Executive Summary:

- Kcentra is a four-factor prothrombin complex concentrate (4F-PCC) of coagulation factors II, VII, IX, and X, prepared from U.S. sourced plasma. Kcentra is therapeutically equivalent to Beriplex, which has been marketed outside of the US since 1996. In 2013, the FDA approved Kcentra for the urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist (VKA) therapy in adult patients with acute major bleeding or need for an urgent surgery/invasive procedure.

- 4F-PCC is dosed based on a patient’s total body weight and International Normalized Ratio (INR) with capped dosing for patients weighing greater than 100 kg. There are no recommend dosage adjustments for renal or hepatic dysfunction, or age.

- In a randomized, plasma-controlled clinical trial, 4F-PCC in patients with acute bleeding associated with VKA therapy demonstrated non-inferiority as compared to plasma for achievement of effective hemostasis within 24 hours and superiority in reduction of INR to ≤ 1.3 within 30 minutes after the completed infusion. Effective hemostasis within 24 hours was defined as cessation of bleeding within 4 hours of the end of the infusion and no additional coagulation intervention required within 24 hours. No statistically significant difference was detected between 4F-PCC and plasma in regards to mortality or length of hospital stay.

- In the same randomized, placebo-controlled clinical trial as above, serious adverse events associated with reversal of VKAs with 4F-PCC were reported in 31% of patients. Of the 66 serious events reported, only 10 were deemed treatment related. When compared to plasma, rates of serious adverse appeared similar; however, no clinical trial has been powered to specifically evaluate differences in safety.

- In a randomized, plasma-controlled clinical trial, 4F-PCC in patients requiring urgent reversal of VKA therapy for surgery or an invasive procedure demonstrated superiority to plasma for maintenance of effective hemostasis from the time of infusion until the completion of the procedure. Effective hemostasis was defined based on actual blood loss as compared to predicted blood loss, subjective hemostasis rating, and no additional coagulation intervention being required. In this study, 4F-PCC also demonstrated superiority over plasma with regards to rapid reduction of INR to ≤ 1.3 within 30 minutes after the completed infusion.
Commonly reported side effects with 4F-PCC include headache, pleural effusion, nausea/vomiting, tachycardia, atrial fibrillation, hypokalemia, hypotension, and insomnia.

Thromboembolic events are associated with the reversal of VKA therapy with 4F-PCC. Four-factor-PCC contains heparin and albumin in addition to factors II, VII, IX, X, and proteins C and S and is contraindicated in patients with disseminated intravascular coagulation or heparin-induced thrombocytopenia.

Because patients with thrombotic events within the preceding 3 months were excluded from randomized clinical trials based on potential increased risk of thromboembolic complications with rapid reversal of VKAs, the safety of 4F-PCC is unknown in this population.

Introduction

Kcentra, a four-factor prothrombin complex concentrate (4F-PCC), was approved by the FDA in 2013 for the urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist (VKA) therapy in adult patients with acute major bleeding or need for an urgent surgery/invasive procedure.\(^1\)

This monograph focuses on Kcentra, which is the only 4F-PCC approved for use in the U.S. and includes data from studies using Beriplex, which has the same composition as Kcentra and is considered therapeutically equivalent.\(^2\) Studies evaluating other 4F-PCC formulations not currently available in the U.S. (e.g., Cofact, Octaplex, and Prothromplex-T) are not included in the efficacy or safety analyses. All 4F-PCCs contain similar amounts of factor IX, but formulations differ significantly in their composition of factors II, VII, and X as well as proteins C and S, and heparin. Because of these differences, it is not appropriate to apply evidence with one 4F-PCC formulation for clinical assessment of others.\(^3,4\) For the purposes of this document, 4F-PCC refers only to Kcentra or Beriplex, unless otherwise noted.

Prior to the approval of 4F-PCC in the U.S., treatment options for urgent reversal of VKA in acute major bleeding were limited to plasma (also known as fresh frozen plasma, FFP), vitamin K, three-factor-PCCs (3F-PCCs), and recombinant factor VIIa (rFVIIa).\(^5,6\) Frequently used for urgent VKA reversal, plasma administration involves extra preparation time for thawing. Further, the large volumes of plasma that may be required for anticoagulant reversal may cause circulatory overload in susceptible patients. Plasma also carries risks of allergic reactions and infection transmission. Though the effects are delayed for 12 to 24 hours after intravenous administration, vitamin K effectively reverses the anticoagulant effects of VKA. Vitamin K is typically given along with plasma (or other PCC or rFVIIa) to help to sustain the effects of the other products. Two 3F-PCCs are available in the U.S., but neither of these is FDA-approved for reversal of anticoagulation.\(^7,8\) Three-factor-PCCs contain factors II, IX, and X but contain little or no factor VII. While no studies have directly compared 3F- and 4F-PCCs for reversal of VKAs, a systematic review comparing INR reduction with 3F- versus 4F-PCCs within 60 minutes concluded that 4F-PCCs (not limited to Kcentra or Beriplex) are more effective in decreasing INR in one hour than 3F-PCCs.\(^6\) Recombinant factor VIIa, which is also not FDA-approved for reversal of VKAs, is not recommended as monotherapy for reversal of VKAs because of concerns for increased risk of thromboembolic events.\(^5,10\) In cases of life-threatening bleeding, it is recommended that INR be corrected as rapidly as possible.\(^11\) It had previously been suggested that 3F-PCCs may be combined with recombinant factor VIIa or plasma to achieve a combination therapy including all four factors, but these combinations have not been evaluated in clinical trials for the reversal of warfarin.\(^12\)
The 2012 American College of Chest Physicians (ACCP) Antithrombotic Therapy and Prevention of Thrombosis guidelines provide a weak preference for the use of 4F-PCC for rapid reversal of anticoagulation for patients with VKA-associated major bleeding over plasma (Grade 2C). These guidelines do not give a recommendation for or against the use of 3F-PCC or rFVIIa. The American Heart Association and American Stroke Association Guidelines for the Management of Spontaneous Intracerebral Hemorrhage do not make a recommendation for PCCs or plasma, but do note that PCCs are a reasonable alternative to plasma in patients with intracerebral hemorrhage associated with warfarin therapy.

