

**Answers to
Frequently Asked Questions (FAQs)
for
PROTHROMBINEX[®]- VF**

**For Use by the AUSTRALIAN RED CROSS BLOOD SERVICE
Updated August 2009**

**CSL Bioplasma does not recommend the use of any product other than as described in the relevant approved Product Information.
Please review the approved Product Information before prescribing.**

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CHARACTERISTICS

What is PROTHROMBINEX®-VF?

PROTHROMBINEX-VF is a sterile lyophilised (freeze-dried) prothrombin complex concentrate (PCC) containing purified human coagulation factors II, IX, X and low levels of factor VII.¹

PROTHROMBINEX-VF distributed in Australia, is prepared from plasma collected from voluntary and non remunerated Australian donors.¹

When reconstituted as recommended, each vial of PROTHROMBINEX-VF contains 500 IU of factor IX, approximately 500 IU of factor II, 500 IU of factor X, 25 IU of antithrombin III, 192 IU of heparin sodium and ≤ 500mg of plasma proteins (which includes low levels of factor V & VII.) Other ingredients include sodium citrate, sodium phosphate and sodium chloride.¹

PROTHROMBINEX-VF is manufactured using two dedicated pathogen inactivation/reduction steps which contribute to the clearance of viruses; dry heat treatment at 80° C for 72 hours, and nanofiltration. The nanofiltration step (size-based removal) is complementary to the dry heat treatment step. This increases the spectrum of pathogens that can potentially be eliminated and hence further enhances the safety profile of PROTHROMBINEX-VF.

PROTHROMBINEX-VF was launched in 2006, replacing PROTHROMBINEX-HT which was launched in 1993. The properties of PROTHROMBINEX-VF do not differ from PROTHROMBINEX-HT. No change has been made to the indications, precautions, adverse events, dosage, route of administration or storage conditions.

Reference

1. PROTHROMBINEX-VF Approved Product Information. Date of most recent amendment: 11 February 2009

PHARMACOLOGY

What is the half-life of the vitamin-K dependant coagulation factors?

The plasma half-life of factors II, VII, IX and X are as follows:

- factor II - 46 to 60 hours^{1,2}
- factor VII – 4 to 6 hours^{1,2}
- factor IX - 14 to 68 hours¹, and
- factor X - 24 to 41 hours¹.

References

1. PROTHROMBINEX-VF Approved Product Information. Date of most recent amendment: 11 February 2009
2. Baker R, Coughlin P, Gallus A, Harper P, Salem H, Wood E. Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis. MJA 2004; 181: 492-497.

CLINICAL EFFICACY

What are the indications for PROTHROMBINEX®-VF?

PROTHROMBINEX–VF is indicated for the 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. PROTHROMBINEX–VF is also indicated for the treatment and prophylaxis of bleeding in patients with single or multiple congenital deficiencies of factor IX, II or X when purified specific coagulation factor product is not available.

Reference

1. PROTHROMBINEX-VF Approved Product Information. Date of most recent amendment: 11 February 2009

What are the contraindications for PROTHROMBINEX®-VF?

PROTHROMBINEX–VF is contraindicated in patients with 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.

Reference

1. PROTHROMBINEX-VF Approved Product Information. Date of most recent amendment: 11 February 2009

Why is PROTHROMBINEX®-VF formulated with antithrombin III and heparin?

Each vial of PROTHROMBINEX-VF contains 25 IU of antithrombin III (ATIII) and 192 IU of heparin sodium.¹

Heparin and ATIII are anti-thrombotic factors that were added to PROTHROMBINEX-VF and other Prothrombin Complex Concentrate (PCCs) formulations to reduce their thrombogenic potential.

Various hypotheses to account for thrombotic events associated with the use of PCCs include:

- activation of a proportion of clotting factors during the manufacturing process
- loss of the coagulation inhibitors protein C and S during production, or
- *in vivo* overloading with factors II and X, which have the longest half life of the administered factors.²

Interestingly, infusion of high-purity factor IX products in haemophilia B did not lead to any significant activation of the coagulation cascade, confirming that a component other than factor IX is responsible for the thrombogenicity of PCCs. Evidence suggests an excess of factor II, rather than the content of activated factors VII, IX or X, may be primarily responsible for such complications.³

The risk of thrombosis following the use of PCCs in warfarin reversal will always remain due to the mode of action of PCCs in replacing diminished levels of clotting factors II, VII, IX and X.

Additionally, warfarin is typically prescribed for patients already at risk of developing thromboembolism due to their underlying medical condition. However, PROTHROMBINEX-VF when used appropriately according to the Warfarin Reversal Consensus Guidelines⁴, can minimise any increase in this risk.

References

1. PROTHROMBINEX-VF Approved Product Information. Date of most recent amendment: 11 February 2009
2. Bagot C et al. *Thromb Haemost*, 2007; 98: 1141-1142
3. Key N and Negrier C. *The Lancet*, 2007;370:439-448
4. Baker R, Coughlin P, Gallus A, Harper P, Salem H, Wood E. Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis. *MJA* 2004; 181: 492-497.

Does the addition of antithrombin III have any effect on warfarin reversal?

The levels of antithrombin III in PROTHROMBINEX-VF are too low to have any counter effect on the reversal of warfarin, and clinical experience with PROTHROMBINEX-VF confirms its ability to successfully and immediately reverse warfarin anticoagulation.^{1,2}

References

1. Baker R, Coughlin P, Gallus A, Harper P, Salem H, Wood E. Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis. *MJA* 2004; 181: 492-497.
2. Crawford JH, Augustson BM. PROTHROMBINEX use for the reversal of Warfarin: Is fresh frozen plasma needed? *MJA* 2006; 184; 365-366.

CLINICAL SAFETY

What is the incidence of thrombotic adverse events with PROTHROMBINEX®-VF?

