

## Product Information

### Prothrombinex<sup>®</sup>-VF

Australia

#### NAME OF THE MEDICINE

Human prothrombin complex, powder for injection.

#### DESCRIPTION

Prothrombinex<sup>®</sup>-VF is a sterile freeze-dried powder containing purified human coagulation factors II, IX and X and low levels of factors V and VII. It is prepared from pooled human plasma donated by Australia's voluntary non-remunerated donors.

The concentrate is prepared by adsorption of coagulation factors from plasma onto an ion-exchange medium followed by selective elution. The manufacturing process of Prothrombinex<sup>®</sup>-VF contains dedicated and complementary steps to reduce the possibility of viral transmission including dry heat treatment (80°C for 72 hours) for viral inactivation and nanofiltration for virus removal.

When reconstituted as recommended, each vial of Prothrombinex<sup>®</sup>-VF contains the ingredients listed in **Table 1**.

**Table 1: Prothrombinex<sup>®</sup>-VF Composition**

	<b>500 IU vial</b>
<b>Active ingredients</b>	
Factor IX	500 IU
Factor II	approx. 500 IU
Factor X	approx. 500 IU
<b>Excipients</b>	
Human plasma proteins (including low levels of factors V and VII)	≤500 mg
Antithrombin III	25 IU
Heparin sodium	192 IU
Sodium <sup>+</sup>	112 mg
Phosphate <sup>+</sup>	65 mg
Citrate <sup>+</sup>	180 mg
Chloride <sup>+</sup>	27 mg

<sup>+</sup> Present as sodium citrate, sodium phosphate and sodium chloride.

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

## **PHARMACOLOGY**

### **Pharmacodynamics**

The coagulation factors II, VII, IX and X, which are synthesised in the liver with the help of vitamin K, are commonly called the prothrombin complex.

Factor VII is the zymogen of the active serine protease factor VIIa by which the extrinsic pathway of blood coagulation is initiated. The tissue factor-factor VIIa complex activates coagulation factors X and IX, whereby factor IXa and Xa are formed. With further activation of the coagulation cascade, prothrombin (factor II) is activated and transformed to thrombin. By the action of thrombin, fibrinogen is converted to fibrin, which results in clot formation. The normal generation of thrombin is also of vital importance for platelet function as a part of the primary haemostasis.

Isolated deficiency of factor IX is one of the classical haemophilias (haemophilia B). Isolated deficiency of factor II or factor X is very rare but in severe form they cause a bleeding tendency similar to that seen in classical haemophilia. Isolated severe deficiency of factor VII leads to reduced thrombin formation and a bleeding tendency due to impaired fibrin formation and impaired primary haemostasis.

Acquired deficiency of the vitamin K dependent coagulation factors occurs during treatment with vitamin K antagonists (such as warfarin and phenindione). It may also result from vitamin K deficiency (malabsorption syndrome, antibiotic therapy, cholestasis, prolonged parenteral alimentation). If the deficiency becomes severe, a severe bleeding tendency results, characterised typically by retroperitoneal or cerebral bleeds rather than muscle and joint haemorrhage.

Severe hepatic insufficiency also results in markedly reduced levels of the vitamin K dependent coagulation factors and a clinical bleeding tendency which, however, is often complex due to a simultaneous ongoing low-grade intravascular coagulation, low platelet levels, deficiency of coagulation inhibitors and disturbed fibrinolysis.

The administration of human prothrombin complex provides an increase in plasma levels of the vitamin K dependent coagulation factors, and can temporarily correct the coagulation defect of patients with deficiency of one or several of these factors.

## Pharmacokinetics

Prothrombin complex concentrates (PCCs) are distributed and metabolised in the same way as endogenous coagulation factors. Intravenous administration means that the preparation is available immediately; bioavailability is 100%.

A pharmacokinetic study with a PCC containing coagulation factors II, VII, IX and X in healthy volunteers, who received a 50 IU/kg intravenous dose, showed that peak plasma concentrations of the coagulation factors occur within 5 minutes of infusion. **Table 2** lists PCC coagulation factor elimination half-lives as median and (inter-quartile range).

