

Factor IX Complex Profilnine® SD

Solvent Detergent Treated

DESCRIPTION

Factor IX Complex, Profilnine® SD, Solvent Detergent Treated, is a sterile, lyophilized concentrate of Factor IX (antihemophilic factor B), Factor II (prothrombin), Factor X (Stuart-Prower Factor), and low levels of Factor VII (proconvertin) derived from human plasma. Factor II content has been assayed at no more than (NMT) 150 Units per 100 Factor IX Units, Factor X at NMT 100 Units per 100 Factor IX Units, and Factor VII at NMT 35 Units per 100 Factor IX Units. Profilnine® SD is intended for intravenous administration only. Each vial is a single dose container.

Profilnine® SD is a non-activated Factor IX Complex prepared from pooled human plasma and purified by DEAE cellulose adsorption. Profilnine® SD is treated with a mixture of the organic solvent tri(n-butyl)phosphate (TNBP) and the nonionic detergent polysorbate 80 (Solvent Detergent Mixture) to reduce risks of transmission of viral infection. However, no procedure has been shown to be totally effective in removing viral infectivity from coagulation factor products.

Each vial of Profilnine® SD is labeled with the Factor IX potency expressed in International Units (IU). Profilnine® SD does not contain heparin. Profilnine® SD contains low levels of activated coagulation factors, as indicated by the non-activated Partial Thromboplastin Time Test.^{1,2} Profilnine® SD contains no preservatives.

When reconstituted with the appropriate volume of Sterile Water for Injection, USP, Profilnine® SD contains not more than 2.5 µg polysorbate 80 and 0.40 µg TNBP per IU of Factor IX.

CLINICAL PHARMACOLOGY

Profilnine® SD is a mixture of vitamin K-dependent clotting factors. The administration of Factor IX Complex, Profilnine® SD, temporarily increases the plasma levels of Factor IX, thus minimizing the hazards of hemorrhage. A clinical study, which evaluated twelve subjects with hemophilia B, indicated that, following administration of Profilnine® SD, Factor IX *in vivo* half-life is 24.68 ± 8.29 hours and recovery is 1.15 ± 0.16 IU/dL per IU infused per kg body weight.³

Administration of Factor IX Complex can result in higher than normal levels of Factor II due to its significantly longer half-life.⁴

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® SD has been shown to provide a very high level of virus kill without compromising protein structure and function.⁵ 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.⁶⁻⁸

The solvent detergent process used in the manufacture of Profilnine® 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 6.0 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® SD process is twice (360 minutes total) that used in the model virus studies.

The ability of the Profilnine® SD 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

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

This product 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 Factor IX Complex, Profilnine® 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 DEAE chromatography and solvent detergent treatment in the manufacturing process.⁹⁻¹⁰ 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 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.¹¹⁻¹³ 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® SD should only be administered to patients when the beneficial effects of use outweigh the serious risk of potential hypercoagulation.

PRECAUTIONS

General

Factor IX Complex, Profilnine® 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. 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.

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.

Pregnancy Category C

Animal reproduction studies have not been conducted with Profilnine® SD. It is also not known whether Profilnine® SD can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Profilnine® 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 for Hemophilia B, the two pediatric patients receiving Profilnine® SD (solvent detergent treated) 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.³

ADVERSE REACTIONS

Adverse reactions characterized by either thrombosis or disseminated intravascular coagulation (DIC) are associated with administration of Factor IX Complex concentrates.¹¹⁻¹⁴ 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 1-888-GRIFOLS (1-888-474-3657) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DOSAGE AND ADMINISTRATION

For adult usage:

Factor IX Complex, Profilnine® SD should be administered intravenously, promptly following reconstitution with the supplied diluent. Although Profilnine® SD 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. Profilnine® SD may be administered by injection (plastic disposable syringe only) or infusion. Administer at room temperature, do not refrigerate after reconstitution and discard any unused contents.

Each vial of Profilnine® SD is labeled with the total units expressed as International Units (IU) which is referenced to the WHO International Standard. One unit approximates the activity in one mL of normal plasma.

