1 PRODUCT NAME

Prothrombinex®-VF powder and diluent for solution for injection

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. 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.

Prothrombinex®-VF contains the following IU of the human coagulation factors in **Table 1.**

Table 1: Active ingredient composition

Active ingredient	Content after reconstitution (IU/mL)	Content per vial (IU)
Human coagulation factor II	Approx. 25	Approx. 500
Human coagulation factor IX	25	500
Human coagulation factor X	Approx. 25	Approx. 500

The content of human plasma proteins (including low levels of factor V and VII) is no more than 500 mg per vial.

Excipients with known effect

Prothrombinex®-VF contains 112 mg (4.9 mmol) sodium and 192 IU heparin per vial.

For the full list of excipients, see section 6.1.

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).

4.2 Dose and method of administration

Dose

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 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 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.

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 reversal is required.

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.

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 life threatening bleeding. In these patients the warfarin reversal should be sustained by the simultaneous injection of vitamin K_1 intravenously. In patients with mild, non-life threatening bleeding, partial correction of the INR (1.4–2) may be sufficient. Consultation with a haematologist is recommended.

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 within the therapeutic range (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.

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.

Table 2: Dosing Algorithm

Initial INR	1.5–2.5	2.6–3.5	3.6–10.0	>10.0
	Dose of Prothrombinex®-VF (IU/kg)			
Target INR				
Complete reversal 0.9–1.3	30	35	50	50†
Partial reversal 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 body weight (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).

Paediatric population

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

Method of administration

For instructions on reconstitution of the medicine before administration, see section 6.6.

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.

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).

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 virus transmission including dry heat treatment (80°C for 72 hours) for virus 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.

Paediatric population

The 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.

Use in the elderly

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

Effect on laboratory tests

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

Other

Prothrombinex®-VF contains 112 mg sodium per vial, equivalent to 5.6% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicines and other forms of interaction

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.

4.6 Fertility, pregnancy and lactation

Fertility

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

Pregnancy and lactation

The use of Prothrombinex®-VF during pregnancy or 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 Undesirable effects

Summary of the safety profile

Allergic or anaphylactic-type reactions can occur in PCCs such as Prothrombinex®-VF (see section 4.4).

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).

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.

Tabulated summary of adverse reactions

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.

Paediatric population

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihaemorrhagics, blood coagulation factors.

ATC code: B02BD01

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 efficacy and safety

Acquired deficiencies

The acquired deficiencies of prothrombin complex in which Prothrombinex®-VF has been studied include warfarin reversal and patients with bleeding who are coagulopathic.

In trials of PCCs similar to Prothrombinex®-VF, the onset of effect on 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 study of 50 adult patients, Prothrombinex®-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 to INR <1.4 or partial reversal 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. 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). This is considered the primary study supporting the use of Prothrombinex®-VF in warfarin reversal.

In a separate study, the use of a single infusion of Prothrombinex®-VF with no supplemental FFP was reported in 50 patients on warfarin who required urgent/semi-urgent surgery. All patients

achieved complete reversal of their anticoagulation (INR 1.0–1.3) within 30 minutes of the infusion. The majority of these patients were able to be returned to a stable anticoagulation state within 2 days.

Another 54 patients who required warfarin reversal prior to a surgical procedure were included in a large prospective study conducted in New Zealand. All 173 patients in this study received Prothrombinex®-VF, with supplemental FFP allowed at the discretion of the treating physician. The majority of patients (79.1%) achieved a post infusion INR <1.5 with no significant difference between the pre- or post-treatment INR between groups who did and did not receive FFP (42% of the patients received FFP). The average dose of Prothrombinex®-VF was reported as 21 IU/kg (range 6–45).

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 both studies bleeding was controlled. One patient in the primary study died as a result of bleeding from a ruptured aortic aneurysm. Although the New Zealand study did not include re-imaging of patients with intra-cranial haemorrhage, no ongoing bleeding after treatment was reported by the clinicians.

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 the subject of published audits. Doses <25 IU/kg have been reported to be effective. However, the best evidence is based on an algorithm developed in the primary study, which has been adapted by ASTH (see section 4.2).

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. The mean dose of Prothrombinex®-VF was 16.8 IU/kg with 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). 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 seven had prolonged APTT contributing to the bleeding. The mean Prothrombinex®-VF dose was 23.0 IU/kg (range 18.6–28.4 IU/kg) and the mean INR was 1.3 both before and after treatment. 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).

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

Absorption

Intravenous administration means that the preparation is available immediately; bioavailability is 100%.

Prothrombinex®-VF contains human coagulation factors II, IX and X and low levels of factors V and VII. 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.

Distribution and metabolism

Prothrombin complex concentrates (PCCs) are distributed and metabolised in the same way as endogenous coagulation factors.

Elimination

PCC coagulation factor elimination half-lives as median and (inter-quartile range) are presented in **Table 5.**

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

Carcinogenicity

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

Genotoxicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Antithrombin III
Heparin sodium (porcine)
Sodium[+]
Phosphate[+]
Citrate[+]
Chloride[+]
[+] *Present as sodium citrate, sodium phosphate and sodium chloride*

Diluent

Water for Injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

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

6.3 Shelf life

24 months

Reconstituted product

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

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

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.

For storage conditions after reconstitution of the medicine, see section 6.3.

6.5 Nature and contents of container

Each Prothrombinex®-VF single pack contains:

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

6.6 Special precautions for disposal and other handling

Reconstitution

1. Before reconstitution, allow the vials of Prothrombinex®-VF and Water for Injections (WFI) to reach a temperature between 20°C and 30°C.
2. Remove the caps from the top of the Prothrombinex®-VF and WFI vials.
3. Apply a suitable antiseptic to the exposed part of the rubber stoppers of both Prothrombinex®-VF and WFI vials 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 WFI vial 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 WFI vial, carefully remove the outer package from the Mix2Vial™, being careful to leave the Mix2Vial™ attached firmly to the WFI 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 WFI vial with the Mix2Vial™ attached and push the transparent plastic cannula end of the Mix2Vial™ firmly through the Prothrombinex®-VF stopper. The water will be drawn into the vial by the vacuum within. **In the unlikely event that the vial does not contain a vacuum, do not use the product, but return it to the New Zealand Blood Service.**
7. With the WFI and Prothrombinex®-VF vials 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.
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 WFI 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.

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

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

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.

7 MEDICINE SCHEDULE

General Sale Medicine

8 SPONSOR

CSL Behring (NZ) Limited
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9 DATE OF FIRST APPROVAL

23 August 2012

10 DATE OF REVISION OF THE TEXT

22 November 2018

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Data sheet reformatted to the SPC format
2	Information about excipients with known effect added
3	Visual description of the product appearance added
4.7	Information about effects on ability to drive and use machines added
6.2	Information about incompatibilities added
6.5	Information about nature of container added
8	Sponsor's address and phone numbers updated

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