	Env	Robust enveloped viruses	NT	≥ 4.9	NT
HIV-1	Env	HIV-1	NT	≥ 12.2	≥ 6.2
HIV-2	Env	HIV-2	NT	≥ 6.0	NT
WNV	Env	WNV	NT	NT	≥ 6.6
BVDV	Env	Hepatitis C	NT	NT	≥ 4.9
Parvo*	Non-Env	Parvovirus B19	NT	NT	≥ 6.1
HAV	Non-Env	HAV	NT	NT	≥ 5.8
PRV	Env	Hepatitis B	NT	NT	≥ 5.3

* Porcine, NT=Not tested, Env=enveloped

CLINICAL PHARMACOLOGY

Profilnine® is a mixture of the vitamin K-dependent clotting factors IX, II, X and low levels of VII. The administration of factor IX complex, Profilnine®, temporarily increases the plasma levels of factor IX, thus enabling a temporary correction of the factor deficiency.

A clinical study that evaluated twelve subjects with hemophilia B indicated that, following administration of Profilnine®, the factor IX *in vivo* half-life was 24.68 ± 8.29 hours and recovery was 1.15 ± 0.16 units/dL per unit infused per kg body weight.[5]

Administration of factor IX complex can result in higher than normal levels of factor II due to its significantly longer half-life.[6]

The retrovirus known as Human Immunodeficiency Virus (HIV-1) has been identified as the 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 Profilnine® has been shown to provide a very high level of virus kill without compromising protein structure and function. The susceptibility of human pathogenic viruses such as HIV-1, hepatitis B virus, hepatitis C virus and marker viruses such as Sindbis and Vesicular Stomatitis Virus (VSV) to inactivation by organic solvent detergent treatment has been discussed in the literature.[4]

The solvent detergent process used in the manufacture of Profilnine® 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 6.0 logs of HIV-2 (as measured by reverse transcriptase assays) when the retrovirus was intentionally added to product samples.

In order to assess the ability of the solvent detergent process to inactivate other viruses such as hepatitis B and C virus, the inactivation of the model viruses, Sindbis virus and vesicular stomatitis virus (VSV), 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 removed 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 Profilnine® process is twice (360 minutes total) that used in the model virus studies.

The ability of the Profilnine® process to eliminate virus, by physically partitioning virus from product, was evaluated at the DEAE chromatography step. Addition of Sindbis virus prior to factor IX complex adsorption by DEAE chromatography showed this step to eliminate 1.4 logs of added virus.

However, no treatment method has yet been shown capable of totally eliminating all potential infective virus in preparations of coagulation factor concentrates.

INDICATIONS AND USAGE

Profilnine® is indicated for the prevention and control of bleeding in patients with factor IX deficiency due to hemophilia B.

Profilnine® contains non-therapeutic levels of factor VII, and is not indicated for use in the treatment of factor VII deficiency.

CONTRAINDICATIONS

None known.

WARNINGS

Because Profilnine® 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 DEAE chromatography, solvent detergent treatment and nanofiltration in the manufacturing process.[3,4] Despite these measures, such products 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 for patients with hemophilia at birth or diagnosis.

In patients undergoing surgery and in patients with known liver disease, thrombosis or disseminated intravascular coagulation (DIC) are serious and potentially fatal adverse reactions associated with the administration of factor IX complex concentrates.[6] Infrequent but consistent reports have been described which indicate that patients are at greater risk of developing thrombosis and DIC in the period following surgery. Cases have also been cited which indicate that patients with liver disease may be predisposed to thrombosis or DIC when treated with factor IX complex. Although the available data is limited, Profilnine® should only be administered to patients when the beneficial effects of use outweigh the serious risk of potential hypercoagulation.

PRECAUTIONS

General

Profilnine® 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 handling due to the limited risk of exposure to viral infection.

Discard any unused Profilnine® vial contents. Discard administration equipment after single use. Do not resterilize components. Do not reuse 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.

