Prothrombinex®-VF
Human prothrombin complex, powder for injection

Product Information

AUSTRALIA
NAME OF THE MEDICINE
Human prothrombin complex, powder for injection.

DESCRIPTION
Prothrombinex®-VF is a sterile freeze-dried powder containing purified human coagulation factors II, IX and X. It is prepared from blood collected from voluntary donors.

The product is prepared by adsorption of coagulation factors from plasma onto an ion-exchange medium followed by selective elution. The manufacturing process of Prothrombinex®-VF involves specific steps to reduce the possibility of viral transmission including dry heat treatment at 80°C for 72 hours for viral inactivation and filtration for virus removal.

When reconstituted as recommended, each vial of Prothrombinex®-VF contains factor IX 500 IU, factors II and X approximately 550 IU each, antithrombin III 25 IU and heparin sodium 192 IU. Other ingredients are human plasma proteins ≤ 500 mg (which includes low levels of factors V and VII), sodium citrate, sodium phosphate and sodium chloride.

The factors II, IX, X, antithrombin III and the human plasma proteins are all of human origin. The heparin sodium is of porcine origin.

PHARMACOLOGY
Factors II, IX and X are components of the intrinsic coagulation pathway. They are synthesised in the liver in a vitamin K dependent manner. Together they form the prothrombin complex. If one or more of these factors are deficient, the blood coagulation is disturbed and appropriate substitution therapy is necessary.

The initial recovery of factor IX in plasma after intravenous injection is about 50%. The plasma half-life of factor IX ranges from 16 to 30 hours, factor II from 40 to 60 hours, and factor X from 30 to 60 hours.

CLINICAL TRIALS
There is limited clinical data available on Prothrombinex®-VF. However, Prothrombinex®-VF is similar to other Prothrombin Complex Concentrates. There are two published reports of the efficacy of Prothrombin Complex Concentrates in the treatment of eleven factor IX deficient patients undergoing bleeding or surgery. There have been no dose ranging studies since only limited data are available on the concomitant use of Prothrombinex®-VF with other drugs. There is also the possibility that other known or unknown infectious agents may be present in such products.

Vaccination for patients in receipt of medicinal products from human plasma should be considered where appropriate.

Check the following before use
Prothrombinex®-VF contains 192 IU heparin sodium in each vial. Heparin is known to cause thrombocytopenia and this possibility should be considered if thrombocytopenia develops during treatment. Consideration should be given to the clinical effect of heparin if high doses of Prothrombinex®-VF are required.

Carcinogenicity/genotoxicity
The carcinogenic or genotoxic effects of Prothrombinex®-VF have not been established in appropriate studies.

Use in pregnancy and lactation
The safe use of Prothrombinex®-VF during human pregnancy or lactation has not been established in appropriate studies.

Paediatric use and use in the elderly
The safe use of Prothrombinex®-VF in the paediatric and elderly populations has not been established in appropriate studies.

Interactions with other medicines
The interaction of Prothrombinex®-VF with other drugs has not been established in appropriate studies, however, see PRECAUTIONS.

Effects on laboratory tests
Prothrombinex®-VF is formulated with heparin sodium and antithrombin III. Therefore, the results of anticoagulant tests should be interpreted with care.

ADVERSE EFFECTS
Allergic reactions or fever are rarely observed in patients receiving factor IX concentrates. If any adverse event occurs while Prothrombinex®-VF is being administered, the rate of injection should be slowed or stopped to alleviate symptoms.

There have been occasional reports of pulmonary embolism, phlebitis, deep-vein thrombosis, anaphylaxis and DIC following the use of Prothrombin Complex Concentrates associated with surgery. There is also the possibility that other known or unknown infectious agents may be present in such products.

Heparin is known to cause thrombocytopenia and this possibility should be considered if thrombocytopenia develops during treatment.

Development of antibodies to one or more of the prothrombin complex factors may occur in rare instances.

There is a potential risk of thrombotic episodes (including myocardial infarction) following the administration of a Prothrombin Complex Concentrate.
As a product made from human plasma, it may contain infectious agents, such as viruses, that can cause disease (see Pathogen safety).

**DOSEAGE AND ADMINISTRATION**

**Dosing**

The following recommendations for doses are provided only as a general guideline for therapy. The exact loading and maintenance doses and dosing intervals should be based on the patient’s clinical condition, response to therapy and plasma factor IX concentration. Laboratory tests should be performed to ensure that the desired factor IX levels are achieved.

### Indication

<table>
<thead>
<tr>
<th>Indication</th>
<th>Desired plasma concentration of factor IX (IU/dL)</th>
<th>Dose (IU/kg)</th>
<th>Frequency of dosing (per day)</th>
<th>Duration of treatment (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor haemorrhage</td>
<td>20 to 50</td>
<td>20 to 30</td>
<td>1</td>
<td>1 to 2</td>
</tr>
<tr>
<td>Moderate to severe haemorrhage</td>
<td>35 to 50</td>
<td>30 to 50</td>
<td>1 to 3</td>
<td>1 to 5</td>
</tr>
<tr>
<td>Thrombosis or DIC</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Minor surgery*</td>
<td>40 to 60</td>
<td>40 to 60</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Loading</td>
<td>20 to 50</td>
<td>15 to 40</td>
<td>2 to 5</td>
<td>-</td>
</tr>
</tbody>
</table>

* Includes dental extraction.

**Initial** (days 1 to 3) aim for levels at the higher end of this range. Gradually reduce to lower level during subsequent days.

Treatment may need to be repeated at varying intervals to maintain the required concentration of factor IX in the plasma. Thrombotic problems may occur if the suggested maximum dose is exceeded.