The purposes of this monograph are to (1) evaluate the available evidence of efficacy, safety, tolerability, cost, and other pharmaceutical issues that would be relevant to evaluating 4F-PCC for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

**Pharmacology**

Kcentra is a non-activated 4F-PCC prepared from U.S. sourced plasma which has been purified, heat-treated, nanofiltered and lyophilized. Kcentra is identical to the product sold elsewhere in the world as Beriplex, except that Kcentra is made solely with U.S.-sourced plasma.

Four-factor-PCC contains vitamin K-dependent coagulation factors II (FII), VII (FVII), IX (FIX), and X (FX) and the antithrombotic proteins C and S. The excipients are human antithrombin III, heparin, human albumin, sodium chloride, and sodium citrate. Product potency varies but exact component contents are labeled on each carton and vial; as such, volumes must be assessed for each vial. Dosing is based on the units of Factor IX. The composition of 4F-PCC is described in Table 1.

<table>
<thead>
<tr>
<th>Therapeutic Components</th>
<th>Excipients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total protein: 240 – 560 mg</td>
<td>Heparin: 16 - 80 units</td>
</tr>
<tr>
<td>Factor II: 760 - 1600 units</td>
<td>Antithrombin III: 8 - 60 units</td>
</tr>
<tr>
<td>Factor VII: 400 - 1000 units</td>
<td>Human albumin: 80 - 160 mg</td>
</tr>
<tr>
<td>Factor IX: 800 – 1240 units</td>
<td>Sodium chloride: 120 - 240 mg</td>
</tr>
<tr>
<td>Factor X: 1000 – 2040 units</td>
<td>Sodium citrate: 80 – 160 mg</td>
</tr>
<tr>
<td>Protein C: 840 - 1640 units</td>
<td>NaOH: Small amounts</td>
</tr>
<tr>
<td>Protein S 480 - 1360 units</td>
<td>HCl: Small amounts</td>
</tr>
</tbody>
</table>

**Pharmacokinetics**

The pharmacokinetics of 4F-PCC were established following the single infusion of 50 units/kg of 4F-PCC in healthy adult volunteers, not on VKAs and without active bleeding. The pharmacokinetic parameters for each therapeutic component of 4F-PCC are presented in table 2.
Four-Factor (II, VII, IX, X)
Prothrombin Complex Concentrate

Table 2. Pharmacokinetic parameters of therapeutic components in 4F-PCC in healthy volunteers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>F II</th>
<th>F VII</th>
<th>F IX</th>
<th>F X</th>
<th>Protein C</th>
<th>Protein S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminal half-life (h)</td>
<td>60.4</td>
<td>5.0</td>
<td>41.2</td>
<td>31.8</td>
<td>49.6</td>
<td>59.4</td>
</tr>
<tr>
<td></td>
<td>(59.7)</td>
<td>(4.2)</td>
<td>(16.7)</td>
<td>(30.7)</td>
<td>(47.2)</td>
<td>(49.1)</td>
</tr>
<tr>
<td>AUC (Units/dL x h)</td>
<td>7282.2</td>
<td>512.9</td>
<td>1850.8</td>
<td>6921.5</td>
<td>5397.5</td>
<td>3651.6</td>
</tr>
<tr>
<td></td>
<td>(6577)</td>
<td>(424)</td>
<td>(1490)</td>
<td>(6707)</td>
<td>(5276)</td>
<td>(3667)</td>
</tr>
<tr>
<td>Clearance (mL/kg x h)</td>
<td>1</td>
<td>7.4</td>
<td>3.7</td>
<td>1.3</td>
<td>1.5</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>(0.97)</td>
<td>(7.06)</td>
<td>(3.63)</td>
<td>(1.25)</td>
<td>(1.1)</td>
<td>(1.1)</td>
</tr>
<tr>
<td>Mean Residence Time (h)</td>
<td>82</td>
<td>7.1</td>
<td>47.3</td>
<td>45.9</td>
<td>62.4</td>
<td>70.3</td>
</tr>
<tr>
<td></td>
<td>(81.7)</td>
<td>(6.1)</td>
<td>(21.6)</td>
<td>(44.3)</td>
<td>(57)</td>
<td>(69.2)</td>
</tr>
<tr>
<td>Vd (mL/kg)</td>
<td>71.4</td>
<td>45</td>
<td>114.3</td>
<td>55.5</td>
<td>62.2</td>
<td>78.8</td>
</tr>
<tr>
<td></td>
<td>(71)</td>
<td>(41.8)</td>
<td>(92.4)</td>
<td>(56.1)</td>
<td>(62.9)</td>
<td>(76.6)</td>
</tr>
</tbody>
</table>

4F-PCC has not been studied in patients with congenital factor deficiencies.

**Mechanism of Action**
Four-factor-PCC increases plasma levels of the vitamin K-dependent coagulation factors II, VII, IX, and X, and the antithrombotic Proteins C and S and thus reverses the effects of VKAs, which inhibit the synthesis of these four factors. When activated, factors II, VII, IX, and X contribute to fibrin clot formation.