Pregnancy Category C

Animal reproduction studies have not been conducted with Profilnine®. It is also not known whether Profilnine® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Profilnine® 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 for Hemophilia B, the two pediatric patients receiving Profilnine® responded similarly when compared with the adult patients. There were no adverse events in the pediatric patients and one mild adverse event in the adult population (headache).

Anecdotal evaluation of the results indicate no safety and efficacy differences between pediatric and adult populations.[5]

ADVERSE REACTIONS

Adverse reactions characterized by either thrombosis or disseminated intravascular coagulation (DIC) are associated with administration of factor IX complex concentrates.[2, 6] In particular, patients who receive prolonged treatment with factor IX complex concentrates postoperatively or with known liver disease should be kept under close observation for signs or symptoms of intravascular coagulation. Continued administration should be left to the discretion of the physician.
Adverse reactions may include urticaria, fever, chills, nausea, vomiting, headache, somnolence, lethargy, flushing or tingling. For most reactive individuals, slowing the rate of infusion relieves the symptoms. For those highly reactive individuals, a different lot may be satisfactory.
To report SUSPECTED ADVERSE REACTIONS, contact Grifols at 1-323-225-2221.

DOSAGE AND ADMINISTRATION

For adult usage:
Factor IX complex, Profilnine® should be administered intravenously, promptly following reconstitution with the supplied diluent. Although Profilnine® is stable for at least three (3) hours at room temperature after reconstitution, prompt administration is recommended to avoid the ill effect of any inadvertent bacterial contamination occurring during reconstitution. Administer at room temperature, do not refrigerate after reconstitution and discard any unused contents.

A 1.0% increase in factor IX (0.01 IU)/IU administered/kg can be expected.[1, 5] The amount of Profilnine® required to establish hemostasis will vary with each patient and depends on the circumstances. The following formula may be used as a guide in determining the number of units to be administered:

Body Weight (in kg)		1.0 IU/kg		Desired increase in Plasma Factor IX (Percent)		Number of Factor IX IU Required
Example:						
50 kg	X	1.0 IU/kg	X	25 (% increase)	=	1,250 IU Factor IX

In normal clinical practice there is variability among patients and their clinical condition. Therefore, the factor IX level of each patient should be monitored frequently during replacement therapy.
Mild to moderate hemorrhages may usually be treated with a single administration sufficient to raise the plasma factor IX level to 20 to 30 percent. In the event of more serious hemorrhage, the patient's plasma factor IX level should be raised to 30 to 50 percent. Infusions are generally required daily.
Surgery in patients with factor IX deficiency requires that the factor IX level should be raised to 30 to 50 percent for at least one week following operation. For dental extractions, the factor IX level should be raised to 50 percent immediately prior to the procedure; additional factor IX complex may be given if bleeding recurs.
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.

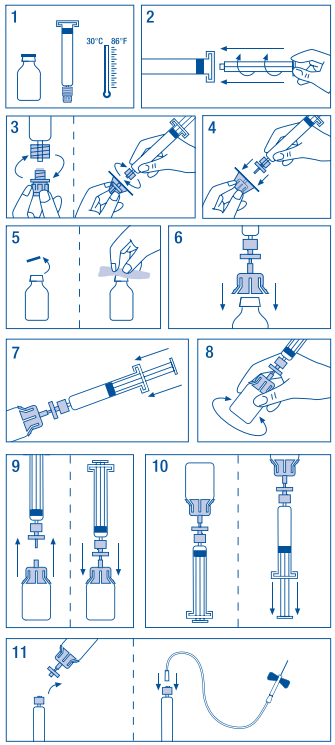
HOW SUPPLIED

Profilnine® is supplied in sterile lyophilized form in single dose vials accompanied by a suitable volume of diluent (Sterile Water for Injections), according to factor IX potency. Profilnine® is packaged with a prefilled syringe with diluent (sterile water for injections) and accessories for injection.

STORAGE

Profilnine® is stable for three years, up to the expiration date printed on its label, provided that the storage temperature does not exceed 25 °C. Do not freeze diluent.

Rx only



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