

Prothrombinex[®]-VF

New Zealand

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 and low levels of factors V and VII. It is prepared from pooled human plasma donated by New Zealand'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[®]-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[®]-VF contains the ingredients listed in **Table 1**.

Table 1:

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

⁺ 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

Pharmacodynamic properties

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.

Pharmacokinetic properties

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 proportional to the dose administered.

Plasma half-life is indicated as follows:

Factor II	40 – 60	hours
Factor VII	3 – 6	hours
Factor IX	16 – 30	hours
Factor X	30 – 60	hours

Published PCC pharmacokinetic data in healthy volunteers demonstrates peak plasma levels of the administered coagulation factors occur within 5 minutes post-infusion. Data from a range of published studies in patients indicate International Normalised Ratio (INR) reductions occur within 10 - 15 minutes post-infusion of PCCs administered alone, and the effect on INR persists for approximately 12 - 24 hours.

CLINICAL TRIALS

There is limited clinical data available on Prothrombinex[®]-VF. However, clinical trials have been published using PCC's similar to Prothrombinex[®]-VF.

Acquired Deficiencies (Warfarin Reversal)

A single retrospective study was conducted among 105 patients on warfarin therapy, who were administered Prothrombinex[®]-VF. Prothrombinex[®]-VF was administered for bleeding in 51 patients (32 had major bleeds). Prothrombinex[®]-VF was given alone, or co-administered with fresh frozen plasma (FFP). All patients with bleeding achieved haemostasis following Prothrombinex[®]-VF treatment.

A prospective trial among six patients with warfarin-related intracranial haemorrhage (ICH) who received a PCC similar to Prothrombinex[®]-VF, reported a reduction in the mean INR

from 4.86 to 1.32 at 15 minutes following PCC administration. PCC achieved more rapid and effective reversal of the acquired coagulation defect than FFP ($p < 0.001$).

An additional retrospective study, using a PCC similar to Prothrombinex[®]-VF, showed a significantly shorter time to INR correction with PCC compared to FFP ($p < 0.001$) among warfarin-related ICH patients. Significantly less progression of ICH signs and symptoms was seen in PCC-treated patients compared to those given FFP ($p < 0.05$).

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[®]-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[®]-VF is also contraindicated in patients who have evidence of active thrombosis or disseminated intravascular coagulation (DIC).

PRECAUTIONS

Specialist advice is recommended in the management of patients receiving PCCs. Patients receiving a vitamin K antagonist (such as warfarin and phenindione) may have an underlying hypercoagulable state and infusion of human prothrombin complex may exacerbate this.

Prothrombinex[®]-VF should be used with caution in patients with a known allergy to constituents of the preparation. In case of anaphylactoid reaction, administration should be stopped immediately.

In patients with acquired deficiency of the vitamin K dependent coagulation factors (e.g. as induced by treatment with vitamin K antagonists), Prothrombinex[®]-VF should only be used when rapid correction of the prothrombin complex levels is necessary (see **DOSAGE AND ADMINISTRATION**). In other cases, reduction of the dose of the vitamin K antagonist or omission of the next dose and/or administration of vitamin K is usually sufficient.

Prothrombinex[®]-VF should not be used for prophylaxis or treatment of haemorrhage in patients with haemophilia B if a highly-purified factor IX preparation is available.

There is a risk of thrombosis, DIC or myocardial infarction when patients, with either congenital or acquired deficiency are treated with PCCs. This risk may be increased with repeated or high doses (especially at dose levels greater than 50 IU/kg of factor IX). Patients given human prothrombin complex should be observed closely for signs or symptoms of intravascular coagulation, thrombosis, embolism and myocardial infarction.

Because of the risk of thromboembolic complications, close monitoring should be exercised when administering PCC to patients with a history of coronary heart disease, to patients with liver disease, to peri- or post-operative patients or to patients at risk of thromboembolic events or DIC. In each of these situations, the potential benefit of treatment should be weighed against the risk of these complications.