**Table 2: Coagulation Factor Elimination Half-Lives**

	<b>Factor II</b>	<b>Factor VII</b>	<b>Factor IX</b>	<b>Factor X</b>
Elimination $t_{1/2}$ (h)	60 (46–66)	4.2 (3.9–6.6)	17 (14–68)	31 (24–41)

There are no data for Prothrombinex<sup>®</sup>-VF, a PCC containing factors II, IX and X. The European Core Summary of Product Characteristics (SPC) for PCCs cites the following recoveries for the coagulation factors: factor II 0.02 IU/mL, factor VII 0.01 IU/mL, factor IX 0.01 IU/mL and factor X 0.017 IU/mL.

## CLINICAL TRIALS

### Acquired deficiencies

Clinical data, from a limited number of studies, are available for Prothrombinex<sup>®</sup>-VF in acquired deficiencies of the prothrombin complex.

In trials of PCCs similar to Prothrombinex<sup>®</sup>-VF, the onset of effect on the International Normalised Ratio (INR) was rapid (within 15 minutes). When given concurrently with vitamin K, the duration of effect in one trial was shown to be up to 48 hours.

### *Warfarin reversal*

Several published investigator initiated phase IV studies have evaluated the efficacy of Prothrombinex<sup>®</sup>-VF in patients requiring warfarin reversal. Three different scenarios requiring warfarin reversal have been examined: a) prior to surgery, b) patients who are actively bleeding, and c) patients with a high INR at risk of bleeding.

In a prospective, non-comparative Australian study of 50 adult patients, Prothrombinex<sup>®</sup>-VF was administered alone (without concomitant fresh frozen plasma; FFP) in patients requiring

urgent warfarin reversal. Patients were grouped either with the intention to achieve complete reversal (n = 35) to INR <1.4 or partial reversal (n = 15) to INR 1.4–2.0, based on the reason for reversal of anticoagulation. Complete reversal was the target for patients with serious active bleeding (n = 11). In patients requiring surgery (n = 22) the aim was either to fully or partially correct the INR depending on the nature of the surgery; and in patients with a high INR deemed at high risk of bleeding, attenuation of the INR to within the therapeutic range (INR 2–3) was the aim (n = 2). All patients were treated with a single infusion of Prothrombinex<sup>®</sup>-VF at a dose of 25–50 IU/kg body weight, with post-INR measured 30 minutes after. The mean INR before reversal was 3.5 in the complete reversal group (range 1.7–20.0) and 5.6 in the partial reversal group (range 2.5–10.0). After reversal the mean INR in the complete reversal group was 1.1, with 32 of 35 patients (91%) achieving complete reversal, the remaining 3 patients achieving INR ≤2.0; the mean dose received was 34.7 IU/kg (range 25–50). In the partial reversal group success was achieved in 14 of 15 patients (93%) with INR in the range 1.4–2.0. In this group the mean dose received was 29.7 IU/kg (range 25–45). On the basis of the results of this study a dosing algorithm based on the initial INR and the target INR was developed (see **DOSAGE AND ADMINISTRATION**). This is considered the primary study supporting the use of Prothrombinex<sup>®</sup>-VF in warfarin reversal. The potential limitation of the study is the small number of patients with INR >3.5 requiring complete reversal (14%).

A total of 173 patients (167 on warfarin) were included in a prospective audit of Prothrombinex<sup>®</sup>-VF use in 2 New Zealand hospitals; 54 (31%) of these patients required warfarin reversal prior to a surgical procedure, and the majority (58%) for acute bleeding. Concomitant FFP and vitamin K were given on the advice of the haematologist; 42% of patients received FFP and 82% vitamin K. The results of the study demonstrated that 79.1% of patients achieved a post-reversal INR of <1.5 (first INR post-treatment, secondary outcome). There was no significant difference in the pre- or post-Prothrombinex<sup>®</sup>-VF INR obtained between groups who did and did not receive FFP (p = 0.91 and 0.13, respectively). There was variability around the time the first INR was collected; the average being 23 hours post-Prothrombinex<sup>®</sup>-VF dose. The average dose of Prothrombinex<sup>®</sup>-VF was reported as 21 IU/kg (range 6–45; based on data from 103 patients for whom a weight was reported).