Although low, there is a potential risk of thrombotic adverse events following the administration of prothrombin complex concentrates (PCCs), such as PROTHROMBINEX-VF. Since 1993, thrombotic events have been reported rarely during PROTHROMBINEX-HT/VF post-marketing safety surveillance*. ¹

The risk of thrombosis following administration of PCCs for warfarin reversal will always remain due to the replacement of diminished levels of clotting factors II, IX and X. Additionally, thrombotic risk may be increased with repeated or high PCC 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.¹ Warfarin is also typically prescribed for patients already at risk of developing thromboembolism due to their underlying medical condition. PROTHROMBINEX-VF when used appropriately according to the approved Product Information¹ and Warfarin Reversal Consensus Guidelines² can minimise any increase in this risk.

In the 1970s and 1980s, large doses of PROTHROMBINEX were used in some patients with haemophilia B to correct low levels of Factor IX. Such use can lead to supranormal levels of Factor II and X. During this time there was international concern about reports of thromboembolism associated with PCC use.³ The PROTHROMBINEX-VF Product Information reflects and states that, based on post-marketing reporting of adverse events* there have been rare reports of thrombosis (potentially including deep-vein thrombosis, myocardial infarction and cerebral infarction), pulmonary embolism, and

disseminated intravascular coagulation (DIC) following the use of PCCs associated with surgery.¹

Various hypotheses to account for thrombotic events associated with PCC use include:

- activation of a proportion of clotting factors during the manufacturing process
- loss of the coagulation inhibitors protein C and S during production, or
- *in vivo* overloading with factors II and X, which have the longest half life of the administered factors⁴.

Interestingly, infusion of high-purity factor IX products in people with haemophilia B did not lead to any significant activation of the coagulation system, confirming that a component other than factor IX is responsible for the thrombogenicity of PCCs. Evidence suggests an excess of factor II, rather than the content of activated factors VII, IX or X, may be primarily responsible for such complications.⁵

Today, purified mono-therapy (Factor IX) is mainly used for the prophylaxis and treatment of patients with haemophilia B and more moderate doses of PCCs are used to treat acquired vitamin K deficiencies such as that occur in warfarinisation. In addition, many manufacturers, including CSL Bioplasma, add small quantities of heparin or similar anti-thrombotic factors (eg ATIII) to reduce the thrombogenic potential of their PCC product.

Such changes have helped to greatly reduce the occurrence of thromboembolism and DIC in patients with haemophilia B and in patients requiring rapid reversal of warfarin. In 2001, Evans *et al* reported zero thrombotic events in 59 patients from three studies where such improved PCCs were used to reverse warfarin.⁶

The current body of medical evidence suggests there is a low risk of thrombotic events associated with the use of PCCs for acute warfarin reversal,^{7,8} which is reduced further to a very low thrombotic risk when a single dose of 30IU/kg or less is used.⁵

Any adverse events associated with the use of PROTHROMBINEX-VF should always be reported to CSL Bioplasma via its Medical Affairs Department ph: 1800 067 140. Such reporting assists CSL Bioplasma to effectively monitor the safety profile of our products.

**Because post-marketing reporting of adverse reactions is voluntary, and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.*

References

1. PROTHROMBINEX-VF Approved Product Information. Date of most recent amendment: 11 February 2009
2. Baker R, Coughlin P, Gallus A, Harper P, Salem H, Wood E. Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis. MJA 2004; 181: 492-497.
3. Scharrer I. The need for highly purified products to treat haemophilia B. Acta Haematol, 1995; 94 (suppl 1): 2-7
4. Bagot C et al. Thromb Haemost, 2007; 98: 1141-1142
5. Key N and Negrier C. The Lancet, 2007;370:439-448
6. Evans G, Luddington R, Baglin T. Beriplex P/N reverses severe warfarin-induced over anticoagulation immediately and completely in patients presenting with major bleeding. Br J Haem 2001; 115:998-1001. (Reference ID: 2348)
7. Makris M. Thrombosis Research, 2005;115:451-453

Warfarin Reversal

What are the benefits of PROTHROMBINEX®-VF in warfarin reversal?

PROTHROMBINEX-VF immediately replaces the vitamin K dependant factors, namely II, IX, and X.^{1,2} Other benefits include:

- the administration of known concentrations of coagulation factors, resulting in a predictable action
- quick infusion times resulting in near immediate action. This is important where emergency warfarin reversal is necessary
- INR reversal within 15 minutes^{1,3}
- a reduced need for large volumes of fresh frozen plasma (FFP) which can cause circulatory overload and possibly result in associated complications
- the product has two complementary and dedicated pathogen reduction steps, which contribute to the clearance of viruses and reduce the risk pathogen transmission
- no need to thaw product prior to administration (as is the case with FFP)
- no need for ABO blood matching prior to administration (as is the case with FFP).

The 2004 *Warfarin Reversal: Consensus Guidelines*, developed by the Australasian Society of Thrombosis & Haemostasis² (ASTH), state that FFP requires ABO group compatibility testing, and the most common adverse events include allergic reactions and volume overload. There is also the potential for transmission of infections, transfusion related acute lung injury (TRALI) and other transfusion reactions.

For further information regarding PROTHROMBINEX-VF please refer to the approved Product Information.¹ For further information comparing the characteristics of PROTHROMBINEX-VF with FFP please refer to table 5 of the above mentioned Warfarin Reversal Guidelines.²

References

1. PROTHROMBINEX-VF Approved Product Information. Date of most recent amendment: 11 February 2009
2. Baker R, Coughlin P, Gallus A, Harper P, Salem H, Wood E. Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis. MJA 2004; 181: 492-497.
3. Freeman WD, Aguilar MI. Management of warfarin related intracranial hemorrhage. Expert Rev Neurotherapeutics. 2008; 8(2); 271-290.

Warfarin Reversal - Dosage and Administration

What dose of PROTHROMBINEX®-VF is required to normalise an elevated International Normalised Ratio (INR) in an adult warfarinised patient with or without bleeding?

