UPMC System Pharmacy and Therapeutics Committee
Formulary Review

Name: Prothrombin Complex Concentrate (Human) (Kcentra®, CSL Behring LLC)

Requested by: Anticoagulation Task Force, L. Alarcon MD (Trauma); S. Gunn MD (CCM)

Recommendations

- It is recommended that four-factor prothrombin complex concentrate (PCC) [Kcentra®] be added to formulary for inpatient/ED use:
  - Urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist (VKA) therapy in adult populations with acute active, life-threatening bleeding or requiring emergency surgery
    - Shown non-inferior to FFP at achieving hemostasis at 24 hours after infusion start (1C)
    - Shown superior to FFP at reducing INR to < 1.3 within 30 minutes of infusion start (1C)
    - Preferred to FFP for the urgent reversal of warfarin according to most recent *CHEST* guidelines (2C)
      - Disadvantages to FFP include time needed to thaw and infuse, and fluid overload due to large volumes needed
  - Urgent reversal of coagulation factor deficiency induced by factor Xa inhibitors (i.e., rivaroxaban, apixaban) in adult populations with acute active, life-threatening bleeding or requiring emergency surgery
    - Alternative to factor VIIa in this scenario
  - If urgent reversal not necessary, bleeding not life-threatening, and patient is not volume-challenged, FFP is recommended. (1E)
- Kcentra® is dosed according to factor IX potency (units) and is individualized based on the patient pre-dose INR and body weight (kg).
  - Dosing = 25 units/kg (INR 2.0 to <4.0); 35 units/kg (INR 4.0-6.0); 50 units/kg (INR > 6.0)
  - Vitamin K is to be administered concurrently to patients receiving Kcentra®.
- Contraindications include patients with known anaphylactic or severe systemic reactions to Kcentra® or any components in Kcentra® including **heparin**, Factors II, VII, IX, X (FII, FVII, FIX, FX), Proteins C and S, antithrombin III (ATIII) and human albumin
- Boxed Warning: Kcentra® may not be suitable in patients with thromboembolic events in the prior three months

Executive Summary

Kcentra® is a four-factor prothrombin complex concentrate (PCC) approved by the FDA on April 29, 2013 for reversal of warfarin anticoagulation in patients experiencing serious bleeding events. It is the only four-factor PCC available in the U.S. at this time. There are currently no direct comparisons of Kcentra® with the available three-factor PCC agents. Kcentra® contains inactive forms of FII, FVII, FIX, FX as well as Proteins C and S, ATIII, heparin, and human albumin. It is prepared from human U.S. Source Plasma and is then purified, heat-treated, nanofiltered, and lyophilized into a powder for reconstitution. Kcentra® is supplied as a 500-unit single dose vial. Kcentra® is dosed according to Factor IX potency and is individualized based on the patient's baseline International Normalized Ratio (INR) and body weight. The cost of Kcentra® is $1.27 per unit; a single dose of Kcentra® for an 80 kg patient costs $5,080. Similar products under different proprietary names (e.g. Beriplex®, CSL Behring) have been available in Europe and Canada since 1996. In available clinical trials, Kcentra® was shown to be non-inferior to fresh frozen plasma (FFP) in achieving hemostasis after 24 hours. Kcentra® and other internationally available four-factor PCC have demonstrated superior efficacy in reducing the INR ≤ 1.3 after 30 minutes and up to 12 hours after the start of the infusion, when compared to FFP in patients with VKA-associated acute major bleeding. Studies and post-marketing data have shown that the risk of thromboembolic events, viral transmission, and heparin-induced thrombocytopenia type II (HIT-II) with Kcentra® is rare, albeit serious. KCentra® carries a boxed warning for arterial and venous thromboembolic complications. The American College of Chest Physicians (ACCP) in their 2012 Guidelines suggest that the use of four-factor PCC over plasma for the rapid reversal of anticoagulation in patients with VKA-associated bleeding.