**Pharmacodynamics**
When administered in combination with intravenous (IV) vitamin K, 4F-PCC results in a rapid decrease in INR in patients previously treated with a VKA. In the plasma-controlled clinical trial of 4F-PCC in patients with acute major bleeding, the difference in INRs between patients receiving plasma and 4F-PCC was statistically significant within 30 minutes and for up to 12 hours after the start of the infusion.

**FDA Approved Indication(s)**
Four-factor-PCC (Kcentra) is indicated for the urgent reversal of acquired coagulation factor deficiency induced by VKA therapy in adult patients with acute major bleeding or need for an urgent surgery/invasive procedure.

**Potential Off-label Uses**
This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety’s Guidance on Off-Label Prescribing (available on the VA PBM Intranet site only).

There is great interest in using 4F-PCC as a reversal agent for non-VKA oral anticoagulants including direct thrombin inhibitors (e.g. dabigatran) and factor Xa inhibitors (e.g. rivaroxaban, apixaban, and edoxaban), as well as patients with coagulopathy secondary to severe liver disease or acute bleeding.

In the setting of both direct thrombin inhibitors and factor Xa inhibitors, animal studies of 4F-PCC (Beriplex) have demonstrated some promising results, but clinical application of animal studies is limited. One small human study comparing 4F-PCC (Beriplex), 3F-PCC, and saline, examined ex vivo bleeding parameters in 35 healthy volunteers given rivaroxaban. The study showed partial correction in some, but not all ex vivo bleeding parameters studied. Of note, anti-
factor Xa activity was not affected by 4F-PCC administration. A small, randomized, double-blind, placebo-controlled, crossover study evaluated the effect of a 4F-PCC (Cofact, non-U.S. product) on various coagulation parameters in 12 healthy human volunteers receiving dabigatran or rivaroxaban. The 4F-PCC (50 IU/kg single dose) was found to correct coagulation parameters in subjects receiving rivaroxaban but not dabigatran. Because Cofact is a different formulation than Kcentra, it is unclear whether similar results would be observed with Kcentra. Further, the correlation of surrogate laboratory coagulation measures with clinical reversal of anticoagulant-associated bleeding with target specific oral anticoagulants cannot be ascertained based on bleeding parameter data alone.

Only one placebo-controlled trial of 4F-PCC (Beriplex) has examined actual bleeding time in human subjects who received a non-VKA oral anticoagulant. In part 2 of this phase 1, 2-period, crossover study, 93 healthy volunteers (not taking oral anticoagulants) were sequentially enrolled into dose cohorts (50 IU/kg, 25 IU/kg, or 10 IU/kg) then randomized to 4F-PCC or placebo in period 1 and the alternate treatment in period 2. After randomization, a baseline punch biopsy was performed without any treatment (day -1). On day 1, each subject received a single oral dose of edoxaban 60mg, followed by an infusion of either placebo or 4F-PCC 2.25 hours later. Thirty minutes after the end of the infusion, a punch biopsy was performed. The primary endpoint was bleeding time, but bleeding volume was also measured. Secondary endpoints included endogenous thrombin potential (ETP) and prothrombin time (PT). This procedure (not including baseline punch biopsy) was repeated for period 2 with each subject receiving the alternative treatment (placebo or 4F-PCC) after a washout period of at least 14 days. Administration of 4F-PCC 50 IU/kg resulted in complete reversal of the effects of edoxaban on bleeding duration, as compared to baseline punch biopsy bleeding duration. The 25 IU/kg dose of 4F-PCC partially reversed the effects of edoxaban on bleeding duration, but the 10 IU/kg dose of 4F-PCC had similar effect to placebo with regards to bleeding duration. This pattern was similar for each dose with regards to bleeding volume. ETP measured 30 minutes after the start of study infusion also reflected this dose-dependent similar pattern of reversal; however, it should be noted that at later time points ETP exceeded pre-edoxaban values for all doses of 4F-PCC. The effect of edoxaban on PT was not completely reversed by 4F-PCC at any dose; however, higher doses of 4F-PCC appeared to produce greater reduction in PT prolongation, suggesting a dose-dependent response. This study did not evaluate anti-factor Xa activity. No deaths, serious adverse events, or thromboembolic events occurred during this study and the most common adverse events were upper respiratory tract infection (n=3) and nausea (n=2). No clinical trials have evaluated any 4F-PCC in patients with acute major bleeding while receiving therapeutic treatment with any non-VKA oral anticoagulant.

One small prospective observational study of 4F-PCC was conducted in patients with a coagulation deficit due to severe liver damage. In this study, 22 patients with either an acute hemorrhagic episode or a necessary urgent surgical intervention were treated with 4F-PCC (Beriplex). Efficacy was assessed by subjective physician rating, with efficacy in 76% of patients classified as ‘very good’ and 24% as ‘satisfactory’ after two treatments with 4F-PCC.

A small, retrospective, industry-funded analysis examined the effect of 4F-PCC (Beriplex) in 50 surgical patients, 38 of whom had bleeding not associated with anticoagulation. All patients received 4F-PCC (median dose in bleeding patients was 2,000 IU), but additional ‘conservative therapies’ were given at the physician’s discretion. These therapies included red blood cells, fresh frozen plasma, platelets, desmopressin, vitamin K, and fibrinogen concentrate. In patients not treated with anticoagulation, the mean pre-treatment INR was 1.7 and was reduced to a mean INR of 1.4 following surgery (p<0.001; mean duration from treatment to post-treatment INR was 147.
minutes). Hemostatic efficacy, including cessation of bleeding, was assessed based on documentation obtained via review of patient charts and medical records. In the 38 patients with acute bleeding, 11 had surgical bleeding and 27 had diffuse bleeding without evidence of damaged blood vessels. Bleeding stopped following 4F-PCC administrations in 4 of the 11 patients with surgical bleeding (36%) and 26 of the 27 patients with diffuse bleeding (96%). However, this study did not include a control group of patients who did not receive 4F-PCC.