The PROTHROMBINEX-VF approved Product Information¹ and the 2004 Warfarin Reversal: Consensus Guidelines developed by the ASTH², provide recommendations regarding the dose of PROTHROMBINEX-VF for warfarin reversal. These recommendations include:

- **In a clinical setting when INR > 9.0 and bleeding is absent, but the patient has a high risk of bleeding[†]**, warfarin therapy should be ceased. PROTHROMBINEX-VF (25-50 IU/kg)* and FFP (150-300 mL) should be considered and 1.0 mg vitamin K should be given intravenously. Measure the INR in 6–12 hours; and resume warfarin therapy at a reduced dose once INR<5.0.
- **In a clinical setting when any clinically significant bleeding exists, and where warfarin induced coagulopathy is considered a contributing factor**, warfarin therapy should be ceased. PROTHROMBINEX-VF (25-50 IU/kg)* and FFP (150-300 mL) should be given plus 5-10 mg vitamin K intravenously. Assess the patient continuously until INR<5.0 and bleeding stops. Other options include PROTHROMBINEX-VF alone or FFP alone if either of these is unavailable.

The combination of PROTHROMBINEX-VF and FFP covers the period before vitamin K has reached its full effect. Vitamin K is then essential for sustaining the reversal achieved by PROTHROMBINEX-VF and FFP.

[†] **Examples of patients in whom an elevated bleeding risk would be expected include those with active gastrointestinal disorders such as peptic ulcer or inflammatory bowel disease, patients on antiplatelet therapy, patients having had a major surgical procedure in the preceding 2 weeks, or those with a low platelet count. PROTHROMBINEX-VF is not recommended for use in patients with an INR >9, but with a low bleeding risk. Additionally, PROTHROMBINEX-VF should not be used in a clinical setting when the INR is ≤9.0 and bleeding is absent. Refer to the 2004 Warfarin Reversal: Consensus Guidelines developed by the ASTH² for management of such patients.**

* The dose of PROTHROMBINEX-VF (25-50 IU/kg) equates to approximately ½ - 1 vial (500 IU/20mL vial) PROTHROMBINEX-VF per 10 kg patient weight, or 3.5 to 7 vials for a 70kg patient.

Additional information: The Warfarin Reversal Pocket Guide and Poster, which summarise these guidelines, are available from CSL Bioplasma. Phone (toll free): 1800 067 140, Email: medicalaffairs_bioplasma@csl.com.au.

References

1. PROTHROMBINEX-VF Approved Product Information. Date of most recent amendment: 11 February 2009
2. Baker R, Coughlin P, Gallus A, Harper P, Salem H, Wood E. Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis. MJA 2004; 181: 492-497.

What clotting factor does the PROTHROMBINEX®-VF dose refer to?

The 2004 Warfarin Reversal: Consensus Guidelines developed by the ASTH¹ recommend PROTHROMBINEX-VF doses of 25-50IU/kg. This is a dose of 25-50IU/kg of factor IX per kg.

References

1. Baker R, Coughlin P, Gallus A, Harper P, Salem H, Wood E. Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis. MJA 2004; 181: 492-497.
2. PROTHROMBINEX-VF Approved Product Information. Date of most recent amendment: 11 February 2009

What is the onset of action of PROTHROMBINEX®-VF?

Specific pharmacokinetic data is not available for PROTHROMBINEX-VF. However, published pharmacokinetic data with another Prothrombin Complex Concentrate (PCC) demonstrates peak plasma levels of the administered coagulation factors occurs 5 minutes post-infusion.¹ Data from a range of published studies indicate INR reductions occur 10 - 15 minutes after PCC administration,^{2,3} and the duration of INR effect is approximately 12 - 24 hours.³

References

1. Ostermann H et al Thromb Haemost. 2007 Oct;98(4):790-7.
2. PROTHROMBINEX-VF Approved Product Information. Date of most recent amendment: 11 February 2009
3. Leissing C et al. Am. J. Hematol, 2008; 83:137-143

What is the duration of action of PROTHROMBINEX®-VF?

Specific pharmacokinetic data is not available for PROTHROMBINEX-VF. However results from a study¹ with another PCC demonstrate that PCC co-administered with vitamin K maintains lowered INR values for 12 to 24 h post-administration.

The 2004 Warfarin Reversal: Consensus Guidelines developed by the ASTH² also state that PCCs and fresh frozen plasma work to immediately reverse clinically significant bleeding, and this covers the period until vitamin K achieves its full effect at 12 to 24 hours after administration.^{2,3}

References

1. Yasaka M, et al. Correction of INR by prothrombin complex concentrate and vitamin K in patients with warfarin related hemorrhagic complication. Thromb Res, 2002 Oct 1;108(1):25-30.
2. Baker R, Coughlin P, Gallus A, Harper P, Salem H, Wood E. Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis. MJA 2004; 181: 492-497.
3. Schulman and Bijsterveld. Anticoagulants and their reversal. Transfusion Med Reviews, 2007; 21/1: 37-48

What dose of PROTHROMBINEX®-VF is required for warfarin reversal during invasive procedures? (according to risk of thromboembolism)

Patients at low Risk of thromboembolism

The PROTHROMBINEX-VF approved Product Information¹ and the 2004 Warfarin Reversal: Consensus Guidelines developed by the ASTH², provide recommendations on PROTHROMBINEX-VF doses for warfarin reversal.

These recommendations suggest PROTHROMBINEX-VF only be used prior to surgery among patients at relatively **low** risk of thromboembolism. For such patients,

- withhold warfarin 4-5 days prior to surgery
- if the patient's INR is >2 the *night before surgery*, give 1-5mg IV vitamin K
- on the *day of surgery* if the INR is ≤1.5, surgery can proceed. However if the patient's INR is > 1.5 and surgery is urgent use either:
 - PROTHROMBINEX-VF (25-50 IU/kg)* and FFP (150-300 mL), or
 - FFP alone (10-15 mL/kg which is approximately 700 – 1,050 mL FFP/70 kg adult).
- After surgery, recommence warfarin the day of surgery at the previous maintenance dose.
- employ thromboprophylaxis as per usual practice.

The Guidelines² do not specify that repeat INR testing is required after administration of either PROTHROMBINEX-VF or FFP (also see 'What is the onset of action of PROTHROMBINEX®-VF?')