***Note: Beriplex® is a four-factor PCC manufactured by CSL Behring that has been available in Europe and Canada since 1996. Kcentra® is the identificalBeriplex® product, given a U.S. trade. All information contained within the manufacturer's information for Kcentra® uses the trade names Beriplex® and Kcentra® interchangeably.*

Pharmacology/Pharmacodynamics

KCentra® is prepared from human U.S. Source Plasma and is then purified, heat-treated, nanofiltered, and lyophilized into a powder for reconstitution. Kcentra® contains the vitamin K-dependent coagulation factors II, VII, IX and X, together known as the "prothrombin complex," and the antithrombotic Proteins C and S. Factor IX is the lead factor in the preparation potency; dosing is based on Factor IX potency units. A dose-dependent acquired deficiency of the vitamin K-dependent coagulation factors occurs during VKA treatment with agents such as warfarin. Vitamin K antagonists exert anticoagulant effects by blocking the carboxylation of glutamic acid residues of the vitamin K-dependent coagulation factors during hepatic synthesis, lowering both factor synthesis and function. The administration of Kcentra® rapidly increases plasma levels of the vitamin K-dependent coagulation factors II, VII, IX, and X as well as the antithrombotic Proteins C and S, thus restoring factor synthesis and clotting function.

A randomized controlled trial comparing Kcentra® to FFP in patients with acute major bleeding demonstrated that Kcentra® was superior in lowering the INR at the all measured study points in a 24-hour time period.[3] The INR differences between Kcentra® and FFP were statistically significant up to 12 hours after the start of infusion (Table 1; no p values reported).

Table 1: Median INR after Start of Infusion[3]

Median INR	Kcentra® (N=98)	Plasma (N=104)
Baseline	3.90 (1.8-20.0)	3.60 (1.9-38.9)
30 min	1.20 (0.9-6.7)	2.4 (1.4-11.4)
1 hr	1.30 (0.9-5.4)	2.1 (1.0-11.4)
2-3 hr	1.30 (0.9-2.5)	1.7 (1.1-4.1)
6-8 hr	1.30 (0.9-2.1)	1.5 (1.0-3.0)
12 hr	1.20 (0.9-2.2)	1.4 (1.0-3.0)
24 hr	1.20 (0.9-3.8)	1.3 (1.0-2.9)

Pharmacokinetics

Pharmacokinetic parameters were obtained from a study of 15 healthy subjects who received a single 50 units/kg dose of Kcentra® (Table 2).[4] Factor II was shown to have the longest terminal half-life and mean residence time, and factor VII had the shortest of both variables. Effects of a single dose are seen in 30 minutes, [3,10] and mean infusion duration is approximately 24 minutes (± 32 minutes).[10] Redosing with Kcentra® has not been studied and is not recommended.

Table 2: Vitamin K-Dependent Coagulation Factor Pharmacokinetics after a Single Kcentra® Infusion in Healthy Subjects (n=15)[4]

