**Factor IX Complex**

**Profilnine®**

**Solvent Detergent Treated/Nonfiltered**

**DESCRIPTION**

Factor IX Complex, Profilnine®, is a solvent detergent treated, nonfiltered, sterile, lyophilized concentrate of coagulation factors IX, II, and X and low levels of factor VII. The factor II content is not more than (NMT) 150 units/L 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, if any, activated factors based on results from the non-activated partial thromboplastin time (APTT) test.1 2

Profilnine is prepared from pooled human plasma and treated 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 nanofiltration3 and solvent/detergent (n-octylphosphoryl) TNP4 treatment5 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 viruses of 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), parvovirus, 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.

<table>
<thead>
<tr>
<th>Virus Type</th>
<th>Model For:</th>
<th>Process Step</th>
<th>Virus Reduction (log10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sindbis</td>
<td>Env</td>
<td>1st DEAE Chromatography</td>
<td>≥ 4.4</td>
</tr>
<tr>
<td>VSV</td>
<td>Env</td>
<td>Robust enveloped viruses</td>
<td>≥ 4.9</td>
</tr>
<tr>
<td>HIV-1</td>
<td>HIV-1</td>
<td>NT</td>
<td>≥ 12.2</td>
</tr>
<tr>
<td>HIV-2</td>
<td>HIV-2</td>
<td>NT</td>
<td>≥ 6.0</td>
</tr>
<tr>
<td>WNV</td>
<td>WNV</td>
<td>NT</td>
<td>≥ 6.6</td>
</tr>
<tr>
<td>BVDV</td>
<td>Env</td>
<td>Hepatitis C</td>
<td>NT</td>
</tr>
<tr>
<td>Parv°</td>
<td>Non-Env</td>
<td>Parvovirus B19</td>
<td>NT</td>
</tr>
<tr>
<td>HRV</td>
<td>Non-Env</td>
<td>HAV</td>
<td>NT</td>
</tr>
<tr>
<td>PRV</td>
<td>Non-Env</td>
<td>Hepatitis B</td>
<td>NT</td>
</tr>
</tbody>
</table>

* Parv°, 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 Profilnine temporarily increases the plasma levels of factor IX, thus enabling a temporary correction of the factor IX deficiency. A clinical study that evaluated twelve subjects with hemophilia B indicated that, following administration of Profilnine, the factor IX in vivo half-life of 24.68 ± 8.23 hours and recovery was 1.15 ± 0.10 units/dL per unit infused/kg body weight.9 Administration of factor IX complex can result in higher than normal levels of factor II due to its significantly longer half-life.

**INDICATIONS AND USAGE**

Profilnine is indicated for the prevention and control of bleeding in patients with factor IX deficiency (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. 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 nanofiltration3 and solvent/detergent (n-octylphosphoryl) TNP4 treatment5 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 viruses of 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), parvovirus, 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.

**PRECAUTIONS**

None known.

**ADVERSE REACTIONS**

A 1% increase in factor IX (0.01 units)/units administered/kg can be expected1,5. 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.

**DOSE**

For adult usage:

Each vial of Profilnine is labeled with total units expressed as international units (IU) according to the WHO International Standard. One unit approximates the activity in one ml of normal plasma. A 1% increase in factor IX (0.01 IU/ml) may be expected.12 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.

<table>
<thead>
<tr>
<th>Body weight</th>
<th>Desired increase in Plasma Factor IX (Percent)</th>
<th>Number of Factor IX Units Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 kg</td>
<td>X 25%</td>
<td>1,250 Units of Factor IX</td>
</tr>
</tbody>
</table>

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.

