

Four-Factor (II, VII, IX, X) Prothrombin Complex Concentrate (4F-PCC) (Kcentra)

Clinical Recommendations for Use

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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.**

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or <http://vaww.pbm.va.gov> for further information.

NOTE: In the setting of emergent, life-threatening situations where 4F-PCC will be used, the product should be made available immediately, when appropriate. Facilities are strongly encouraged to proactively develop local policies and processes to avoid any delays in care regarding emergent 4F-PCC requests (for details on dealing with such situations, please see VHA Formulary Management Process Handbook 1108.08). It is further recommended that 4F-PCC be restricted to, or overseen by, locally designated specialty service(s) (e.g., hematology, critical care, emergency, etc.).

Note that the following criteria/ recommendations may be used to educate providers, pharmacy, and other staff on safe and appropriate use of 4F-PCC in advance of need, to retrospectively conduct a review of 4F-PCC use, or to facilitate an immediate review in emergency situations.

Exclusion Criteria *Patients with any of the following should NOT receive 4F-PCC*

- Patient with disseminated intravascular coagulation (DIC)
- History of heparin-induced thrombocytopenia (See Issues for Consideration, Heparin Induced Thrombocytopenia)
- History of anaphylactic or severe systemic reaction to 4F-PCC or any components in 4F-PCC including heparin, Factors II, VII, IX, X, Proteins C and S, Antithrombin III and human albumin
- Situation in which administration of intravenous vitamin K and withdrawal of warfarin therapy alone would be expected to adequately reverse anticoagulation within time frame of required urgent invasive procedure or surgery
- Patients in whom complete correction of International Normalized Ratio (INR) is not clinically appropriate or necessary. See Thromboembolic Risk in Issues for Consideration.

Inclusion Criteria

General Inclusion Criteria

- Receiving treatment with vitamin K antagonist (e.g., warfarin) therapy with INR of 2 or higher
(For patients receiving treatment with a non-warfarin oral anticoagulant, see Issues for Consideration)
AND
- Standard measures for bleeding cessation (e.g. vitamin K, fresh frozen plasma, supportive measures) or reversal are contraindicated or insufficient
(Note, 4F-PCC should be co-administered with vitamin K)

PLUS ONE OF THE FOLLOWING INDICATIONS:

- Acute life-threatening major bleeding*, including intracranial hemorrhage
- Need for urgent life-saving surgery or invasive procedure

*There are multiple definitions for life-threatening bleeding, and ultimately this determination must be made clinically. The GUSTO criteria specifically define severe or life-threatening bleeding as "intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention." TIMI bleeding definitions do not specify a category of "life-threatening" bleeding, but major bleeding is defined as "intracranial hemorrhage, a decrease in hemoglobin concentration by $\geq 5\text{g/dl}$, or an absolute decrease in hematocrit of $\geq 15\%$."

Dosage and Administration

- Four-factor-PCC is administered as a single dose IV infusion, which is determined based on a patient's current, pre-treatment international normalized ratio (INR) and actual body weight.
- Dosing calculations are based on the quantity (international units) of factor IX in the product. ***Exact contents are labeled on the vial and will vary from vial to vial*** (e.g., 500 unit vial may contain a range of 400 to 620 units per vial, and 1000 unit vial may contain a range of 800-1240 units per vial).

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- Dosing calculations based on actual body weight for patients weighing up to 100 kg. For patients weighing more than 100 kg, maximum doses should not be exceeded.

Pre-treatment INR	4F-PCC Dose (IU of factor IX per kg body weight*)	Maximum dose (IU of factor IX)
2 to <4	25	2500
4 to 6	35	3500
>6	50	5000

*Dosing is based on actual body weight. Dose based on actual potency as stated on the carton, which will vary from 20-31 Factor IX units/mL after reconstitution. Nominal potency is 500 or 1000 units per vial, approximately 25 units per mL after reconstitution.

- Four-factor-PCC should be given concomitantly with intravenous vitamin K to help replenish clotting factors after the effects of 4F-PCC have diminished.
- Do not mix 4F-PCC with other products. It should be administered through a separate infusion line from other drugs. 4F-PCC should be administered at a rate of 0.12mL/kg/min, up to a maximum rate of 8.4mL/min. No blood should enter the syringe with 4F-PCC, given the possibility of fibrin formation.
- The effectiveness and safety of repeat dosing has not been established and is not recommended.

Monitoring

- Because INR may fluctuate in the setting of acute major bleeding or other urgent setting where surgery or invasive procedure is needed, a current, pre-treatment INR taken close to the time of 4F-PCC dosing should be used.
- Following administration of 4F-PCC, it may be prudent to evaluate laboratory coagulation parameters in conjunction with clinical signs of hemostasis and thromboembolism.