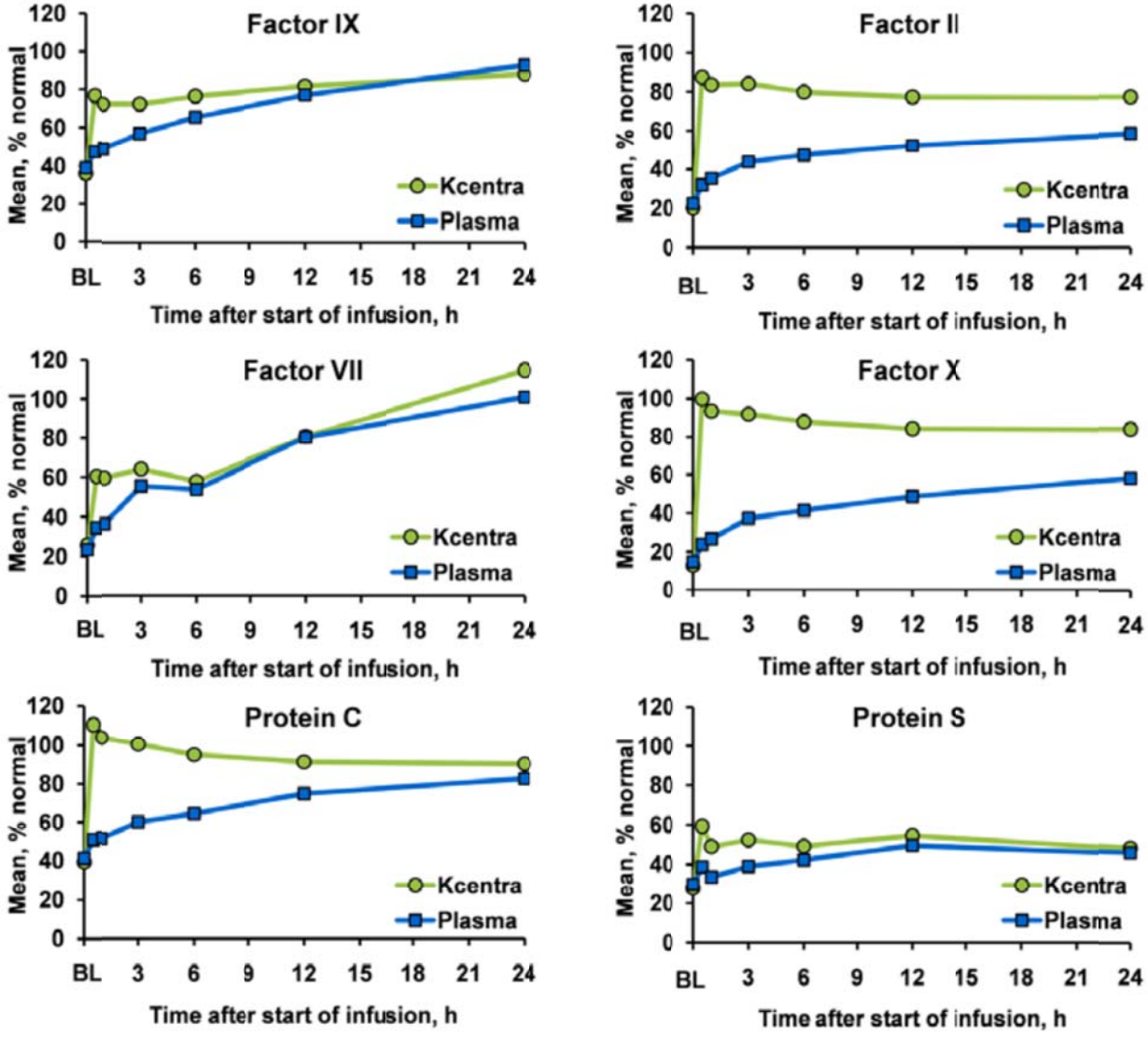
Parameter	Factor IX*	Factor II*	Factor VII*	Factor X*	Protein C†	Protein S†
Terminal half-life (h)	16.7 (14.2-67.7)	**59.7** (45.5-65.9)	**4.2** (3.9-6.6)	30.7 (23.7-41.4)	47.2 (9.3-121.7)	49.1 (33.1-83.3)
In-vivo Recovery (%/units/kg bw)	1.57 (1.38-1.90)	2.11 (1.95-2.45)	2.43 (2.33-2.77)	2.08 (1.94-2.39)	2.76 (2.16-3.31)	2.02 (1.46-2.70)
AUC (IU/dL x h)	14,90 (1,153-2,376)	6,577 (5,870-7,912)	424 (331-742)	6,707 (5,234-8,577)	5,276 (1,772-10,444)	3.667 (2,218-3,667)
Clearance (mL/kg x h)	3.63 (2.27-4.68)	0.97 (0.81-1.09)	7.06 (4.04-9.05)	1.25 (0.98-1.60)	1.1 (0.6-3.3)	1.1 (0.7-1.8)
Mean Residence Time (h)	21.6 (17.1-83.8)	**81.7** (62.0-87.6)	**6.1** (5.6-9.5)	44.3 (34.2-59.8)	57.0 (13.4-161.4)	69.2 (45.3-113.5)
Vd_{ss} (mL/kg)	92.4 (76.2-182.2)	71.0 (61.2-78.9)	41.8 (39.3-52.5)	56.1 (52.9-60.1)	62.9 (43.9-109.3)	76.6 (61.9-105.0)

* Values are reported as Median (Interquartile Range)

† Values are reported as Median (Min-Max)

Plasma levels of Coagulation Factors II, VII, IX, X and Antithrombotic Proteins C and S were measured after the infusion of Kcentra® versus FFP in studies of subjects requiring urgent reversal due to acquired deficiency of Vitamin K-dependent coagulation factors (Figure 1).[3] This study is not fully published (no p values reported). Administration of Kcentra® appears to result in quicker increases in mean factor plasma levels when compared to FFP from timepoint 0 – 12 hours, with eventual near convergence of factor levels except for Factor II and X, at 24 hours.