**TREATMENT GUIDELINES FOR HEMORRHAGIC EVENTS AND SURGERY IN PATIENTS WITH FACTOR IX DEFICIENCY**

<table>
<thead>
<tr>
<th>Type of Hemorrhage or Surgical Procedure</th>
<th>Treatment Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to moderate Hemorrhages</td>
<td>Mild to moderate hemorrhage usually can be effectively treated with a single dose of product sufficient to raise plasma factor IX levels to 20 to 30 percent of normal. Daily infusions are generally required.</td>
</tr>
<tr>
<td>Major Hemorrhages</td>
<td>For more severe hemorrhage, factor IX plasma factor IX levels should be raised to 30 to 50 percent of normal. Daily infusions are generally required.</td>
</tr>
<tr>
<td>Surgery</td>
<td>Surgery associated with bleeding in factor IX deficient patients requires factor IX levels of 30 to 50 percent for at least one week postoperatively. For dental extractions, the factor IX level should be raised to 50 percent immediately prior to procedure, additional factor IX complex may be given if bleeding recurs.</td>
</tr>
</tbody>
</table>

**For pediatric usage:** See PRECAUTIONS

**RECONSTITUTION**

Use Aseptic Technique

1. Ensure that concentrate (Profilnine) and diluent (Sterile Water for Injection, USP) are at room temperature (but not above 37°C) before reconstitution.

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 particulate matter.

4. Open the Mix2Vial® package by peeling away the lid (Figure 1). Leave the Mix2Vial in the clear outer packaging.

5. While holding onto the diluent vial, carefully remove the clear outer packaging from the Mix2Vial set, ensuring that the diluent will not transfer into the product vial.

6. Place the product vial upright on an even surface, invert the diluent vial with the Mix2Vial attached.

7. After reconstitution, parenteral drug products should be inspected visually for particulate matter and color, clarity and other signals of contamination before use. Do not reconstitute the solution.

8. While holding the diluent vial carefully, remove the clear outer packaging from the Mix2Vial set, ensuring the Mix2Vial remains attached to the diluent vial (Figure 3).

9. Place the product vial upright on a flat surface, invert the diluent vial with the Mix2Vial attached.

10. While holding the diluent vial securely, invert the mix2vial set vertically down through the diluent vial stopper (Figure 4).

11. While holding the diluent vial, carefully remove the clear outer packaging from the Mix2Vial set, ensuring the Mix2Vial remains attached to the diluent vial (Figure 3).

12. Place product vial upright on a flat surface, invert the diluent vial with the Mix2Vial attached.

13. While 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).

14. 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).

15. If the syringe plunger is depressed, the contents of the Mix2Vial may be drawn into the same syringe through a separate unused Mix2Vial set before attaching to the needle or syringe set.

16. Use the prepared drug as soon as possible within three hours after reconstitution.

17. 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.

* Unit refers to International Unit in the labeling of Profilnine.
16. Discard all administration equipment after use into the appropriate safety container. Do not reuse.

**ADMINISTRATION**

Intravenous administration of Profilnine should be initiated promptly following reconstitution with the supplied diluent. Although Profilnine is stable for at least three hours at room temperature after reconstitution, prompt administration is recommended to avoid ill effects of any inadvertent bacterial contamination occurring during reconstitution. Profilnine 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. Do not administer Profilnine at a rate exceeding 10 mL/minute. Rapid administration may result in vasomotor reactions.

**HOW SUPPLIED**

Profilnine 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 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:

<table>
<thead>
<tr>
<th>Potency</th>
<th>Carton NDC</th>
<th>Assay Color Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 units FIX/5 mL</td>
<td>68516-3201-1</td>
<td>500 units FIX Range - blue</td>
</tr>
<tr>
<td>1000 units FIX/10 mL</td>
<td>68516-3202-2</td>
<td>1000 units FIX Range - red</td>
</tr>
<tr>
<td>1500 units FIX/10 mL</td>
<td>68516-3203-2</td>
<td>1500 units FIX Range - black</td>
</tr>
</tbody>
</table>

**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 (77 °F). Do not freeze.

Rx only

**REFERENCES**

5. Data on file at Grifols Biologics Inc.

Manufactured by:

Grifols Biologics Inc.
5555 Valley Boulevard
Los Angeles, CA 90032, U.S.A.

U.S. License No. 1694

DATE OF REVISION: November 2013

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