Issues for Consideration

Thromboembolic Risk

- Four-factor-PCC carries a Boxed Warning for arterial and venous thromboembolic complications
- Randomized, plasma-controlled studies of 4F-PCC have not been adequately powered to demonstrate a difference in safety outcomes including thromboembolic events. It is unclear whether the thromboembolic risk is associated specifically with the use of 4F-PCC or if it is a result of reversal of anticoagulation, regardless of reversal agent used. See VA National PBM-MAP-VPE Monograph for additional information regarding rates of thromboembolism. In the trial evaluating 4F-PCC use in acute major bleeding, patients with any history of prior thromboembolic event or coronary, cerebrovascular, or peripheral vascular disease who received 4F-PCC experienced more thromboembolic events than those who received plasma.
- The following populations, who are at high risk of thromboembolic events were excluded from the randomized, plasma-controlled trials of 4F-PCC; therefore, the thromboembolic risk in these population is unknown. It is unclear if the benefits of rapid INR reversal with 4F-PCC outweigh the potentially increased risk of thromboembolism, and this should be considered based on individual circumstances requiring urgent reversal of warfarin therapy.
 - Patients with a recent history of thrombotic event, myocardial infarction, cerebrovascular accident, transient ischemic attack, unstable angina pectoris, severe peripheral vascular disease, or DIC within the last 3 months
 - Known history of antiphospholipid syndrome
 - Known inhibitors to coagulation factors II, VII, IX, or X
 - Known hereditary protein C or protein S deficiency

Use for patients receiving non-warfarin oral anticoagulants:

- There is insufficient clinical evidence to support off-label use of 4F-PCC in patients receiving non-warfarin anticoagulants, and use is not FDA approved. The application of animal studies and human studies using non-clinical endpoints is limited. Therefore, consideration of use of 4F-PCC should be limited to severe, life-threatening situations where all other measures have failed or are not indicated (e.g., discontinuation of anticoagulant, maintenance of adequate diuresis, and implementation of supportive measures [compression, surgical hemostasis, fluid and/or blood replacement], consideration of hemodialysis for dabigatran). Though data are of poor quality, there may be a weak preference for the use of activated PCC (FEIBA) for reversal of dabigatran and 4F-PCC for reversal of rivaroxaban and apixaban. Carefully weigh hypothesized clinical benefit with risk of thromboembolism. See VA National PBM-MAP-VPE Monograph for additional information.

Fluid Status

- Randomized, plasma-controlled studies of 4F-PCC have not been adequately powered to demonstrate a difference in safety outcomes including volume overload; however, 4F-PCC was associated with a numerically lower rate of fluid overload or cardiac events compared to plasma.

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- Mean volume of 4F-PCC infused was less than 100 mL (range 50 – 230 mL) in the randomized, plasma-controlled trials. Comparatively, the mean volume of plasma was between approximately 815 mL (range 400 – 1525 mL).
- Four-factor-PCC may be preferred if there is reason to believe the patient would not tolerate the additional volume required to administer plasma.

Timing of Reversal

- INR correction with 4F-PCC was greater compared to plasma at 30 minutes post-infusion until 12 hours after infusion. The first time-point assessed at which the difference was no longer evident was 24 hours after the infusion. Therefore, 4F-PCC may be preferable in adult patients requiring rapid reversal of anticoagulation within 24 hours such as those with intracranial hemorrhage, life-threatening bleeding, or a need for a life-saving surgical or invasive intervention.
- Rates of effective hemostasis achieved at 24 hours did not significantly differ between plasma and 4F-PCC; the benefit seen was in regards to rapid reversal of INR only. No statistically significant difference was detected between 4F-PCC and plasma in regards to mortality or length of hospital stay.

History of Heparin-induced Thrombocytopenia

- **4F-PCC contains heparin.** Patients with known heparin-induced thrombocytopenia (HIT) were excluded from both randomized, plasma-controlled, phase III studies of 4F-PCC. As such, any history of HIT is considered a contraindication according to the FDA-approved labeling.

According to the ACCP guidelines for the treatment and prevention of HIT it may be reasonable to give short-term (intraoperative) heparin therapy in patients in whom heparin antibodies have been shown to be absent who require cardiac surgery. Although evidence is very limited, the risk of HIT must be weighed against the potential benefit of 4F-PCC in the setting of life-threatening bleeding and 4F-PCC should only be considered if patient has had such negative antibody testing. **Infectious Disease**

Transmission

- Because 4F-PCC is made from human blood, it may carry a risk of transmitting infection. 4F-PCC is manufactured using two virus reduction steps to minimize the risk of transmitting potentially infectious agents; however, blood-derived products may still carry risk.

For women of childbearing potential

- Pregnancy should be considered prior to administration of 4F-PCC; however, 4F-PCC should be reserved for instances considered life-threatening, and potential risks and benefits to the mother and fetus must be considered.
- Four-factor-PCC [Category C] has not been studied in pregnancy

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