Figure 1: Mean Factor Levels (Factors II, VII, IX, X, Proteins C & S) over 24 hours[3]



Indications

FDA-approved indication(s)[10]

Kcentra® is indicated for the urgent reversal of acquired coagulation factor deficiency induced by VKA therapy in adult patients with acute major bleeding. Kcentra® is NOT indicated for urgent reversal of VKA anticoagulation in patients without acute major bleeding.

Off-label indication(s)

Kcentra® has been studied in the reversal of anticoagulation of rivaroxaban and dabigatran, although the data is limited to animal studies and one healthy human volunteer randomized, controlled trial (RCT).[2]

Clinical Trials

There are several clinical trials demonstrating the efficacy of four-factor PCC commercially available in non-U.S. countries (Table 3). Beriplex® is manufactured by CSL Behring and Kcentra® is the U.S. trade name given to Beriplex® (the package insert uses the trade names Beriplex® and Kcentra® interchangeably). An industry-sponsored, prospective, randomized, open-label, active controlled, multicenter Phase IIIb, non-inferiority study comparing Kcentra® (n = 88) and FFP (n = 88) has completed in November 2012.[11] Patients age >18 years requiring urgent surgery or invasive procedure within 24 hours, receiving a VKA with INR $\geq$2 were enrolled in the study. Efficacy data are not yet available. Safety data are presented in the Safety section of this review (see below).

Table 3: Summary of Efficacy Endpoints in Clinical Trials of Kcentra® [studies with N >10 patients]

Author Year Study Design	N	Patient population Age % Female (F)	Treatments	Efficacy Outcomes				Grade
				Hemostasis (24-hrs) n/% patients [95% CI]		Reduction of INR (≤1.3) at end of infusion n/% patients [95% CI]		
				Kcentra® (Beriplex®)	FFP	Kcentra® (Beriplex®)	FFP	
CSL Behring-sponsored[3] 2010 R, AC, OL, P, MC, non-inferiority	212	Elective, Acute major bleeding on VKA with INR ≥ 2 Age range 27-94 yrs % F not reported	Beriplex® 25, 35, or 50 units x 1 dose based on body weight (kg) and INR (n = 98) vs. FFP (n = 104)	71/72.4% [62.3; 82.6]	68/65.4% [52.9; 75.8]	61/62.2% (after 30 min) [52.6; 71.8]	10/9.6% (after 30 min) [3.9; 15.3]	1C (not fully published)
				Difference Kcentra – FFP (%) [95% CI] (7.1%) [-5.8; 19.9] **Non-inferior**		**Difference Kcentra – FFP (%) [95% CI]** (52.6%) [39.4; 65.9] **Superior**		
Comment: *202 patients completed the study of the original 212 (103 Kcentra®; 109 FFP). Kcentra® was deemed non-inferior to FFP if lower limit of 95% CI > -10%; Kcentra® was deemed superior to FFP if lower limit of 95% CI > 0. Efficacy was adjudicated as "effective" or "not effective" by a blinded, independent Endpoint Adjudication Board. All patients received concomitant Vitamin K*								
Pabinger et al.[5] 2008 O, P, SA, MC	43	Elective, Required surgical or invasive diagnostic intervention (n = 26) or acute bleeding on VKA with INR ≥ 2 (n = 17) 14% pts were < 60 yrs and 19% pts were > 80 yrs 51% F	Beriplex® 25, 35, or 50 units x 1 dose based on body weight (kg) and INR	93%	N/A	16/17 (94%) decrease within 30 min 40/93% ("very good" after 30 min) 2/4.7% ("satisfactory" after 30 min)	N/A	1C
Comment: Ratings for clinical hemostatic efficacy were "very good," "satisfactory," "questionable," and "none" *All patients received concomitant Vitamin K*								