* The dose of PROTHROMBINEX-VF (25-50 IU/kg) equates to approximately ½ - 1 vial (500 IU/20mL vial) PROTHROMBINEX-VF per 10 kg patient weight, or 3.5 to 7 vials for a 70kg patient.

High Risk Patients

The Warfarin Reversal: Consensus Guidelines¹, do not recommend use of PROTHROMBINEX-VF doses for warfarin reversal among risk high patients (for further information see 'What is a high thrombotic risk patient in the setting of warfarin reversal?')

The Guidelines² recommend:

- withholding warfarin 4-5 days prior to surgery
- commencing unfractionated heparin (IV) or low molecular weight heparin (LMWH) (SC) 2-3 days prior to surgery
- if using LMWH, the last dose should be given at least 24 hours before surgery. Or, if using unfractionated heparin, discontinue use 4-6 hours before surgery.
- recommencing warfarin ASAP, and starting heparin or LMWH 12-24 hours post-operatively. If using LMWH, give a thromboprophylactic dose. If using unfractionated heparin, aim to prolong APTT 1.5x.

- anticoagulating the patient fully 72 hours postoperatively, as long as there is no evidence of bleeding
- ceasing heparin or LMWH therapy 48 hours after the target INR is reached.

Additional information: Please refer to Table 6 of the 2004 Warfarin Reversal: Consensus Guidelines.¹ *The Warfarin Reversal Pocket Guide and Poster, which summarises these guidelines, are available from CSL Bioplasma. Phone (toll free): 1800 067 140, Email: medicalaffairs_bioplasma@csl.com.au.*

References

1. PROTHROMBINEX-VF Approved Product Information. Date of most recent amendment: 11 February 2009
2. Baker R, Coughlin P, Gallus A, Harper P, Salem H, Wood E. Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis. MJA 2004; 181: 492-497.

Should warfarin therapy be halted prior to all invasive procedures?

No. The 2004 Warfarin Reversal: Consensus Guidelines developed by the ASTH¹, state that some procedures entail a low risk of bleeding and therefore do not require interruption of warfarin therapy. Examples include: simple dental procedures, periodontal therapy, and minor dermatological procedures where pressure can be applied if needed.

References

1. Baker R, Coughlin P, Gallus A, Harper P, Salem H, Wood E. Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis. MJA 2004; 181: 492-497.

What is a high thrombotic risk patient in the setting of warfarin reversal?

The 2004 Warfarin Reversal: Consensus Guidelines developed by the ASTH¹, provide recommendations on PROTHROMBINEX-VF doses for warfarin reversal. Patients on vitamin K antagonist (VKA) therapy who are at relatively high risk of thromboembolism are those that have:

- prosthetic heart valves ¹
- suffered acute thrombosis within preceding 3 months ¹
- extensive venous thrombosis ¹

The Guidelines¹ recommend that expert advice on management should be sought whenever there is bleeding in patients taking warfarin and who have a high risk of a disabling thromboembolic event in the absence of anti-coagulation therapy.

Also, in the clinical situation where surgery is urgent and the patient's INR is >1.5, the Guidelines¹ recommend, for patients at relatively **high** risk of thromboembolism, a management plan that involves the use of unfractionated heparin or low molecular weight heparin. Note such bridging anticoagulation is not required for patients taking an anticoagulant for atrial fibrillation, or in whom the index event requiring anticoagulation occurred more than 3 months ago; such patients are considered at relatively low risk of thromboembolism.

The Warfarin Reversal Pocket Guide and Poster, which summarise these guidelines, are available from CSL Bioplasma. Phone (toll free): 1800 067 140, Email: medicalaffairs_bioplasma@csl.com.au.

References

1. Baker R, Coughlin P, Gallus A, Harper P, Salem H, Wood E. Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis. MJA 2004; 181: 492-497.

What are the risk factors for bleeding while on warfarin therapy?

The most common complication of vitamin K antagonist therapy such as warfarin, is bleeding. Bleeding risk has a close relationship with INR.

- bleeding risk increases exponentially from INR 5 to 9 ^{1,2,3}
- INR ≥ 6 should be monitored closely ¹

However, 50% of bleeding episodes still occur with an INR of < 4 ^{1,4} therefore the INR is a guide of bleeding risk, but not an absolute indicator.

Observational studies also suggest that the risk of bleeding is increased in the presence of the following factors:

- age > 65 yrs ^{5,6,7}
- history of past bleeding ^{5,6,7}
- specific co-morbid conditions including: ^{5,6,7}
 - cardiac (uncontrolled hypertension)
 - gastrointestinal disorders (peptic ulcer, inflammatory bowel disease etc)
 - haematologic (thrombocytopenia etc)
 - neurologic (stroke etc)
 - renal
 - trauma (recent trauma or surgery within last 2 weeks etc)*
 - alcohol
 - medications (concomitant anti-platelet therapy, NSAIDs, natural therapies etc)*

Note: Risk factors can be additive. Patients who have two or three risk factors have a much higher incidence of warfarin-associated bleeding than those with none or one.⁷

References

1. Baker R, Coughlin P, Gallus A, Harper P, Salem H, Wood E. Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis. MJA 2004; 181: 492-497.
2. [Palareti G, Leali N, Coccheri S, Poggi M, Manotti C, et al.](#) Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). Italian Study on Complications of Oral Anticoagulant Therapy. Lancet. 1996 Aug 17;348(9025):423-8.

3. A randomized trial of anticoagulants versus aspirin after cerebral ischemia of presumed arterial origin. The Stroke Prevention in Reversible Ischemia Trial (SPIRIT) Study Group. [Ann Neurol](#). 1997 Dec;42(6):857-65.
4. Campbell P, Roberts G, Eaton V, et al. Managing warfarin therapy in the community. *Aust Prescriber* 2001; 24: 86-89
5. [Levine MN](#), [Raskob G](#), [Landefeld S](#), Hemorrhagic complications of anticoagulant treatment. [Chest](#). 2001 Jan;119(1 Suppl):108S-121S.
6. Institute for Clinical Systems Improvement. Anticoagulant therapy supplement 2003, www.icsi.org
7. Hirsh J, Fuster V, Ansell J, Halperin JL. American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. *Circulation*. 2003 Apr 1;107(12):1692-711

Is re-dosing of PROTHROMBINEX®-VF necessary in the setting of warfarin reversal?