Prothrombinex[®]-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.

Prothrombinex[®]-VF is not recommended for the management of patients with isolated factor V or factor VII deficiency, in view of the low levels present.

Prothrombinex[®]-VF contains heparin sodium which may cause heparin-induced thrombocytopenia (HIT). The possibility of HIT developing during treatment should be considered if high doses of Prothrombinex[®]-VF are required (see **CONTRAINDICATIONS**).

Replacement therapy may rarely lead to the formation of circulating antibodies known as ‘inhibitors’, inhibiting one or more of the human prothrombin complex factors. If such inhibitors occur, the condition will manifest itself as a poor clinical response.

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[®]-VF on fertility are unknown.

Use in pregnancy

The use of Prothrombinex[®]-VF during pregnancy has not been established in clinical studies.

Use in lactation

The effects of Prothrombinex[®]-VF on lactation are unknown.

Paediatric use

The use of Prothrombinex[®]-VF in the paediatric population has not been established in clinical studies.

Use in the elderly

The use of Prothrombinex[®]-VF in the elderly has not been established in clinical studies.

Carcinogenicity

The effects of Prothrombinex[®]-VF on carcinogenicity are unknown.

Genotoxicity

The effects of Prothrombinex[®]-VF on genotoxicity are unknown.

Interactions with other medicines

The interaction of Prothrombinex[®]-VF with other drugs has not been established in specific studies.

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

Effects on laboratory tests

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

ADVERSE EFFECTS

Allergic or anaphylactic-type reactions (such as angioedema, injection site reactions, chills, flushing, generalised urticaria, headache, pruritis, hypotension, lethargy, nausea and vomiting, restlessness, tachycardia, tingling, swelling, wheezing or shortness of breath) have been rarely observed in patients. In some cases, these reactions have progressed to severe anaphylaxis, particularly in patients with factor IX inhibitors. If any adverse event occurs while Prothrombinex[®]-VF is being administered, the rate of injection should be slowed or stopped to alleviate symptoms.

Development of antibodies to one or more of the prothrombin complex factors may occur in rare instances in recipients who have a congenital rather than acquired factor IX deficiency.

Although low, there is a potential risk of thromboembolic episodes (including myocardial infarction) following the administration of a PCC. 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.

The summary of adverse reactions in **Table 2** are based on clinical studies and on post-marketing experience of Prothrombinex[®]-VF and the previous generation product,

Prothrombinex[™]-HT. 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. There have been no spontaneously reported cases in the post-marketing period that changed the risk/benefit ratio of Prothrombinex[®]-VF.

Table 2:

System Organ Class	Adverse Drug Reaction
Blood & Lymphatic Disorders	Hypercoagulability, Disseminated Intravascular Coagulation (DIC)
Immune System Disorders	Anaphylactic reaction
Nervous System Disorders	Somnolence
Vascular Disorders	Thrombosis (including potential deep vein thrombosis, myocardial infarction and cerebral infarction), Phlebitis, Vasodilation
Respiratory, Thoracic & Mediastinal Disorders	Pulmonary Embolism, Dyspnoea
Gastrointestinal Disorders	Vomiting
Skin & Subcutaneous Tissue Disorders	Pruritis, Rash
General Disorders & Administration Site Conditions	Injection site reaction, Pain, Pyrexia, Feeling cold, Peripheral oedema

DOSAGE AND ADMINISTRATION

It is recommended that specialist guidelines are referred to when administering Prothrombinex[®]-VF. The recommended dosages of Prothrombinex[®]-VF are expressed in units (IU) of factor IX per kg body weight.

Acquired PCC Deficiency – Warfarin Reversal

Elevated INR with or without bleeding

Clinical strategies concerning the management of warfarin reversal are based on the Australasian Society of Thrombosis and Haemostasis' consensus guidelines. There is a close relationship between INR and risk of bleeding. The risk of bleeding increases noticeably once INR exceeds 4. Management options will depend on the INR level and whether bleeding is present. The choice of strategy should be based on clinical judgement, and may include: stopping warfarin therapy, treating with vitamin K and replacing coagulation factors with a PCC and/or FFP. It should be noted that no randomised clinical trials have compared strategies in terms of clinical outcomes.