Under certain circumstances larger amounts than those calculated can be required, especially in the case of the initial dose.

For long term prophylaxis against bleeds in patients with congenital factor IX deficiency, doses of 25 to 40 IU of factor IX per kg bodyweight can be given twice weekly.

Experience in the treatment of congenital deficiency in factors II or X is limited. Because of the long half-life of factors II and X, patients with congenital factor II or factor X deficiency require lower amounts of Prothrombinex Complex Concentrate.

**Monitoring**

It is recommended that plasma factor IX concentrations be monitored during the treatment period.

Patients requiring more than 4 to 5 days of treatment with Prothrombinex-VF should be monitored carefully for signs of thrombosis or DIC.

**Reconstitution**

1. Before reconstitution, allow the vials of Prothrombinex-VF® and Water for Injections to reach a temperature between 20°C and 30°C.
2. Remove the dust covers from the tops of the Prothrombinex-VF® and Water for Injections vials.
3. Apply a suitable antiseptic to the exposed part of the rubber stoppers of both the Prothrombinex-VF® and Water for Injections and allow to dry.
4. Open the outer package of the Mix2Vial® filter transfer set by peeling away the lid. If the seal of the lid is not intact or there are any concerns about the integrity of the Mix2Vial® do not use it but return it to the Australian Red Cross Blood Service. Place the Water for Injections on a level surface and hold the vial firmly. Take the Mix2Vial® together with its outer package and invert it. Push the blue plastic cannula of the Mix2Vial® firmly through the rubber stopper of the Water for Injections.
5. While holding onto the vial of Water for Injections, carefully remove the outer package from the Mix2Vial®, being careful to leave the Mix2Vial® attached firmly to the Water for Injections vial. Ensure that only the package and not the Mix2Vial® is removed.
6. With the Prothrombinex-VF® vial held firmly on a level surface, invert the Water for Injections with the Mix2Vial® attached and push the transparent plastic cannula end of the Mix2Vial® firmly through the Prothrombinex-VF® stopper. The water will be drawn into the vial by the vacuum within. In the unlikely event that the vial does not contain a vacuum, do not use the product, but return it to the Australian Red Cross Blood Service.
7. With the Water for Injections and Prothrombinex-VF® vial still attached, gently swirl the product vial to ensure the product is fully dissolved. Avoid excessive frothing. A clear or slightly opalescent solution is usually obtained in 10 minutes or less. The solution should be used immediately as described below under Administration.
8. Once the contents of the Prothrombinex-VF® vial are completely dissolved, firmly hold both the transparent and blue parts of the Mix2Vial®. Unscrew the Mix2Vial® into two separate pieces, and discard the empty Water for Injections vial and the blue part of the Mix2Vial® in an appropriate waste container.

**CAUTION**

The product does not contain an antimicrobial preservative. It must, therefore, be used immediately after reconstitution. Any unused solution should be discarded appropriately. Use in one patient on one occasion only. If clots or a gel form, do not use the product but return it to the Australian Red Cross Blood Service.

**Administration**

1. With the Prothrombinex-VF® vial upright, attach a plastic disposable syringe to the Mix2Vial® (translucent plastic part). Invert the system and draw the reconstituted Prothrombinex-VF® into the syringe by pulling the plunger back slowly. One large syringe may be used to pool several vials of reconstituted Prothrombinex-VF®.
2. Once the Prothrombinex-VF® has been transferred into the syringe, firmly hold the barrel of the syringe (keeping the syringe plunger facing down) and detach the Mix2Vial® from the syringe. Discard the Mix2Vial® (translucent plastic part) and empty Prothrombinex-VF® vial in an appropriate waste container.

**Spillage or Breakage**

Should a break in the container or spillage occur, due precautions should be taken to avoid contamination of cuts and abrasions, as well as to avoid inhalation or swallowing of the spillage. Adequate disinfection can be obtained with the application of 1% sodium hypochlorite for 15 minutes. Commercial bleach may be diluted appropriately to obtain this concentration.

**OVERDOSE**

Overdose may lead to an increased risk of DIC, thrombosis, myocardial infarction and pulmonary embolism.

**PRESENTATION**

Prothrombinex-VF® is available in vials containing 500 IU of factor IX, 500 IU of factor II and 500 IU of factor X. Each single pack contains one vial of product, one 20 mL vial of Water for Injections and one Mix2Vial® filter transfer set.

**STORAGE CONDITIONS**

Store at 2°C to 8°C. (Refrigerate. Do not freeze). Protect from light. Do not use after the expiry date.

**REFERENCES**

7. Clinical data from the Scottish National Blood Transfusion Service

**NAME AND ADDRESS OF THE SPONSOR**

CSL Limited ABN 99 051 588 348
Bioplasma Division
189 - 209 Camp Road
Broadmeadows VIC 3047

**POISON SCHEDULE OF THE MEDICINE**

Unscheduled

Distributed by: Australian Red Cross Blood Service
Date of Therapeutic Goods Administration approval: 18 January 2006
Date of most recent amendment: 07 December 2007
Prothrombinex® is a registered trademark of CSL Limited.
Mix2Vial® is a trademark of Medipom Medical Projects Ltd.

**Address for correspondence:**

Bioplasma Division
189-209 Camp Road
Broadmeadows VIC 3047

**Email:** medicalaffairs_bioplasma@csl.com.au
**Email:** bioplasma.customer.service@csl.com.au

**Date of Therapeutic Goods Administration approval:**

18 January 2006

**Date of most recent amendment:**

07 December 2007

**Prothrombinex® is a registered trademark of CSL Limited.**

**Mix2Vial® is a trademark of Medipom Medical Projects Ltd.**