Re-dosing is not discussed in the PROTHROMBINEX-VF Product Information (PI)¹, in the context of warfarin reversal. Additionally, the 2004 Warfarin Reversal: Consensus Guidelines developed by the ASTH² do not specify that re-dosing with PROTHROMBINEX®-VF is required.

The PROTHROMBINEX-VF PI¹ contains a precautionary statement that patients receiving repeat doses or high doses (greater than 50 IU/kg of factor IX) may be at increased risk of thrombotic adverse events due to the accumulation of the coagulation factors with long half-lives such as factor II. Such patients should be observed closely for symptoms or signs of thrombosis, embolism, disseminated intravascular coagulation or myocardial infarction.

The PI and Warfarin Reversal Consensus Guidelines^{1,2} recommend PROTHROMBINEX-VF doses of 25-50 IU/kg* be given with FFP (150-300 mL) in various clinical settings.

* The dose of PROTHROMBINEX-VF (25-50 IU/kg) equates to approximately ½ - 1 vial (500 IU/20mL vial) PROTHROMBINEX-VF per 10 kg patient weight, or 3.5 to 7 vials for a 70kg patient.

References

1. PROTHROMBINEX-VF Approved Product Information. Date of most recent amendment: 11 February 2009
2. Baker R, Coughlin P, Gallus A, Harper P, Salem H, Wood E. Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis. *MJA* 2004; 181: 492-497.

What parameters should be monitored when using a PROTHROMBINEX®-VF for warfarin reversal?

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.¹

The Prothrombinex-VF Product Information¹ and the 2004 Warfarin Reversal Consensus Guidelines developed by the ASTH² recommend:

- **during a clinically significant bleed where warfarin is a contributing factor**, patients should be assessed continuously until the INR is <5 and bleeding stops. In all situations carefully reassess the need for ongoing warfarin therapy.^{1,2}

- **in patients with INR >9 and absent bleeding**, the INR should be checked 6-12 hrs after administration of PROTHROMBINEX®-VF. Once the INR is <5, warfarin therapy can be resumed.^{1,2}

Also see 'What is the onset of action of PROTHROMBINEX®-VF?', and 'What dose of PROTHROMBINEX®-VF is required for warfarin reversal during invasive procedures (according to risk of thromboembolism)?'

References

1. PROTHROMBINEX-VF Approved Product Information. Date of most recent amendment: 11 February 2009
2. Baker R, Coughlin P, Gallus A, Harper P, Salem H, Wood E. Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis. MJA 2004; 181: 492-497.

Is the INR a good parameter to monitor once warfarin reversal has been initiated?

Yes. The 2004 Warfarin Reversal: Consensus Guidelines developed by the ASTH¹ recommend use of INR measurements after warfarin reversal, since they state there is a close relationship between the INR and the risk of bleeding.

However, debate exists in the literature around this relationship, as some authors suggest there may be not a good correlation between the INR and bleeding risk, and that the INR may have limitations once reversal has been initiated i.e. bleeding may reduce rapidly without reduction in INR^{2,3,4}

It is thought that this is due to the fact that:

- the INR was designed for stable anti-coagulated patients and may have limited value once reversal has been indicated¹
- the INR is dependant on factor VII, but not factor IX^{2,4}, and the INR may be normal even with an abnormal factor IX²⁻⁴
- as PROTHROMBINEX®-VF is more likely to correct coagulopathy through increased thrombin rather than through factor VII replacement, the INR may not be the best test for monitoring haemostatic changes after PROTHROMBINEX-VF.

Therefore, once reversal has been initiated, it is important not to rely solely on INR laboratory results, but as stated in the 2004 Warfarin Reversal: Consensus Guidelines¹, to also monitor clinical signs and ensure that bleeding has stopped.

References

1. Baker R, Coughlin P, Gallus A, Harper P, Salem H, Wood E. Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis. MJA 2004; 181: 492-497.
2. Makris M, Greaves M, Phillips WS, et al. Emergency oral anticoagulant reversal: the relative efficacy of infusions of fresh frozen plasma and clotting factor concentrate on correction of the coagulopathy. Thromb Haemost. 1997 Mar;77(3):477-80.
3. Steiner T, Rosand J, Dringer M. Intracerebral hemorrhage associated with oral anticoagulant therapy: current practices and unresolved questions. Stroke. 2006 Jan;37(1):256-62.
4. Crawford JH, Augustson BM. PROTHROMBINEX use for the reversal of warfarin: is fresh frozen plasma needed? Med J Aust. 2006 Apr 3;184(7):365-6.

Do you need to use FFP every time PROTHROMBINEX®-VF is administered for warfarin reversal?

The PROTHROMBINEX-VF approved Product Information¹ (PI) and the 2004 Warfarin Reversal: Consensus Guidelines developed by the ASTH² recommend use of both PROTHROMBINEX-VF and FFP in warfarin reversal. PROTHROMBINEX-VF contains factors II, IX and X and low levels of factor VII. FFP is added to provide an additional source of factor VII.

However, in a situation of any clinically significant bleeding where warfarin-induced coagulopathy is considered a contributing factor and where FFP is unavailable PROTHROMBINEX-VF may be used alone. Specifically, the PI and guidelines recommend:

- **in a situation of any clinically significant bleeding where warfarin-induced coagulopathy is considered a contributing factor**, to cease warfarin therapy, give 5.0-10.0 mg vitamin K IV, and administer PROTHROMBINEX-VF and FFP. However, in situations where FFP is unavailable, PROTHROMBINEX-VF can be administered alone. Also if PROTHROMBINEX-VF is unavailable, FFP can be used alone.
- **in patients with INR >9 and bleeding is absent**, however there is a high risk of bleeding, cease warfarin therapy, give 1.0 mg vitamin K intravenously and consider PROTHROMBINEX-VF and FFP.