Management of elevated INR in adult patients with or without bleeding is detailed in **Table 3**.

Table 3:

Clinical Setting	Action / Strategy
Any clinically significant bleeding where warfarin-induced coagulopathy is considered a contributing factor	Cease warfarin therapy, give 5-10 mg vitamin K ₁ intravenously, as well as Prothrombinex [®] -VF 25-50 IU/kg and FFP 150-300 mL. Assess patient continuously until INR < 5 and bleeding stops. [†] Prothrombinex [®] -VF can be used alone if FFP is unavailable; management should otherwise continue as described. [§]
INR > 9; bleeding absent, at high risk of bleeding [‡]	Cease warfarin therapy, give 1 mg vitamin K ₁ intravenously. Consider Prothrombinex [®] -VF 25-50 IU/kg and FFP 150-300 mL. Measure INR in 6-12 hours, resume warfarin therapy at a reduced dose once INR < 5.

Important points:

- Bleeding risk increases exponentially from INR 5 to 9, therefore INR ≥ 6 should be monitored closely.
- Vitamin K₁ effect on INR can be expected within 6-12 hours.

[†] In all situations carefully reassess the need for ongoing warfarin therapy.

[§] FFP (10–15 mL/kg) can be used alone if Prothrombinex[®]-VF is unavailable; management should otherwise continue as described.

[‡] Bleeding risk is high in patients with active GI disorders, receiving concomitant antiplatelet therapy, who have undergone major surgery in the two weeks prior, and those with a low platelet count.

Invasive procedures

The individual patient's risk of thromboembolism should be considered prior to any invasive procedure. PCC use is not recommended among high thromboembolic risk patients, such as those with prosthetic heart valves, or those who have suffered an acute thrombosis within the preceding three months (i.e. a recent pulmonary embolism or extensive venous thrombosis). Such patients should receive intravenous or subcutaneous bridging anticoagulation in the peri- and post-operative period. Prolonged immobility during surgery and afterwards also increases the risk of venous thromboembolism.

Patients at low thromboembolic risk such as those receiving warfarin because of atrial fibrillation, or in whom the index event requiring anticoagulation occurred more than three months ago, can be managed without bridging anticoagulation.

Management of oral anticoagulation during invasive procedures among patients with a low risk of thromboembolism is detailed in **Table 4**.

Table 4:

Time	Patients at relatively low risk of thromboembolism
Before surgery	<ul style="list-style-type: none"> • Withhold warfarin therapy 4–5 days before surgery. • <i>Night before surgery:</i> If INR > 2, give 1–5 mg vitamin K₁ intravenously. • <i>Day of surgery:</i> If INR ≤ 1.5 surgery can proceed. If INR > 1.5, defer surgery, or if surgery is urgent, give Prothrombinex[®]-VF (25–50 IU/kg) plus 150–300 mL FFP[§]
After surgery	<ul style="list-style-type: none"> • Start warfarin therapy on the day of surgery, at the previous maintenance dose. • Employ thromboprophylaxis as per usual practice.

[§] or give 10–15 mL/kg of FFP if Prothrombinex[®]-VF is not used

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. The guidelines do not specify that redosing with Prothrombinex[®]-VF is required. Refer to **PRECAUTIONS** and **ADVERSE EFFECTS**.

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 calculation of the required dosage of PCC is based on the empirical findings that 1 IU of factor IX per kg body weight raises the plasma factor IX activity by 0.8% of normal and that 1 IU of factor II or X per kg body weight raises the plasma factor II or X activity by 1.5% of normal.