**Current VA National Formulary Alternatives**

Phytonadione (vitamin K) is on the VA National Formulary; however, in instances of urgent acute bleeding in which 4F-PCC or plasma would be used, vitamin K alone would not be considered an alternative. In instances requiring 4F-PCC or plasma for urgent reversal of VKA, vitamin K should be co-administered.

**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.\(^1\)\(^,\)\(^2\)\(^1\)
- Dosing calculations are based on the quantity (international units) of factor IX in the product.\(^1\)Exact contents are labeled on the vial and will vary from vial to vial\(^1\) (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).\(^1\) The Institute for Safe Medication Practices (ISMP) reported that several dosing errors have occurred because of calculations based on 500 units or 1000 units per vial rather than on the exact potency per vial, which varies.\(^2\)\(^2\)
- 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.\(^1\) In the randomized, plasma-controlled clinical trial of 4F-PCC used for FDA-approval of Kcentra, the protocol stipulated that the baseline INR be obtained within 3 hours prior to infusion.\(^2\)\(^3\)
- 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.\(^1\)\(^,\)\(^2\)\(^1\)

<table>
<thead>
<tr>
<th>Pre-treatment INR</th>
<th>4F-PCC Dose (IU of factor IX per kg body weight(^*))</th>
<th>Maximum dose (IU of factor IX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 to &lt;4</td>
<td>25</td>
<td>2500</td>
</tr>
<tr>
<td>4 to 6</td>
<td>35</td>
<td>3500</td>
</tr>
<tr>
<td>&gt;6</td>
<td>50</td>
<td>5000</td>
</tr>
</tbody>
</table>

*Dosing is based on actual body weight.\(^2\)\(^4\) 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.\(^1\)

- Four-factor-PCC should be given concomitantly with vitamin K to help replenish clotting factors after the effects of 4F-PCC have diminished. In the largest randomized controlled trial of 4F-PCC, patients received slow IV infusion of vitamin K in accordance with ACCP 2008 guidelines (5 to 10 mg) or by local clinical practice.\(^5\)\(^,\)\(^2\)\(^3\) The subsequent 2012 ACCP guidelines include the same recommendations for vitamin K administration.\(^1\)\(^1\)
- Four-factor-PCC should not be mixed with other products and should be administered through a separate infusion line from other drugs. 4F-PCC should be administered at a
rate of 3 units/kg/min, up to a maximum rate of ~210 units/min. No blood should enter the syringe with 4F-PCC, given the possibility of fibrin formation.\(^1\)

- The effectiveness and safety of repeat dosing has not been established and is not recommended.\(^1\)
- Four-factor-PCC requires reconstitution with the provided diluent via the Mix2Vial transfer set included within Kcentra packaging prior to administration.\(^1\)

**Efficacy**

**Efficacy Measures**

- Achievement of “effective” hemostasis for those with acute bleeding, defined as cessation of bleeding in \(\leq 4\) hours after the end of infusion and no additional coagulation intervention required within 24 hours from the start of infusion (or similar)
- Maintenance of “effective” hemostasis for those requiring urgent surgical or invasive procedures is determined based on the comparison between actual and predicted blood loss, a subjective hemostasis rating, and no additional coagulation intervention being required
- Rapid INR reduction to \(\leq 1.3\) at 30 minutes after the end of infusion

FDA initial approval of 4F-PCC in the setting of acute major bleeding was based on one published randomized, open-label plasma-controlled trial.\(^{14,23}\) The FDA-approval of the expanded indication to include patients requiring urgent surgical or invasive intervention was based on an originally unpublished randomized, plasma-controlled trial in patients requiring urgent surgery or invasive procedures,\(^{1,14}\) which has since been published\(^{24}\) as well as one single-arm study in patients with either acute bleeding or requiring urgent invasive procedures.\(^{1}\)

The published open-label, randomized controlled trial comparing 4F-PCC (Beriplex) to plasma in adult subjects with acute major bleeding associated with an elevated INR (i.e., \(\geq 2\)) secondary to VKA therapy.\(^{23}\) Subjects were excluded if expected survival was less than 3 days or if invasive surgery was planned in less than 1 day. Patients with acute trauma for which reversal of VKA alone would not be expected to control or resolve the acute bleeding event were also excluded. Additional exclusions included patients receiving heparin or low-molecular weight heparin within the last 24 hours, those with a history of a thromboembolic event, acute coronary syndrome, cerebrovascular accident, transient ischemic attack, severe peripheral artery disease, or disseminated intravascular coagulation (DIC) within the last 3 months, and those with a known history of antiphospholipid syndrome or deficiency in factors II, VII, IX, X or protein C or S.\(^{23}\)

One hundred three patients received 4F-PCC and 109 received plasma, per protocol. 4F-PCC was administered utilizing weight-based dosing according to the baseline INR. The mean age of the study population was 70 years old. The most common indication for anticoagulation was arrhythmia (57.1% and 51% in the 4F-PCC and plasma groups, respectively), followed by thromboembolic events (18.4% and 20.2%, respectively). The majority of bleeding events were gastrointestinal or other nonvisible bleeding; 12% of patients presented with an intracranial hemorrhage. The median baseline INR was 3.9 in the 4F-PCC group and 3.6 in the plasma group, but overall baseline INRs ranged from 1.8 to 38.9. All except 4 patients in the 4F-PCC group and 2 patients in the plasma group received vitamin K during the study. Outcomes were adjudicated by a blinded efficacy adjudication board (EAB). In regards to the first co-primary efficacy endpoint, 4F-PCC was noninferior to plasma for achieving effective hemostasis (see table 4). The second co-primary efficacy endpoint demonstrated 4F-PCC superiority over plasma in regards to rapid INR reduction to \(\leq 1.3\) at 30 minutes after the end of the study infusion.
Despite superiority of 4F-PCC with regards to rapid correction of INR, there was no difference in length of hospital stay between the two groups.\textsuperscript{23}