A 1.0% increase in Factor IX (0.01 IU/IU administered/kg can be expected.¹⁵ The amount of Profilnine® SD required to establish hemostasis will vary with each patient and depend 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) | X | Desired increase in Plasma Factor IX (Percent) | X | 1.0 IU/kg | = | Number of Factor IX IU Required |
| Example: 50 kg | X | 25 (% increase) | X | 1.0 IU/kg | = | 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 daily 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.

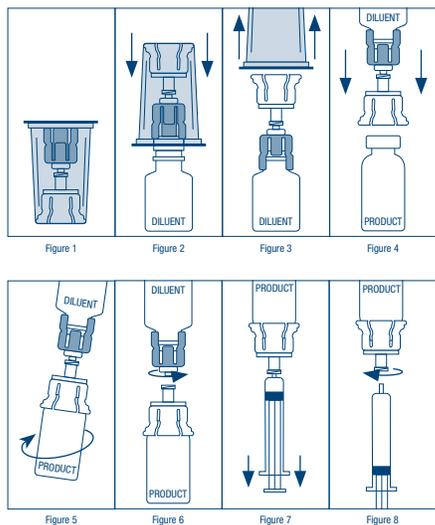
For pediatric usage: See PRECAUTIONS

RECONSTITUTION

Use Aseptic Technique

1. Warm diluent (Sterile Water for Injection, USP) and concentrate (Profilnine® SD) to at least room temperature (but not above 37 °C).
2. Remove the plastic flip off cap from the diluent vial.
3. Gently swab the exposed stopper surface with a cleansing agent such as alcohol trying to avoid leaving any excess cleansing agent on the stopper.
4. Open the Mix2Vial™ package by peeling away the lid (Figure 1). Leave the Mix2Vial™ in the clear outer packaging.
5. Place the diluent vial upright on an even surface and hold the vial tight and pick up the Mix2Vial™ in its clear outer packaging. Holding the diluent vial securely, push the **blue** end of the Mix2Vial™ vertically down through the diluent vial stopper (Figure 2).
6. While holding onto the diluent vial, carefully remove the clear outer packaging from the Mix2Vial™ set, ensuring the Mix2Vial™ remains attached to the diluent vial (Figure 3).
7. Place the product vial upright on an even surface, invert the diluent vial with the Mix2Vial™ attached.
8. While holding the product vial securely on a flat surface, push the **clear** end of the Mix2Vial™ set **vertically** down through the product vial stopper (Figure 4). The diluent will automatically transfer out of its vial into the product vial. (NOTE: If the Mix2Vial™ is connected at an angle, the vacuum may be released from the product vial and the diluent will not transfer into the product vial.)
9. With the diluent and product vials still attached to the Mix2Vial™, gently swirl the product vial to ensure the product is fully dissolved (Figure 5). Reconstitution requires less than 10 minutes. Do not shake the vial.
10. Disconnect the Mix2Vial™ into two separate pieces (Figure 6) by holding each vial adapter and twisting counterclockwise. After separating, discard the diluent vial with the **blue** end of the Mix2Vial™.
11. Draw air into an empty, sterile syringe. Keeping the product vial upright with the **clear** end of the Mix2Vial™ attached, screw the disposable syringe onto the luer lock portion of the Mix2Vial™ device by pressing and twisting clockwise. Inject air into the product vial.
12. While keeping the syringe plunger depressed, invert the system upside down and draw the reconstituted product into the syringe by pulling the plunger back slowly (Figure 7).
13. When the reconstituted product has been transferred into the syringe, firmly hold the barrel of the syringe and the clear vial adapter (keeping the syringe plunger facing down) and unscrew the syringe from the Mix2Vial™ (Figure 8). Hold the syringe upright and push the plunger until no air is left in the syringe. Attach the syringe to a venipuncture set.
14. NOTE: If the same patient is to receive more than one vial of concentrate, the contents of two vials may be drawn into the same syringe through a separate unused Mix2Vial™ set before attaching to the venipuncture set.
15. Use prepared drug as soon as possible after reconstitution.
16. After reconstitution, parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. When reconstitution procedure is strictly followed, a few small particles may occasionally remain. The Mix2Vial™ set will remove particles and the labeled potency will not be reduced.