It is important to note that when using PROTHROMBINEX-VF plus FFP, only a small volume of FFP is required when used in this combination (150-300 mL). This is an important consideration, since FFP used alone requires doses of 10-15mL/kg, and in patients where large volumes are required this may cause circulatory overload possibly resulting in associated complications.

In three separate studies, PROTHROMBINEX-VF alone has been shown to reverse warfarin coagulopathy, without the use of FFP.^{3,4,5} For further information please contact CSL Bioplasma. Phone (toll free): 1800 067 140 or Email: medicalaffairs_bioplasma@csl.com.au

The Warfarin Reversal Pocket Guide and Poster, which summarises the ASTH Warfarin Reversal Consensus Guidelines, are available from CSL Bioplasma. Phone (toll free): 1800 067 140 or Email: medicalaffairs_bioplasma@csl.com.au.

References

1. PROTHROMBINEX-VF Approved Product Information. Date of most recent amendment: 11 February 2009
2. Baker R, Coughlin P, Gallus A, Harper P, Salem H, Wood E. Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis. MJA 2004; 181: 492-497.
3. Hatem JS, Poulton L. Warfarin Anticoagulation Can Be Effectively Reversed with Prothrombinex®-VF without the Need for Fresh Frozen Plasma. Abstract 053 HAA 2008 Perth
4. Chiu D, Grigg M and Levi E. Operating on patients with warfarin: Simpler alternative approach. ANZ Journal of Surgery. 2009; 79 (5): 409-410.
5. Crawford JH, Auguston BM. Prothrombinex use for the reversal of warfarin: is fresh frozen plasma needed. MJA 2006; 184: 7: 365-366

Warfarin Reversal - Vitamin K antagonist (VKA) Therapy Related Intracranial Haemorrhage (VKA-ICH)

Can PROTHROMBINEX®-VF be used in VKA-ICH?

Yes. The PROTHROMBINEX-VF approved Product Information¹ (PI) and 2004 Warfarin Reversal: Consensus Guidelines developed by the ASTH² recommend the use of PROTHROMBINEX-VF in various clinical situations including the immediate reversal of warfarin for any clinically significant bleeding as a result of warfarin therapy. Hence, if a patient suffers an intracranial haemorrhage² where warfarin-induced coagulopathy is a contributing factor, the Guidelines² support use of PROTHROMBINEX-VF for immediate reversal of the bleed.

References

1. PROTHROMBINEX-VF Approved Product Information. Date of most recent amendment: 11 February 2009
2. Baker R, Coughlin P, Gallus A, Harper P, Salem H, Wood E. Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis. MJA 2004; 181: 492-497.

Why it is important to consider rapid reversal of vitamin K antagonist (VKA)-associated ICH?

It is important to note that ICH is recognised as one of the most disabling forms of stroke, which can occur as a spontaneous intracranial haemorrhage (S-ICH) following trauma, or as a result of vitamin K antagonist (VKA) (warfarin) therapy (VKA-ICH).¹ Also, major bleeding, which includes VKA-ICH and bleeding leading to death and hospitalisation, has been reported in 1.2% - 8.1% of warfarinised patients during each year of long-term warfarin therapy.²⁻⁴

Recent studies have shown that the outcome for VKA-ICH is much worse than for S-ICH.⁵ The incidence of VKA-ICH can be as high as 1% in patients on warfarin and is seen as the most serious and potentially life threatening complication of VKA therapy. There is an 8-10 fold increased risk of ICH in VKA patients over 50 years of age compared to non-warfarinised patients.⁶ Patients receiving warfarin have been reported to make up 14% of all those presenting to neurosurgical units with ICH.⁷ Also, more protracted bleeding and larger haematomas are found in patients with VKA-ICH than in S-ICH.⁸ Unfortunately, early haematoma growth is strongly associated with a poor outcome.¹

The incidence of VKA-ICH is expected to increase in the coming years as the result of an anticipated rise in the incidence of atrial fibrillation attributable to an aging population.⁹ Despite this growing acutely ill patient group, there are still no worldwide universally accepted treatment regimens for patients with VKA-ICH, and randomised controlled trials do not exist.^{10,11}

The PROTHROMBINEX-VF approved Product Information¹² (PI) and 2004 Warfarin Reversal: Consensus Guidelines developed by the ASTH⁴, recommend the use of PROTHROMBINEX-VF in various clinical situations including the immediate reversal of warfarin for any clinically significant bleeding as a result of warfarin therapy. Hence, if a patient suffers an intracranial haemorrhage where warfarin-induced coagulopathy is a contributing factor, then the guidelines support use of PROTHROMBINEX-VF for immediate reversal of the bleed.

References:

1. Brott T, Broderick J, Kothari R, et al. Early haemorrhage growth in patients with intracerebral haemorrhage. *Stroke*. 1997 Jan;28(1):1-5. (Refman No: 8332)
2. Levine MN et al. *Chest*, 1998 Nov;114(5 Suppl):511S-523S
3. Gallus AS et al. *Med. J. Aust.* 2000; 172/12: 600-605
4. Baker R, Coughlin P, Gallus A, Harper P, Salem H, Wood E. Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis. *MJA* 2004; 181: 492-497.
5. Cartmill M, Dolan G, Byrne JL, et al Prothrombin complex concentrate for oral anticoagulant reversal in neurosurgical emergencies. *Br J Neurosurg*. 2000 Oct;14(5):458-61. (Refman No: 3434)
6. Hart RG, Boop BS, Anderson DC. Oral anticoagulants and intracranial haemorrhage. Facts and hypotheses. *Stroke*. 1995 Aug; 26(8):1471-7. (Refman No: 8331)
7. Wintzen AR, de Jonge H, Loeliger EA, Bots GT. The risk of intracerebral haemorrhage during oral anticoagulant treatment: a population study. *Ann Neurol*. 1984 Nov;16(5):553-8. (Refman No: 8345)
8. Radberg JA, Olsson JE, Radberg CT. Prognostic parameters in spontaneous intracerebral hematomas with special reference to anticoagulant treatment. *Stroke*. 1991 May;22(5):571-6. (Refman No: 8371)
9. Kase CS, Robinson RK, Stein RW, DeWitt LD, Hier DB, Harp DL, Williams JP, Caplan LR, Mohr JP. Anticoagulant-related intracerebral haemorrhage. *Neurology*. 1985 Jul;35(7):943-8. (Refman No: 8615)
10. Rosand J, Eckman MH, Knudsen KA, Singer DE, Greenberg SM. The effect of warfarin and intensity of anticoagulation on outcome of intracerebral haemorrhage. *Arch Intern Med*. 2004 Apr 26;164(8):880-4. (Refman No: 8610)
11. Huttner HB, Schellinger PD, Hartmann M, et al Hematoma growth and outcome in treated neurocritical care patients with intracerebral haemorrhage related to oral anticoagulant therapy: comparison of acute treatment strategies using vitamin K, fresh frozen plasma, and prothrombin complex concentrates. *Stroke*. 2006 Jun;37(6):1465-70. (Refman No: 8227)
12. PROTHROMBINEX-VF Approved Product Information. Date of most recent amendment: 11 February 2009