Table 4: Co-primary efficacy endpoint results for open-label randomized controlled trial in patients with acute bleeding events\textsuperscript{23}

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>4F-PCC</th>
<th>Plasma</th>
<th>Absolute difference [95% CI]</th>
<th>Results of 4F-PCC vs. Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achievement of effective hemostasis within 24 hours</td>
<td>72.4%</td>
<td>65.4%</td>
<td>7.1% [-5.8 to 19.9]</td>
<td>Noninferior</td>
</tr>
<tr>
<td>Achievement of INR ≤1.3 at 30 minutes after the end of infusion</td>
<td>62.2%</td>
<td>9.6%</td>
<td>52.6% [39.4 to 65.9]</td>
<td>Superior</td>
</tr>
</tbody>
</table>

An open-label, randomized, plasma-controlled trial evaluated 4F-PCC in patients who had received VKA therapy, with an INR ≥ 2, and in whom an emergency surgical or invasive intervention was required within 24 hours.\textsuperscript{1,14,24} Patients were excluded based on similar criteria to the published trial in acute major bleeding with regard recent use of parenteral anticoagulants, and recent thromboembolic events. Additionally patients were excluded if IV vitamin K or cessation of VKA alone could adequately correct the coagulopathy before the urgent surgical procedure, or if vitamin K had been given IV more than 3 hours prior or by mouth more than 6 hours prior to study intervention, or if the patient had a life expectancy of less than 2 months.\textsuperscript{24}

A total of 176 patients were randomized to, and received treatment with either 4F-PCC or plasma, based on the same weight-based dosing protocol as the published acute bleeding randomized trial.\textsuperscript{14,24} Median baseline INR for both groups was 2.9 and ranged from 2 to 17 in the 4F-PCC group and from 2 to 26.7 in the plasma group.\textsuperscript{24} The majority of patients in both groups (64% and 70%, respectively) had a history of thromboembolic events including coronary artery, cerebrovascular, or peripheral vascular disease.\textsuperscript{14} The most common type of surgical intervention was major orthopedic surgeries (21%), but the category of “other surgical” procedures comprised 58% of all procedures.\textsuperscript{24} Four-factor-PCC was superior to plasma in regards to the primary efficacy outcome of hemostatic efficacy from the time of infusion until the end of surgery (see table 5). Hemostatic efficacy was assessed based on the difference between predicted and actual blood losses, subjective hemostasis rating, and the need for additional blood products containing coagulation factors. Four-factor-PCC was also superior to plasma with regard to the reduction in INR to ≤ 1.3 thirty minutes after the end of study infusion was completed.\textsuperscript{24} In regards to secondary endpoints, there was no difference in the number of patients requiring red blood cells (16% in the 4F-PCC group and 15% in the plasma group; p=0.83) or the mean number of red blood cells transfused (0.3 units and 0.4 units, respectively; p=0.91).

Table 5: Efficacy results for randomized controlled trial in patients requiring urgent surgical or invasive intervention\textsuperscript{1}

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>4F-PCC</th>
<th>Plasma</th>
<th>Absolute difference [95% CI; p-value]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective hemostasis throughout procedure</td>
<td>89.7%</td>
<td>75.3%</td>
<td>14.3% [2.8 to 25.8; 0.0142]</td>
</tr>
<tr>
<td>Achievement of INR ≤1.3 at 30 minutes after the end of infusion</td>
<td>55.2%</td>
<td>9.9%</td>
<td>45.3% [31.9 to 56.4; &lt;0.0001]</td>
</tr>
</tbody>
</table>
The small non-controlled prospective clinical trial of 4F-PCC (Beriplex) demonstrated rapid reversal of VKAs, as measured by INR ≤ 1.3 thirty minutes after completion of 4F-PCC infusion, and ‘very good’ hemostatic efficacy in over 90% of adult patients presenting with an INR > 2 on VKA therapy and either acute bleeding or requiring emergency surgical or invasive diagnostic intervention. Hemostatic efficacy was assessed by treating physician with ‘very good’ hemostatic efficacy defined as “prompt cessation of existing bleeding and/or a rapid decline in INR” as compared to ‘satisfactory’ efficacy being that requiring “>1-2 hours,” ‘questionable’ efficacy as that having a “>2 hour delay in bleeding cessation and INR decrease,” or ‘none’ having no effect on bleeding or INR. This study excluded patients having received blood products within 2 weeks, with known hereditary protein C deficiency, life expectancy < 3 months, patients with less than 2 weeks of stable anticoagulation following a recent venous thromboembolism, acute ischemic cardiovascular disorders, DIC, or sepsis. A total of 43 patients were included, with 40% presenting for acute bleeding and 60% requiring urgent invasive procedures. The median baseline INR was 3.2, with 61% of patients having a baseline INR greater than 2 and less than 4, and 23% of patients with INR >6. The primary endpoint of INR ≤ 1.3 30 minutes postinfusion was met by 93% of patients; those not meeting this endpoint all had 30 minute postinfusion INRs of 1.4. Physician rated clinical hemostatic efficacy was ‘very good’ in 93% of patients.

