AUSTRALIAN PRODUCT INFORMATION

Prothrombinex®-VF

(Human prothrombin complex)

Powder and diluent for solution for injection

1 NAME OF THE MEDICINE

Human prothrombin complex.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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. Prothrombinex®-VF is manufactured from human plasma collected by Australian Red Cross Lifeblood.

The concentrate is prepared by adsorption of coagulation factors from plasma onto an ion-exchange medium followed by selective elution.

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

Table 1: Prothrombinex®-VF Active Ingredient Composition

	500 IU vial
Active ingredients	
Factor IX	500 IU
Factor II	approx. 500 IU
Factor X	approx. 500 IU

For the full list of excipients, see section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Powder and diluent for solution for injection

Powder: white

Diluent (Water for Injections): clear, colourless

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC 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 section 4.4: Special warnings and precautions for use).

4.2 DOSE AND METHOD OF ADMINISTRATION

It is recommended that specialist guidelines are referred to when administering Prothrombinex®-VF. It is recommended that prescribed dosages of Prothrombinex®-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 Australasian Society of Thrombosis and Haemostasis (ASTH). There is a close relationship between the International Normalised Ratio (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®-VF and/or fresh frozen plasma (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®-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 2**.

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_1. 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 2**.

In order to determine an appropriate dose of Prothrombinex®-VF the dosing algorithm in **Table 2** should be used in conjunction with consideration of the setting in which INR reversal is required.

Table 2: 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.

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

† 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®-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 3** 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 3: 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 maintenance	 40 to 60 20 to 50	 40 to 60 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®-VF should be monitored carefully for signs of thrombosis or Disseminated Intravascular Coagulation (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 Australian Red Cross Lifeblood.** 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 Australian Red Cross Lifeblood.**

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, 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 Australian Red Cross Lifeblood.

Administration

1. With the reconstituted 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.

4.3 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).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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®-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®-VF.

Prothrombinex®-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®-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 Prothrombin Complex Concentrates (PCCs) such as Prothrombinex®-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®-VF administration should be stopped immediately and appropriate measures implemented.

Prothrombinex®-VF contains heparin sodium which may cause (HIT). The possibility of HIT developing during treatment should be considered if high doses of Prothrombinex®-VF are required (see section 4.3: Contraindications).

Inhibitors

The use of Prothrombinex®-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®-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®-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, 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. 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.

Use in the elderly

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

Paediatric use

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

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.

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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The interaction of Prothrombinex®-VF with other medicines 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effects of Prothrombinex®-VF on fertility are unknown.

Use in pregnancy

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

Use in lactation

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Allergic or anaphylactic-type reactions can occur in PCCs such as Prothrombinex®-VF (see section 4.4: Special warnings and precautions for use).

Although low, there is a potential risk of thromboembolic episodes (including myocardial infarction) following the administration of a PCC such as Prothrombinex®-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 section 4.4: Special warnings and precautions for use).

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 4** are based on post-marketing experience of Prothrombinex®-VF and the previous generation product, Prothrombinex®-HT.

Table 4: Adverse Drug Reactions

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

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

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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.

Clinical trials

Acquired deficiencies

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

In trials of PCCs similar to Prothrombinex®-VF, the onset of effect on the 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®-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®-VF was administered alone (without concomitant; 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®-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 section 4.2: Dose and method of administration). This is considered the primary study supporting the use of Prothrombinex®-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®-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®-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®-VF dose. The average dose of Prothrombinex®-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®-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®-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 intra-cranial haemorrhage, however in other patients who received Prothrombinex®-VF for bleeding, no ongoing bleeding was observed. Similarly, no excess or ongoing bleeding was observed in patients receiving Prothrombinex®-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®-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®-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 ASTH (see section 4.2: Dose and method of 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®-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®-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 Activated Partial Thromboplastin Time (APTT) contributing to the bleeding. Haemostasis was achieved in all cases, however the contribution of Prothrombinex®-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 section 4.2: Dose and method of 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.

5.2 PHARMACOKINETIC PROPERTIES

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 5** lists PCC coagulation factor elimination half-lives as median and (inter-quartile range).

Table 5: Coagulation Factor Elimination Half-Lives

	Factor II	Factor VII	Factor IX	Factor X
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®-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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Plasma proteins (human)

Antithrombin III (human)

Heparin sodium (porcine)

Sodium[+]

Phosphate[+]

Citrate[+]

Chloride[+]

[+] *Present as sodium citrate, sodium phosphate and sodium chloride*

6.2 INCOMPATIBILITIES

The reconstituted solution must not be added to or mixed with any other fluids to be given, including whole blood.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the carton packaging.

Reconstituted product

The product does not contain an antimicrobial preservative. It must, therefore, be used immediately after reconstitution.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C (Refrigerate. Do not freeze). Prothrombinex®-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.

Reconstituted product

Do not refrigerate Prothrombinex®-VF once it has been reconstituted.

6.5 NATURE AND CONTENTS OF CONTAINER

Each Prothrombinex®-VF single pack contains:

- One glass vial containing 500 IU of factor IX, approximately 500 IU of factor II and approximately 500 IU of factor X, with a rubber stopper closed with an aluminium seal and plastic flip-top cap
- One glass vial of 20 mL Water for Injections with a rubber stopper closed with an aluminium seal and plastic flip-top cap
- One Mix2Vial™ filter transfer set.

Prothrombinex®-VF is packaged in latex free materials.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Not applicable

CAS number

37224-63-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

Unscheduled

8 SPONSOR

CSL Behring (Australia) Pty Ltd
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Distributor: Australian Red Cross Lifeblood

9 DATE OF FIRST APPROVAL

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10 DATE OF REVISION

23 March 2020

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SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All sections	PI reformatted in line with TGA requirement
All sections	Australian Red Cross name change
3.0	Pharmaceutical form information added
4.7	Information on effects on ability to drive and use machines added
6.4	Storage conditions for reconstituted solution added
6.5	Nature and contents of container added
6.7	CAS number added
10	Trademark statement added