17. Discard all administration equipment after use into the appropriate safety container. Do not reuse.



HOW SUPPLIED

Profilnine® SD is supplied in sterile lyophilized form in single dose vials accompanied by a suitable volume of diluent (Sterile Water for Injection, USP), according to Factor IX potency.

Each vial is labeled with the Factor IX potency expressed in International Units which is referenced to the WHO International Standard. Profilnine® SD is packaged with a Mix2Vial™ filter transfer set for use in administration. It is available in the following potencies, and the product is also color coded based upon assay on the carton and vial label as follows:

| Potency | NDC | Assay Color Code |
|------------------------------------|--------------|-------------------------|
| 500 IU FIX/5 mL single dose vial | 68516-3201-1 | MID in blue box |
| 1000 IU FIX/10 mL single dose vial | 68516-3202-2 | HIGH in red box |
| 1500 IU FIX/10 mL single dose vial | 68516-3203-2 | SUPER HIGH in black box |

STORAGE

Profilnine® SD should be stored at temperatures between 2 and 8 °C. Do not freeze diluent. May be stored at room temperature not to exceed 30 °C for up to 3 months. When removed from refrigeration, record the date on the vial or carton.

Rx only

REFERENCES

- Kingdon, H.S., Lundblad, R.L., Veltkamp, J.J., Aronson, D.L. Potentially thrombogenic materials in Factor IX Concentrates. *Thromb Diath Haemorrh* 33:617-631, 1975.
- Middleton, S.M., Forbes, C.D., Prentice, C.R.M. Thrombogenic Potential in Factor IX Concentrates Comparison of Tests. *Thromb Haemost* (Stuttg) 40:574-576, 1979.
- Data on file at Grifols Biologicals Inc.
- Aronson, D.L. Factor IX Complex. *Semin Thromb Hemostas* 6(1):28-43, 1979.
- Horowitz, B. Investigations into the Application of Tri(n-butyl) phosphate/Detergent Mixtures to Blood Derivatives. In *Viral Inactivation of Plasma Products*, Morgenthaler J.J. (ed), Karger.
- Horowitz, B., Wiebe, M.E. et al. Inactivation of viruses in labile blood derivatives. *Transfusion* 25:516-522, 1985.
- Edward, C.A., Piet, M.P.J. et al. Tri(n-butyl)phosphate/detergent treatment of licensed therapeutic and experimental blood derivatives. *Vox Sang* 52:53-59, 1987.
- Prince, A.M., Horowitz, B., Horowitz, M. et al. The development of virus-free labile blood derivatives-a review. *Eur J Epidemiology*, 3:103-118, 1987.
- Menache, D., Roberts, H.R. Summary Report and Recommendations of the Task Force Members and Consultants. *Thromb Diath Haemorrh* 33:645-647, 1975.
- Carnelli, V., Gomperts, E.D., Friedman, A., et al. Assessment for Evidence of Non A-Non B Hepatitis in Patients Given n-Heptane-Suspended Heat-Treated Clotting Factor Concentrate. *Thromb Res*, 46:827-834, 1987.
- Lusher, J.M. Management of Hemophiliacs with Inhibitors. *Hemophilia in the Child and Adult*. Raven Press, Ltd., New York, 1989, pp. 121-136.
- Aledort, L.M. Factor IX and Thrombosis. *Scand J Haematol*, Suppl 30:40-42, 1977.
- Kasper, C.K. Thromboembolic Complications. *Thromb Diath Haemorrh* (Stuttg) 33:640-644, 1975.
- Chistolini, A., Mazzucconi, M.G., Tirindelli, M.L., LaVerde, G., Ferrari, A., Mandelli, F. Disseminated intravascular coagulation and myocardial infarction in a haemophilia B patient during therapy with prothrombin complex concentrate. *Acta Haematol* 83:163-165, 1990.
- Zauber, N.P., Levin, J. Factor IX Levels in Patients with Hemophilia B (Christmas Disease) Following Transfusion with Concentrates of Factor IX or Fresh Frozen Plasma (FFP). *Medicine* 56(3):213-224, 1977.

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