The use of Prothrombinex<sup>®</sup>-VF to reverse warfarin anticoagulation in patients who were actively bleeding was also assessed in the studies cited above. There were 14 patients in the primary study and 100 in the New Zealand study. In the primary study all patients received Prothrombinex<sup>®</sup>-VF alone, while in the New Zealand study a proportion of the total patient population (42%) also received FFP. In the primary study all patients with active bleeding achieved haemostasis and those undergoing procedures or surgery had no bleeding

complications. One patient in the primary study died as a result of bleeding from a ruptured aortic aneurysm. The New Zealand study did not include re-imaging of patients with intracranial haemorrhage, however in other patients who received Prothrombinex<sup>®</sup>-VF for bleeding, no ongoing bleeding was observed. Similarly, no excess or ongoing bleeding was observed in patients receiving Prothrombinex<sup>®</sup>-VF for warfarin reversal prior to emergency procedures.

There is very limited data on patients with supratherapeutic INR (>3.5) that required warfarin reversal. In patients on warfarin with a high INR and a high risk of bleeding (2 in the primary study and 10 in the New Zealand study), the infusion of Prothrombinex<sup>®</sup>-VF resulted in the reduction in INR to <2.0; including a patient with a pre-treatment INR of 20 (primary study).

The optimum dose of Prothrombinex<sup>®</sup>-VF for warfarin reversal has been evaluated in a limited number of studies/audits. The best evidence for dosing in different clinical scenarios is based on an algorithm developed in the primary study, which has been adapted by the Australasian Society of Thrombosis and Haemostasis (ASTH) (see **DOSAGE AND ADMINISTRATION**). The dose recommended is 25–50 IU/kg.

### ***Non-warfarin related coagulopathy***

Relatively fewer patients with non-warfarin related coagulopathy have been reported. A published audit of the use of Prothrombinex<sup>®</sup>-VF included 19 patients with a coagulopathy and a prolonged INR not due to warfarin. An overall reduction in INR from 2.2 pre-treatment (range 1.9–2.6) to 1.7 post-treatment (range 1.4–1.9) was reported. Nine of the 13 patients were actively bleeding and in these patients haemostasis was achieved. In another 8 patients who required surgery the use of Prothrombinex<sup>®</sup>-VF reduced the INR, enabling surgery to proceed.

This audit also reported on 18 patients, predominantly undergoing cardiothoracic surgery, who had intraoperative bleeding. Six patients were thrombocytopenic and 7 had prolonged APTT contributing to the bleeding. Haemostasis was achieved in all cases, however the contribution of Prothrombinex<sup>®</sup>-VF was difficult to determine as these patients also received other haemostatic agents.

### **Congenital deficiencies**

There are two published reports on the efficacy of PCCs in the treatment of eleven haemophilia B (factor IX deficient) patients undergoing bleeding or surgery. In a separate study eight haemophilia B patients who received prophylactic treatment with PCC at doses up to 25–40 IU/kg twice weekly showed reduced joint damage compared to age matched

historical controls who only received on demand therapy. However, as there have been no dose ranging studies performed with PCCs the doses recommended are based on accumulated clinical experience (see **DOSAGE AND ADMINISTRATION**).

There are very few published case reports on the efficacy of PCCs in the treatment of bleeds in patients with congenital factor II or X deficiency.

## **INDICATIONS**

Prothrombinex<sup>®</sup>-VF is indicated in:

- Treatment and perioperative prophylaxis of bleeding in acquired deficiency of prothrombin complex factors, such as deficiency caused by treatment with vitamin K antagonists, or in case of overdose of vitamin K antagonists, when rapid correction of the deficiency is required.
- Treatment and prophylaxis of bleeding in patients with single or multiple congenital deficiency of factor IX, II or X when purified specific coagulation factor product is not available (see **PRECAUTIONS**).

## **CONTRAINDICATIONS**

Hypersensitivity to the active substances or to any of the excipients including known allergy to heparin or history of heparin-induced thrombocytopenia (HIT).

Prothrombinex<sup>®</sup>-VF is also contraindicated in patients who have evidence of active thrombosis or disseminated intravascular coagulation (DIC).

## **PRECAUTIONS**

### **General**

The advice of a specialist experienced in the management of coagulation disorders should be sought.