Summary of efficacy findings
- Four-factor-PCC is non-inferior to plasma for achievement of effective hemostasis within 24 hours of initiating infusion in patients with acute bleeding associated with VKA therapy.
- Four-factor-PCC is superior to plasma for achievement of INR≤1.3 within 30 minutes of completed infusion of study drug.
- Four-factor-PCC is superior to plasma for the maintenance of effective hemostasis from time of infusion until completion of the urgent surgery or invasive procedure for patients on VKA therapy without active bleeding but requiring urgent surgical or invasive procedures.
- Four-factor-PCC did not reduce length of hospital stay as compared to plasma in patients with acute major bleeding (not assessed in surgical patients).

Adverse Events (Safety Data)
Safety data for FDA approval of 4F-PCC is based on one published randomized, plasma-controlled trial in patients with acute bleeding and one unpublished randomized, plasma-controlled trial in patients requiring urgent surgery or invasive procedures, which has since been published, as well as one single-arm study in patients with either of the above indications for VKA reversal.1,14,23,24

Deaths and Other Serious Adverse Events
In the phase IIIb randomized plasma-controlled trial of 4F-PCC for reversal of VKA in patients with acute major bleeding, serious adverse events were reported in 31.1% and 23.9% of patients treated with 4F-PCC and plasma, respectively. The study was not powered to compare safety events, but these were reported. Of note, 6 serious adverse events were deemed to be treatment-related, 2 in the 4F-PCC group and 4 in the plasma group. In the 4F-PCC group, there was one deep vein thrombosis on day 13 post-infusion and one ischemic stroke on day 43 post-infusion. In the plasma group, there were 2 myocardial infarctions, both on day one, one instance of fluid overload on day 3, and one instance of respiratory failure on day one. Thromboembolic events occurred in 8 patients receiving 4F-PCC and 7 in patients receiving plasma (7.8% and 6.4%, respectively, no p-value provided). Not all thromboembolic events were considered serious or treatment related. Because it is logical that reversal of anticoagulation would increase the risk of
thromboembolic events, and because no studies have been powered to detect a difference in thromboembolic events between 4F-PCC and plasma, the association of thromboembolism specifically with 4F-PCC is unclear. Within the 45 day follow-up period, 10 deaths occurred in the 4F-PCC group and 5 occurred in the plasma group. One death in the 4F-PCC group was deemed possibly related to treatment; none of the deaths in the plasma group were considered treatment related.\textsuperscript{23}

Rates of all adverse events and serious adverse events in the urgent surgical or invasive procedures trial, were similar between the two groups, but the specifics of all serious adverse events are not available.\textsuperscript{14,24} Table 7 presents the information available as of March 2015.

Table 7: Safety data from the randomized controlled trial in patients requiring urgent surgical or invasive intervention\textsuperscript{14,24,26}

<table>
<thead>
<tr>
<th>Event</th>
<th>4F-PCC</th>
<th>Plasma</th>
<th>Difference [95% CI; p-value]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>49 (55.7%)</td>
<td>53 (60.2%)</td>
<td>-4.5% [NR; 0.54]</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>22 (25%)</td>
<td>23 (26.1%)</td>
<td>-1.1% [NR; NR]</td>
</tr>
<tr>
<td>Death (at 45 days)</td>
<td>3 (3.4%)</td>
<td>8 (9.1%)</td>
<td>-5.7% [-14.6 – 2.7; 0.21]</td>
</tr>
<tr>
<td>Thromboembolic event</td>
<td>6 (6.8%)</td>
<td>7 (8%)</td>
<td>-1.1% [-10.3 – 8.0; 0.77]</td>
</tr>
<tr>
<td>Serious thromboembolic event</td>
<td>3 (3.4%)</td>
<td>6 (6.8%)</td>
<td>-3.4% [-11.8 – 4.6; NR]</td>
</tr>
<tr>
<td>Fluid overload or similar cardiac event</td>
<td>3 (3.4%)</td>
<td>11 (12.5%)</td>
<td>-9.1 [-18.6 – 0.1; 0.0478]</td>
</tr>
<tr>
<td>Serious fluid overload or similar cardiac event\textsuperscript{26}</td>
<td>1 (1.1%)</td>
<td>2 (2.3%)</td>
<td>-1.1 [-7.7 – 5.1; NR]</td>
</tr>
</tbody>
</table>

CI - confidence interval; NR - not reported

Within the small non-controlled prospective clinical trial of 4F-PCC, 58% of patients experienced an adverse event, including 14% of all patients experiencing a serious adverse event. Only one serious adverse event, a fatal pulmonary embolism, was deemed possibly 4F-PCC-related; although without a control, it is difficult to evaluate the significance of this.\textsuperscript{25}
Common Adverse Events
No adverse effects were reported in greater than 10% of patients receiving 4F-PCC in randomized controlled trials. The most commonly reported adverse effects are listed below.¹

Table 8: Common adverse events associated with 4F-PCC from RCTs¹

<table>
<thead>
<tr>
<th>Event</th>
<th>4F-PCC (n=191)</th>
<th>Plasma (n=197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>14 (7.3%)</td>
<td>7 (2.6%)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>8 (4.2%)</td>
<td>3 (1.5%)</td>
</tr>
<tr>
<td>Respiratory distress/dyspnea/hypoxia</td>
<td>7 (3.7%)</td>
<td>10 (5.1%)</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>3 (1.6%)</td>
<td>10 (5.1%)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>12 (6.3%)</td>
<td>8 (4.1%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (2.1%)</td>
<td>7 (3.6%)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>9 (4.7%)</td>
<td>2 (1.0%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>8 (4.2%)</td>
<td>6 (3.0%)</td>
</tr>
<tr>
<td>Fluid overload including cardiac congestion</td>
<td>5 (2.6%)</td>
<td>16 (8.1%)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>9 (4.7%)</td>
<td>6 (3.0%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>9 (4.7%)</td>
<td>6 (3.0%)</td>
</tr>
<tr>
<td>Hypotension including orthostatic hypotension, hypotension, and hemorrhagic shock</td>
<td>14 (7.3%)</td>
<td>10 (5.1%)</td>
</tr>
<tr>
<td>Skin laceration/contusion/subcutaneous hematoma</td>
<td>8 (4.2%)</td>
<td>5 (2.5%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>11 (5.8%)</td>
<td>16 (8.1%)</td>
</tr>
</tbody>
</table>