What are the Australian recommendations for Vitamin K antagonist (VKA)-associated ICH?

PROTHROMBINEX-VF is indicated in the 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.¹

The PROTHROMBINEX-VF approved Product Information¹ (PI) and 2004 Warfarin Reversal: Consensus Guidelines developed by the ASTH², recommend that in the situation of "Any clinically significant bleeding where warfarin induced coagulopathy is considered a contributing factor" (which includes VKA-ICH), to cease warfarin therapy, give 5.0-10.0 mg vitamin K intravenously, and either:

- administer PROTHROMBINEX-VF (25-50IU/kg) and fresh frozen plasma (FFP) (150-300mL), or
- PROTHROMBINEX-VF (25-50IU/kg) can be administered alone, in situations where FFP is unavailable, or
- FFP (10-15mL/kg) can be used alone, if PROTHROMBINEX-VF is unavailable.

References

1. PROTHROMBINEX-VF Approved Product Information. Date of most recent amendment: 11 February 2009
2. Baker R, Coughlin P, Gallus A, Harper P, Salem H, Wood E. Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis. *MJA* 2004; 181: 492-497.

Overdosage

What are the implications of PROTHROMBINEX®-VF overdosage?

The PROTHROMBINEX-VF Product Information states overdose may potentially lead to an increased risk of disseminated intravascular coagulation (DIC), thrombosis, myocardial infarction or pulmonary embolism.¹ Therefore, in case of overdose, the risk of development of thromboembolic complications or DIC is enhanced.^{1,2}

It is therefore important that PCCs be used for approved indications and that doses do not result in much higher than physiological levels of the administered coagulation factors.

In patients with haemophilia B, the exact loading dose, maintenance dose and dosing intervals of PROTHROMBINEX-VF should be based on the patient's clinical condition, response to therapy and plasma factor IX concentration. Laboratory tests should be performed to ensure that the desired factor IX levels are achieved, since thrombotic problems may occur if the suggested maximum dose is exceeded.¹

References

1. PROTHROMBINEX-VF Approved Product Information. Date of most recent amendment: 11 February 2009
2. EMEA Core SPC for Human Prothrombin Complex Products: Date effective: April 2005

Presentation

How is PROTHROMBINEX®-VF presented?

PROTHROMBINEX-VF is available in single packs containing one vial of PROTHROMBINEX-VF, one 20 mL vial of Water for Injections and one Mix2Vial™ filter transfer set.¹

When reconstituted as recommended, each vial of PROTHROMBINEX-VF contains 500 IU factor IX, approximately 500 IU of factor II, 500 IU of factor X, 25 IU of antithrombin III, 192 IU of heparin sodium and ≤ 500mg of plasma proteins (which includes low levels of factors V & VII.)¹

Reference

1. PROTHROMBINEX-VF Approved Product Information. Date of most recent amendment: 11 February 2009

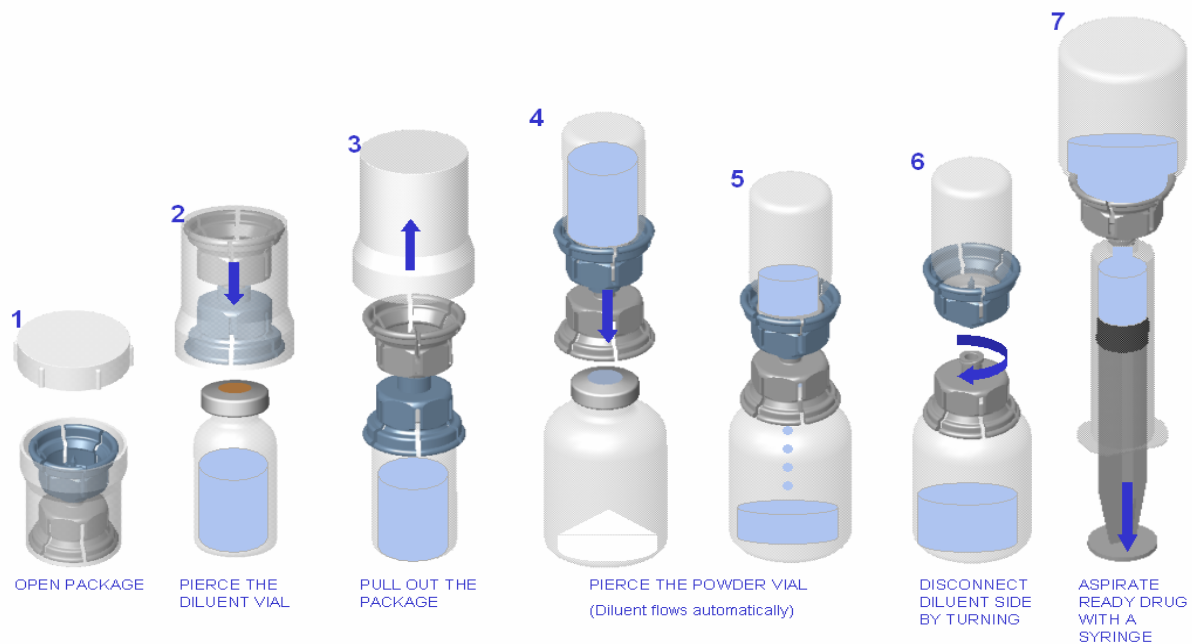
Reconstitution

How is PROTHROMBINEX®-VF reconstituted?