In patients with acquired deficiency of vitamin K dependent coagulation factors (e.g. induced by treatment with vitamin K antagonists such as warfarin or phenindione),

Prothrombinex<sup>®</sup>-VF should only be used when rapid correction of the prothrombin complex factor levels is necessary. In other cases, reduction of the vitamin K antagonist dose or omission of the next dose and/or administration of vitamin K is usually sufficient.

In congenital deficiency of any of the vitamin K dependent factors, specific coagulation factor product should be used when available because of the incremental risk of thrombosis with Prothrombinex<sup>®</sup>-VF.

Prothrombinex<sup>®</sup>-VF is not recommended for the management of patients with isolated factor V or factor VII deficiency because of the low levels of factors V and VII in the product.

## **Hypersensitivity**

Prothrombinex<sup>®</sup>-VF should be used with caution in patients with a known allergy to constituents of the preparation. Allergic or anaphylactic-type reactions (e.g. angioedema, injection site reactions, chills, flushing, generalised urticaria, headache, pruritus, hypotension, lethargy, nausea, vomiting, restlessness, tachycardia, tingling, swelling, wheezing or shortness of breath) have been rarely observed in patients receiving PCCs such as Prothrombinex<sup>®</sup>-VF. In some cases, these reactions have progressed to severe anaphylaxis, particularly in patients with factor IX inhibitors. If allergic or anaphylactic-type reactions occur, Prothrombinex<sup>®</sup>-VF administration should be stopped immediately and appropriate measures implemented.

Prothrombinex<sup>®</sup>-VF contains heparin sodium which may cause HIT. The possibility of HIT developing during treatment should be considered if high doses of Prothrombinex<sup>®</sup>-VF are required (see **CONTRAINDICATIONS**).

## **Inhibitors**

The use of Prothrombinex<sup>®</sup>-VF in patients with congenital deficiency of any of the vitamin K dependent factors may lead to the formation of circulating antibodies known as ‘inhibitors’ to one or more of the factors in the product and manifest as a poor clinical response.

## **Thrombosis**

Patients receiving a vitamin K antagonist may have an underlying hypercoagulable state and infusion of a PCC may exacerbate this.

There is a risk of thrombosis, embolism, DIC or myocardial infarction when patients are treated with PCCs such as Prothrombinex<sup>®</sup>-VF. Such events may be fatal. The risk may be increased with repeated or high doses (especially at dose levels greater than 50 IU/kg of factor IX). Therefore, patients treated with PCCs should be observed closely for symptoms or signs of thrombosis, embolism, DIC or myocardial infarction.

Special care should be taken in patients with a history of venous thromboembolism, coronary artery or cerebrovascular disease or patients with liver disease. In these patients, the potential benefit of Prothrombinex<sup>®</sup>-VF should be weighed against the risk of precipitating a thrombotic event.

### **Pathogen safety**

This product is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses and theoretically Creutzfeldt-Jakob Disease (CJD) agents, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain infectious agents and by testing for the presence of certain viral markers.

In addition, virus removal and inactivation procedures are included in the manufacturing process. The procedures applied in the manufacture of this product are effective against enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B (HBV) and hepatitis C (HCV) viruses, and non-enveloped viruses, such as hepatitis A (HAV). These procedures may have some effect against non-enveloped viruses such as human parvovirus B19.

Despite these measures, such products may still potentially transmit disease. 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.

### **Effects on fertility**

The effects of Prothrombinex<sup>®</sup>-VF on fertility are unknown.

### **Use in pregnancy**

The safe use of Prothrombinex<sup>®</sup>-VF during pregnancy has not been established in clinical studies.

### **Use in lactation**

The safe use of Prothrombinex<sup>®</sup>-VF during lactation has not been established in clinical studies.

## **Paediatric use**

The safe use of Prothrombinex<sup>®</sup>-VF in the paediatric population has not been established in clinical studies.

Prothrombinex<sup>®</sup>-VF should be used with caution in neonates, in whom immature hepatic function may lead to delayed clearance of activated coagulation factors and an increased risk of thrombotic complications.

## **Use in the elderly**

The safe use of Prothrombinex<sup>®</sup>-VF in the elderly has not been established in clinical studies.

## **Carcinogenicity**

The effects of Prothrombinex<sup>®</sup>-VF on carcinogenicity are unknown.