Tolerability
Given the difference in infusion volumes between 4F-PCC and plasma, it has been hypothesized that 4F-PCC may be associated with lower risk of fluid overload compared to plasma. Reported mean infusion volumes from the two randomized controlled trials are displayed in table 9. Given the smaller volume to be infused, the 4F-PCC infusion is faster than that of plasma. In the acute bleeding randomized controlled trial, the median infusion duration for 4F-PCC was 17 minutes, compared to 148 minutes for plasma.²³ In the urgent surgery or invasive procedure trial, the mean duration of infusion was 20.9 minutes compared to 140.7 minutes for plasma.²⁴ Neither of the randomized, plasma-controlled studies was powered to detect a difference in safety or tolerability outcomes, but there is a numerically lower rate of fluid overload events in patient having received 4F-PCC compared to plasma (table 8).²³²⁴ In the acute bleeding trial, 5 patients receiving 4F-PCC and 14 receiving plasma had fluid overload or cardiac events (4.9% and 12.9%, respectively) but none of those in the 4F-PCC and 7 in the plasma group were deemed treatment related by investigators.²³ With so few events, the significance of this difference is unknown. In the trial of 4F-PCC in urgent invasive procedures or surgery, the difference in all fluid overload events was statistically significant based on the 95% confidence interval and p-value²⁴, but serious fluid
overload events, as documented in the FDA clinical review\textsuperscript{14} and in manufacturer-supplied data\textsuperscript{26}, were similar (table 7). Because some of this data remains unpublished in peer-reviewed literature, interpretation and clinical application is difficult.\textsuperscript{14,24,26}

Table 9: Mean infusion volumes in plasma-controlled clinical trials of 4F-PCC\textsuperscript{23,24}

<table>
<thead>
<tr>
<th>RCT:</th>
<th>4F-PCC</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute bleeding\textsuperscript{23}</td>
<td>99.4 mL</td>
<td>813.5 mL</td>
</tr>
<tr>
<td>Urgent invasive procedure\textsuperscript{24}</td>
<td>89.7 mL</td>
<td>818.7 mL</td>
</tr>
</tbody>
</table>

**Contraindications\textsuperscript{1}**

Kcentra is contraindicated in:

- Patients with known anaphylactic or severe systemic reactions 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.
- Patients with disseminated intravascular coagulation (DIC).
- Patients with known heparin-induced thrombocytopenia (HIT). 4F-PCC contains heparin
  - **Heparin-induced Thrombocytopenia**: Patients with known HIT were excluded from both randomized, plasma-controlled, phase III studies of 4F-PCC because 4F-PCC contains heparin. As such, any history of HIT is considered a contraindication according to the FDA-approved labeling.\textsuperscript{1} However, 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.\textsuperscript{27} 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.

**Warnings and Precautions\textsuperscript{1}**

**Boxed Warning: Arterial and Venous Thromboembolic Complications\textsuperscript{1}**

Patients being treated with VKA therapy have underlying disease states that predispose them to thromboembolic events. Potential benefits of reversing VKA should be weighed against the potential risks of thromboembolic events, especially in patients with the history of a thromboembolic event. Resumption of anticoagulation should be carefully considered as soon as the risk of thromboembolic events outweighs the risk of acute bleeding.\textsuperscript{1}

- Both fatal and non-fatal arterial and venous thromboembolic complications have been reported with 4F-PCC in clinical trials and post marketing surveillance. Monitor patients receiving 4F-PCC for signs and symptoms of thromboembolic events.\textsuperscript{1}
- Four-factor-PCC was not studied in subjects who had a thromboembolic event, myocardial infarction, disseminated intravascular coagulation, cerebral vascular accident, transient ischemic attack, unstable angina pectoris, or severe peripheral vascular disease within the prior 3 months. Four-factor-PCC may not be suitable in patients with thromboembolic events in the prior 3 months.\textsuperscript{1}

**Hypersensitivity Reactions\textsuperscript{1}**
Hypersensitivity reactions including flushing, urticaria, tachycardia, anxiety, angioedema, wheezing, nausea, vomiting, hypotension, tachypnea, dyspnea, pulmonary edema, and bronchospasm have been observed with 4F-PCC. If severe allergic reaction or anaphylactic type reactions occur, immediately discontinue 4F-PCC, and institute appropriate treatment.

**Thromboembolic Risk/Complications**

As anticoagulation with VKAs is indicated to reduce the risk of thromboembolic events, reversal of VKA increases the risk of such events. As would be expected, venous and arterial thromboembolic events (including acute myocardial infarction, arterial thrombosis, pulmonary embolism and venous thrombosis) and disseminated intravascular coagulation have been reported with 4F-PCC. Because patients with a history of thrombotic events, myocardial infarction, cerebral vascular accident, transient ischemic attack, unstable angina pectoris, severe peripheral vascular disease, or disseminated intravascular coagulation, within the previous 3 months were excluded from participating in the plasma-controlled randomized controlled trials, the safety in this population is unknown.