The initial dose (e.g. factor IX) is determined using the following formula:

$$\text{Required units} = \text{body weight (in kg)} \times \text{desired factor IX rise (as \%)} \times 1.2$$

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:

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 bodyweight can be given twice weekly.

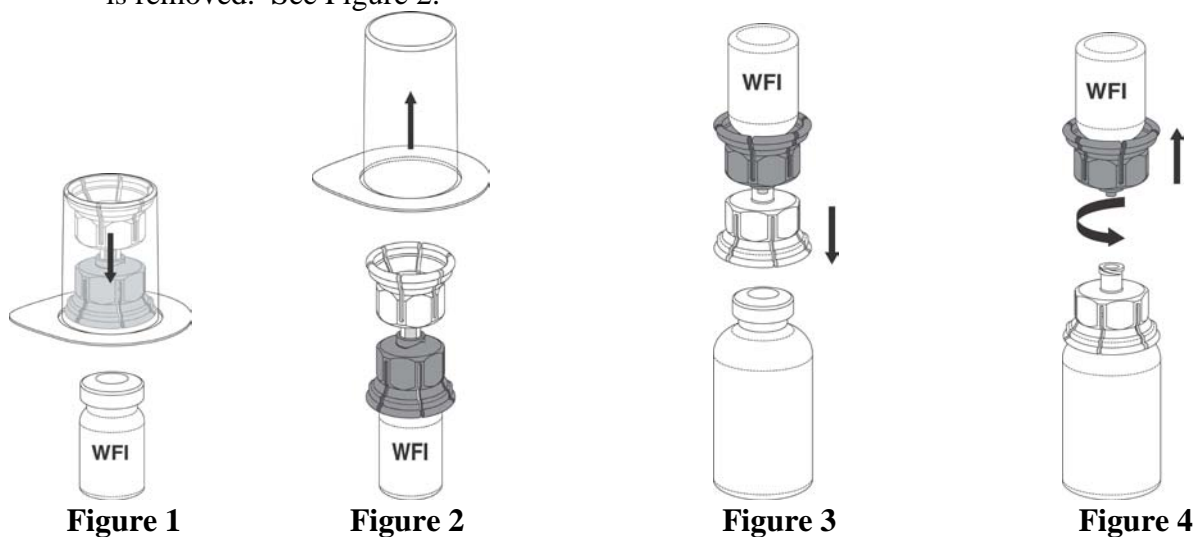
It is recommended that plasma factor IX concentrations be monitored during the treatment period.

Patients requiring more than 4 to 5 days of treatment with Prothrombinex[®]-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 caps from the top of the Prothrombinex[®]-VF and Water for Injections vials.
3. Apply a suitable antiseptic to the exposed part of the rubber stoppers of both 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 New Zealand 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. See Figure 1.
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. See Figure 2.



WFI = Water for Injections

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. See Figure 3. 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 New Zealand 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 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 (see Figure 4), and discard the empty Water for Injections vial and the blue part of the Mix2Vial[™] in an appropriate waste container.

Note: The Mix2Vial[™] is intended to filter the contents of a single vial of Prothrombinex[®]-VF only.

If multiple vials of Prothrombinex[®]-VF are to be administered, a separate Mix2Vial[™] must be used for each vial.

Do not refrigerate Prothrombinex[®]-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 New Zealand Blood Service.

Administration

1. With the Prothrombinex[®]-VF vial upright, attach a plastic disposable syringe to the Mix2Vial[™] (transparent 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[™] (transparent plastic part) and empty Prothrombinex[®]-VF vial in an appropriate waste container. Fit the syringe to a suitable injection needle to administer the reconstituted Prothrombinex[®]-VF. Do not use the Mix2Vial[™] 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

To avoid overdose, regular monitoring of coagulation status is indicated during treatment as the use of high doses of PCC (overdosage) has been associated with instances of myocardial infarction, DIC, thrombosis and pulmonary embolism.

PRESENTATION AND STORAGE CONDITIONS

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.

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

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

General Sale Medicine

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