## **Genotoxicity**

The effects of Prothrombinex<sup>®</sup>-VF on genotoxicity are unknown.

## **Effect on laboratory tests**

Prothrombinex<sup>®</sup>-VF is formulated with heparin sodium and antithrombin III. Therefore, the results of coagulation tests should be interpreted with care.

## **INTERACTIONS WITH OTHER MEDICINES**

The interaction of Prothrombinex<sup>®</sup>-VF with other medicines has not been established in specific studies.

The use of Prothrombinex<sup>®</sup>-VF with tranexamic acid is not recommended since only limited data are available on the concomitant administration of prothrombin complex products and antifibrinolytic agents.

## **ADVERSE EFFECTS**

Allergic or anaphylactic-type reactions can occur in PCCs such as Prothrombinex<sup>®</sup>-VF (see **PRECAUTIONS**).

Although low, there is a potential risk of thromboembolic episodes (including myocardial infarction) following the administration of a PCC such as Prothrombinex<sup>®</sup>-VF. This risk is increased in patients predisposed to thrombosis, or in patients receiving repeated or high

doses. Thrombotic events, particularly pulmonary embolism, may result in a fatal outcome (see **PRECAUTIONS**).

In the post-marketing period from 2001 spontaneous reporting of adverse events has been rare. Post-marketing reporting of adverse reactions is voluntary and from a population of uncertain size, and consequently it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.

The adverse reactions in **Table 3** are based on post-marketing experience of Prothrombinex<sup>®</sup>-VF and the previous generation product, Prothrombinex<sup>®</sup>-HT.

**Table 3: Adverse Drug Reactions**

<b>System Organ Class</b>	<b>Adverse drug reaction</b>
<b>Blood &amp; lymphatic disorders</b>	Hypercoagulability, Disseminated Intravascular Coagulation (DIC)
<b>Immune system disorders</b>	Anaphylactic reaction
<b>Vascular disorders</b>	Thrombosis (potentially including deep vein thrombosis, myocardial infarction and cerebral infarction)
<b>Respiratory, thoracic &amp; mediastinal disorders</b>	Pulmonary embolism
<b>Skin &amp; subcutaneous tissue disorders</b>	Rash
<b>General disorders &amp; administration site conditions</b>	Injection site reaction

Other reactions may include somnolence, phlebitis, vasodilation, dyspnoea, vomiting, pain, fever, feeling cold and peripheral oedema.

## **DOSAGE AND ADMINISTRATION**

It is recommended that specialist guidelines are referred to when administering Prothrombinex<sup>®</sup>-VF. It is recommended that prescribed dosages of Prothrombinex<sup>®</sup>-VF are expressed in International Units (written in full) of factor IX per kg body weight (bw).

### **Acquired prothrombin complex deficiency - warfarin reversal**

Clinical strategies concerning the management of warfarin reversal are based on guidelines developed by the ASTH. There is a close relationship between INR and risk of bleeding. Management options will depend on the INR level and whether bleeding is present. The choice of strategy should be based on the clinical indication for reversing the warfarin, and may include: stopping warfarin therapy for a few days, using vitamin K or replacing

coagulation factors with Prothrombinex<sup>®</sup>-VF and/or FFP. It should be noted that no randomised clinical trials have compared strategies in terms of clinical outcomes.

***Patients on warfarin with very high INR (>10), at high risk of bleeding***

In patients with very high INR (>10) and those with marked elevation of the INR (7–9) and who have additional risk factors for bleeding (liver disease, renal failure, thrombocytopenia, the concomitant use of anti-platelet or anti-inflammatory drugs), Prothrombinex<sup>®</sup>-VF can be administered with the aim of reducing the INR to a therapeutic range of 2–3. It is important that these patients are assessed for the cause of the elevation of the INR and their warfarin dose appropriately adjusted to prevent re-occurrence of the problem.

***Reversal prior to surgery when rapid correction of warfarin is required***

In patients requiring surgery, a target INR of <1.4 is recommended. Higher figures may be associated with bleeding which depending on the type of surgery may or may not be of concern. Refer to **Table 4**.