**Transmissible Infectious Agents**

Because 4F-PCC is made from human blood, it may carry a risk of transmitting infection. There is also the possibility that unknown infectious agents may be present in such products. Kcentra is manufactured using two virus reduction steps to minimize the risk of transmitting potentially infectious agents; however, blood-derived products may still carry risk. Concomitant administration of blood components and/or other plasma-derived products generally confounded reports of virus transmission. No causal relationship to 4F-PCC administration was established for any of these reports since introduction of a virus filtration step in 1996.

**Special Populations**

**Pregnancy, Labor, and Delivery**

Four-factor-PCC has not been studied in pregnant humans or animals; therefore, it is classified as an FDA Pregnancy Category C because its potential to cause fetal harm is unknown. Safety and efficacy have also not been studied in labor and delivery.

**Lactation**

No studies have been performed to determine if 4F-PCC is excreted in human breast milk.

**Geriatric Use**

In clinical trials of 4F-PCC, 66% of patients were at least 65 years of age or older and 39% were 75 years or older. Safety of 4F-PCC was similar in these subgroups compared with younger adult patients.

**Renal and Hepatic Disease**

Patients with renal or hepatic disease were not specifically excluded from the randomized, plasma-controlled trial of 4F-PCC; however, data on renal and hepatic function were not reported. One non-randomized trial evaluated off-label use of 4F-PCC in 22 patients with severe liver damage, but did not compare it to those with normal liver function. No precautions or dose adjustments are recommended regarding the use of 4F-PCC in patients with renal or hepatic disease.

**Sentinel Events**

None
Look-alike / Sound-alike (LA / SA) Error Risk Potential

As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

<table>
<thead>
<tr>
<th>NME Drug Name</th>
<th>Lexi-Comp</th>
<th>First DataBank</th>
<th>ISMP</th>
<th>Clinical Judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin complex concentrate 500, 1000 unit SDV</td>
<td>Factor IX Complex (Human) [Factors II, IX, X]*</td>
<td>None</td>
<td>None</td>
<td>Protein C Concentrate (Human) Protamine Thrombin</td>
</tr>
<tr>
<td>Kcentra</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Kayexalate Kaletra</td>
</tr>
</tbody>
</table>

*The term “Prothrombin Complex Concentrate” or “PCC” has been used to describe both Factor IX Complex (Human) [Factors II, IX, X] and Prothrombin Complex Concentrate (Human) [(Factors II, VII, IX, X), Protein C, Protein S]. Prothrombin Complex Concentrate (Human) [(Factors II, VII, IX, X), Protein C, Protein S] (Kcentra, Octaplex) contains therapeutic levels of factor VII component and should not be confused with Factor IX complex (Human) [Factors II, IX, X] (Bebulin, Profilnine) which contains low or nontherapeutic levels of factor VII.

Drug Interactions

Drug-Drug Interactions
None known

Drug-Lab Interactions
None known

Acquisition Costs

Please refer to the last page for VA drug acquisition costs. Prices shown in this internal document may include additional discounts available to VA. This information is considered strictly confidential and must not be shared outside of VA. All cost information will be removed from the document when posted to the PBM website.

Pharmacoeconomic Analysis

At the time of writing, there are no published pharmacoeconomic evaluations of Kcentra.

Conclusions

Based on one open-label, randomized controlled trial, 4F-PCC was shown to be non-inferior to plasma in achieving effective hemostasis (cessation of bleeding within 4 hours of the end of the infusion and no additional coagulation intervention required within 24 hours) for the reversal of VKAs in adults with acute major bleeding. Although superiority over plasma was not demonstrated in regards to achievement of effective hemostasis at 24 hours, length of hospital stay, or mortality, 4F-PCC was superior to plasma in achieving an INR of ≤ 1.3 within 30 minutes after the completed infusion. For patients treated with VKAs requiring urgent surgical or invasive procedures, not related to acute bleeding, 4F-PCC was found to be superior to plasma for maintaining effective hemostasis (based on comparison of actual and predicted blood loss,
subjective hemostasis rating, and no additional coagulation products being required) through the procedure based on one open-label randomized study. While no randomized controlled trials have been powered to compare the safety of 4F-PCC versus plasma, reported rates of serious and non-serious adverse events appear to be similar overall. Because of the larger volume of plasma required compared to 4F-PCC, patients prone to volume overload may tolerate 4F-PCC better than plasma. Fluid overload events were numerically less frequent in patients treated with 4F-PCC compared to plasma; however, further evaluation is needed to determine the validity of this finding as overall numbers of volume overload in the randomized plasma-controlled trials were small. Logistically, 4F-PCC can also be administered faster than plasma, as it does not need to be thawed, it does not require blood typing, and the smaller infusion volume can be infused more rapidly. Reversal of anticoagulation with 4F-PCCs is associated with a risk of thromboembolic events. Rates of thromboembolic events with 4F-PCC were between 6 and 8 percent in the two randomized, plasma-controlled trials; however, based on the current evidence, it is unclear if 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.

Without clear evidence of superior tolerability, effective hemostasis at 24 hours, length of hospital stay, or mortality compared to plasma, and a cost per patient more than 20 times that of plasma, Kcentra should not replace plasma for routine reversal of VKAs in acute major bleeding. 4F-PCC is superior to plasma with respect to rapid INR correction and for maintenance of effective hemostasis during urgent invasive procedures. It may be beneficial for VKA reversal in adult patients with intracranial hemorrhage, life threatening bleeding or a need for urgent surgery or invasive procedure. There is insufficient evidence to support off-label use of 4F-PCC at this time.

Appendix: Clinical Trials

A literature search was performed on PubMed/Medline (1966 to August 2014) using the search terms four-factor prothrombin complex concentrate, 4-factor prothrombin complex concentrate, Beriplex and Kcentra. The search was limited to studies performed in humans and published in English language. Reference lists of review articles and the manufacturer’s AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.
References


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