A Mix2Vial™ reconstitution device is packaged with each vial of PROTHROMBINEX-VF to allow needle-free reconstitution.

The Mix2Vial™ is designed so the blue end is first attached to the vial of Water for Injections (ie blue plastic cannula of the Mix2Vial™ attaches to the water diluent vial).¹

The diagram below shows the step by step process. Please refer to the PROTHROMBINEX-VF Product Information for further step-by-step instructions.¹



Reference

1. PROTHROMBINEX-VF Approved Product Information. Date of most recent amendment: 11 February 2009

Can several vials of reconstituted PROTHROMBINEX®-VF be pooled for administration?

Each vial of PROTHROMBINEX-VF must be reconstituted with 20mL of Water for Injections¹. One vial of Water for Injection is provided with each vial of PROTHROMBINEX-VF.¹

If more than one vial of PROTHROMBINEX-VF is to be administered, each vial can be administered individually, or alternatively, the contents of all the vials can be pooled aseptically into one large sterile syringe, burette or sterile bag for administration as a single dose.¹

Please note:

- if vials are pooled together and infused, the reconstituted PROTHROMBINEX-VF solution must not be mixed with any other fluids (the infusion line may be primed with sterile Water for Injection or PROTHROMBINEX-VF itself). If a giving set is used, PROTHROMBINEX-VF must be administered alone.
- a Mix2Vial™ is packaged with each vial of PROTHROMBINEX-VF to allow needle-free reconstitution. Each 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 reconstitution of each vial.¹
- give the total dose slowly (approximately 3 mL per minute, or as tolerated by the patient) by the intravenous route.¹
- as PROTHROMBINEX-VF does not contain an antimicrobial preservative, to reduce microbiological hazard, the reconstituted solution should be used as

stored after reconstitution and infusion should be completed within three hours of reconstitution. ¹ not be

- any unused portion remaining in the vial must be discarded appropriately. ¹

Reference

1. PROTHROMBINEX-VF Approved Product Information. Date of most recent amendment: 11 February 2009

Storage

What are the recommended storage conditions for unreconstituted PROTHROMBINEX[®]-VF?

CSL Bioplasma recommends that PROTHROMBINEX-VF be stored at 2-8°C (refrigerate, but do not freeze) and protected from light. CSL Bioplasma does not recommend the use of PROTHROMBINEX-VF if it has deviated from these approved storage conditions.¹

Reference

1. PROTHROMBINEX-VF Approved Product Information. Date of most recent amendment: 11 February 2009

How long can reconstituted PROTHROMBINEX[®]-VF be stored?

As PROTHROMBINEX-VF does not contain an antimicrobial preservative, it should be used as soon as practicable after reconstitution.¹ PROTHROMBINEX-VF must not be stored after reconstitution, and infusion should be completed within three hours of reconstitution.¹ Any unused portion remaining in the vial must be discarded appropriately.¹

Reference

1. PROTHROMBINEX-VF Approved Product Information. Date of most recent amendment: 11 February 2009

PROTHROMBINEX®-VF
Minimum Product Information

Please review the approved Product Information (PI) before prescribing. **INDICATIONS:** Treatment and perioperative prophylaxis of bleeding in acquired deficiency of prothrombin complex factors, such as deficiency caused by treatment or overdose with vitamin K antagonists when rapid correction of the deficiency is required. Treatment and prophylaxis of bleeding due to congenital deficiency of factors II, IX, or X when purified specific coagulation factor concentrate not available. **CONTRAINDICATIONS:** Hypersensitivity or allergy to any constituents of preparation, including heparin. Evidence of active thrombosis or disseminated intravascular coagulation (DIC). **PRECAUTIONS:** High doses may predispose to thrombotic complications or heparin-induced thrombocytopenia. Safety has not been established in pregnancy and lactation. PROTHROMBINEX®-VF 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, and by dedicated virus removal and inactivation procedures included in the manufacturing process. Despite these measures, such products may still potentially transmit disease. Vaccination for patients in receipt of medicinal products from human plasma should be considered where appropriate. **ADVERSE EFFECTS:** Allergic or anaphylactic type reactions may occur rarely. Although low, there is a potential risk of thrombosis (including myocardial infarction). Spontaneous post-marketing adverse event reports for PROTHROMBINEX®-VF include pulmonary embolism, hypercoagulability, DIC, anaphylactic reactions, thrombosis, rash and injection site reaction. Other reactions: somnolence, phlebitis, vasodilation, dyspnoea, vomiting, pain, fever, feeling cold and peripheral oedema. **DOSAGE & ADMINISTRATION:** Warfarin reversal: Any clinically significant bleeding where warfarin- induced coagulopathy is considered a contributing factor, cease warfarin, give vitamin K (5-10 mg) intravenously, PROTHROMBINEX®-VF 25-50 IU/kg and fresh frozen plasma (FFP) 150-300 mL. If INR > 9, bleeding absent and high risk of bleeding, cease warfarin, give vitamin K (1.0 mg), PROTHROMBINEX®-VF 25-50 IU/kg and FFP 150-300 mL. Invasive procedures: On day of surgery if INR > 1.5 and surgery urgent give PROTHROMBINEX®-VF (25-50 IU/kg) and FFP 150-300 mL. PROTHROMBINEX®-VF can be used alone if FFP is unavailable. Administer intravenously at approximately 3 mL/min. Review approved PI. The approved PI is available from CSL Limited (ABN 99 051 588 348), Bioplasma Division, 189-209 Camp Road Broadmeadows VIC 3047 Australia. For Medical/Technical inquiries: (Toll free) 1800 067 140.