***Patients on warfarin who are actively bleeding***

In patients who are actively bleeding, warfarin should be fully reversed to an INR of 0.9–1.3, particularly in situations of clinically significant or life-threatening bleeding. In these patients the warfarin reversal should be sustained by the simultaneous injection of intravenous vitamin K<sub>1</sub>. In patients with minor active bleeding, partial correction of the INR (1.4–2) may be sufficient. Consultation with a haematologist is recommended. Refer to **Table 4**.

In order to determine an appropriate dose of Prothrombinex<sup>®</sup>-VF the dosing algorithm in **Table 4** should be used in conjunction with consideration of the setting in which INR reversal is required.

**Table 4: Dosing Algorithm**

On the basis of the results of the primary study, a dosing algorithm based on the initial INR and the target INR is provided to guide dosage.

<b>Initial INR</b>	<b>1.5–2.5</b>	<b>2.6–3.5</b>	<b>3.6–10.0</b>	<b>&gt;10.0</b>
	<b>Dose of Prothrombinex<sup>®</sup>-VF (IU/kg)</b>			
<b>Target INR</b>				
0.9–1.3	30	35	50	50 <sup>†</sup>
1.4–2.0	-	25	30	40

<sup>†</sup> May not fully correct INR, higher or repeat doses not recommended.

Whether for elevated INR with or without bleeding or invasive procedures, it is essential that clinical signs of bleeding and laboratory results (INR) are monitored.

### **Congenital deficiency of factors II, IX and X**

The dosage and duration of the substitution therapy depend on the severity of the coagulation disorder, on the location and extent of the haemorrhage and on the clinical condition of the patient.

The initial dose of a specific coagulation factor may be estimated from the recovery of that factor. In the absence of recovery data for Prothrombinex<sup>®</sup>-VF, it is recommended that the recovery data in the SPC be used:

- 1 IU of factor II per kg bw (IU/kg) raises the plasma factor II activity by 0.02 IU/mL,
- 1 IU/kg of factor VII raises the plasma factor VII activity by 0.01 IU/mL,
- 1 IU/kg of factor IX raises the plasma factor IX activity by 0.01 IU/mL and
- 1 IU/kg of factor X raises the plasma factor X activity by 0.017 IU/mL.

The calculation is as follows:

Dose (IU) = Body Weight (kg) x Desired Factor Rise (IU/mL) x the reciprocal of the estimated recovery

For example, for a factor X deficiency:

Dose (IU) = Body Weight (kg) x Desired Factor Rise (IU/mL) x 60

The exact loading and maintenance doses and dosing intervals should be based on the patient's clinical condition, response to therapy and plasma factor concentration. Maintenance doses should gradually reduce over the period of treatment (from the higher end of the range to the lower). Laboratory tests should be performed to ensure that the desired factor levels are achieved.

### **Congenital deficiency of factor IX (Haemophilia B)**

The recommendations for doses in **Table 5** are provided only as a general guideline for therapy. 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, however in some circumstances larger amounts than those calculated may be required (in terms of an initial loading dose).

**Table 5: Dosage Guidelines (Haemophilia B)**

Indication	Desired plasma concentration of factor IX (IU/dL)	Dose (IU/kg)	Frequency of dosing (per day)	Duration of treatment (days)
Minor haemorrhage	20 to 30	20 to 30	1	1 to 2
Moderate to severe haemorrhage	30 to 50	30 to 50	1 to 2	1 to 5
Minor surgery:				
loading dose	40 to 60	40 to 60	-	-
maintenance	20 to 50	15 to 40	1 to 2	7 to 10

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

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<sup>®</sup>-VF should be monitored carefully for signs of thrombosis or DIC.

## Reconstitution

1. Before reconstitution, allow the vials of Prothrombinex<sup>®</sup>-VF and Water for Injections to reach a temperature between 20°C and 30°C.
2. Remove the caps from the top of the Prothrombinex<sup>®</sup>-VF and Water for Injections vials.
3. Apply a suitable antiseptic to the exposed part of the rubber stoppers of both Prothrombinex<sup>®</sup>-VF and Water for Injections and allow to dry.
4. Open the outer package of the Mix2Vial<sup>™</sup> 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<sup>™</sup>, 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<sup>™</sup> together with its outer package and invert it. Push the blue plastic cannula of the Mix2Vial<sup>™</sup> 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<sup>™</sup>, being careful to leave the Mix2Vial<sup>™</sup> attached firmly to the Water for Injections vial. Ensure that only the package and not the Mix2Vial<sup>™</sup> is removed.

6. With the Prothrombinex<sup>®</sup>-VF vial held firmly on a level surface, invert the Water for Injections with the Mix2Vial<sup>™</sup> attached and push the transparent plastic cannula end of the Mix2Vial<sup>™</sup> firmly through the Prothrombinex<sup>®</sup>-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<sup>®</sup>-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 under **Administration**.
8. Once the contents of the Prothrombinex<sup>®</sup>-VF vial are completely dissolved, firmly hold both the transparent and blue parts of the Mix2Vial<sup>™</sup>. Unscrew the Mix2Vial<sup>™</sup> into two separate pieces, and discard the empty Water for Injections vial and the blue part of the Mix2Vial<sup>™</sup> in an appropriate waste container.

Note: The Mix2Vial<sup>™</sup> is intended to filter the contents of a single vial of Prothrombinex<sup>®</sup>-VF only. If multiple vials of Prothrombinex<sup>®</sup>-VF are to be administered, a separate Mix2Vial<sup>™</sup> must be used for each vial.

Do not refrigerate Prothrombinex<sup>®</sup>-VF once it has been reconstituted.

**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 a clot or gel forms, do not use the product but return it to the Australian Red Cross Blood Service.**

## **Administration**

1. With the Prothrombinex<sup>®</sup>-VF vial upright, attach a plastic disposable syringe to the Mix2Vial<sup>™</sup> (transparent plastic part). Invert the system and draw the reconstituted Prothrombinex<sup>®</sup>-VF into the syringe by pulling the plunger back slowly. One large syringe may be used to pool several vials of reconstituted Prothrombinex<sup>®</sup>-VF.
2. Once the Prothrombinex<sup>®</sup>-VF has been transferred into the syringe, firmly hold the barrel of the syringe (keeping the syringe plunger facing down) and detach the Mix2Vial<sup>™</sup> from the syringe. Discard the Mix2Vial<sup>™</sup> (transparent plastic part) and empty Prothrombinex<sup>®</sup>-VF vial in an appropriate waste container. Fit the syringe to a suitable injection needle to administer the reconstituted Prothrombinex<sup>®</sup>-VF. Do not use the Mix2Vial<sup>™</sup> for injection.

3. Give the dose slowly (approximately 3 mL per minute or as tolerated by the patient) by the intravenous route. When the contents of more than one vial are to be given, it may be convenient to pool the total amount prior to administration in a large syringe or sterile bag. This must be done aseptically.
4. To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. The solution must not be stored and infusion should be completed within three hours of reconstitution. Any unused portion remaining in the vial must be discarded appropriately.
5. The solution must not be added to or mixed with any other fluids to be given, including whole blood.

### **Spillage or breakages**

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 bleaches may be diluted appropriately to obtain this concentration.

### **OVERDOSAGE**

The use of high doses of PCCs has been associated with instances of myocardial infarction, DIC, venous thrombosis and pulmonary embolism. Therefore, in overdose, the risk of thromboembolic complications or DIC is enhanced.

### **PRESENTATION AND STORAGE CONDITIONS**

Prothrombinex<sup>®</sup>-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<sup>™</sup> filter transfer set.

Store at 2°C to 8°C (Refrigerate. Do not freeze). Prothrombinex<sup>®</sup>-VF can be stored below 25°C for a single period of 6 months. The product must not be returned to refrigeration after storage below 25°C. Protect from light. Do not use after the expiry date.

### **NAME AND ADDRESS OF THE SPONSOR**

CSL Behring (Australia) Pty Ltd  
ABN 48 160 734 761  
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Broadmeadows VIC 3047  
Australia

**DISTRIBUTED BY**

Australian Red Cross Blood Service

**POISON SCHEDULE OF THE MEDICINE**

Unscheduled

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF  
THERAPEUTIC GOODS (THE ARTG)**

30 January 2006

**DATE OF MOST RECENT AMENDMENT**

8 April 2016

Prothrombinex<sup>®</sup> is a registered trademark of CSL Limited

Mix2Vial<sup>™</sup> is a trademark of West Pharmaceutical Services, Inc. or a subsidiary thereof

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