Preston et al.[6] 2002 OL, P, SA, SC	42	Elective, Required immediate VKA reversal for: GIH, head injury, SDH, spontaneous hemorrhage, emergency surgery, post-trauma, acute pancreatitis, ICH Median age 70 yrs (range 26-83) 37.1% F	Beriplex® 25, 35, or 50 units x 1 dose based on body weight (kg) and INR	N/A	N/A	33/78.6% (after 20min) Mean pretreatment INR = 3.98 (2.0-27.6). Complete INR reduction <1.3 achieved in 33 patients (see above). Remaining 9 patients had INR 1.3-1.9.	N/A	1C
Comment: All patients received concomitant Vitamin K								
Lorenz et al [14] 2003 OL, P	21	Vitamin K dependent clotting factor supplementation in severe liver disease in patients with bleeding or before urgent surgery or invasive intervention Median age 45 yrs (29-65) 31.8% F	Beriplex® 25.7 IU/kg (median dose). Range from 1000 to 4000 IU (median 1500 IU)	In vivo recovery of vitamin K-dependent clotting factors was 49.7-57.4%. (ratio of measured to expected increase) Quick's Test: PT patient/PT normal; %) increased from 36.6% to 70.2% (mean) in all patients	N/A	Clinical efficacy judged 'very good' in 76% (16) and 'satisfactory' in 24% (5) patients.	N/A	1C
Comment: Clinical efficacy assessed using scale range from "very good" to "none"								

R= Randomized, AC = Active Control, OL=Open-Label, P=Prospective, MC=Multi-Center, O=Observational, SA=Single-Arm, SC=Single-Center; GIH = gastrointestinal hemorrhage; SDH = subdural hematoma; IU = International units; PT = prothrombin time

Off-label Studies
There is only one RCT assessing the utility of four-factor PCC in reversing the anticoagulant effect of rivaroxaban and dabigatran.[2] In this randomized, double-blind, placebo-controlled crossover study, 12 healthy male volunteers received rivaroxaban (n=6) or dabigatran (n=6) for 2½ days followed by a single 50 unit/kg dose of four-factor PCC (Cofact®) or similar volume of saline placebo. After an 11-day washout period, subjects were crossed over to receive 2½ days of treatment with the other anticoagulant. Four-factor PCC significantly reversed the prothrombin time in patients to baseline normal of 12.8 $\pm$1 seconds from 15.8 $\pm$ 1.3 seconds ($p < 0.001$) who received rivaroxaban, but it did not restore coagulation assays (activated partial thromboplastin time, ecarin clotting time, and thrombin time) in patients receiving dabigatran. There was no evaluation of the ability to achieve hemostasis in this trial. (Grade 1B)

Comparative Therapies
There are no studies directly comparing four-factor PCC to three-factor PCC for the reversal of warfarin anticoagulation. However, a case series study with retrospective controls performed by Holland and colleagues demonstrated that three-factor PCC (Profilnine® SD) was ineffective for the treatment of patients with significant warfarin-associated coagulopathy when used as a single agent.[7] Results showed that the addition of a mean of 2 units of FFP to three-factor PCC significantly improved adequate INR lowering (to < 3.0). Forty-two (42) historical controls (mean INR > 5.0 on admission) treated with FFP alone (mean 3.6 units) lowered the INR < 3.0 in 63% of patients. Forty (40) patients treated with low-dose (25 units/kg) and high-dose (50 units/kg) PCC alone lowered INR < 3.0 in 50% and 43% patients, respectively. After supplemental FFP infusion to PCC treatment, the goal INR < 3.0 was achieved in 89% and 93% for low- and high-dose PCC, respectively. (Grade 1C)

A comprehensive literature review evaluating the evidence for the use of rFVIIa in the acute reversal of warfarin showed that rFVIIa rapidly corrects the INR with doses ranging from 10 to 90 μg/kg, especially when co-administered with vitamin K and FFP.[8] Studies supporting this consists of small (1-16 patients), non-randomized, retrospective, case series and case reports without active controls.

A retrospective analysis performed by Sarode and colleagues demonstrated the use of three-factor PCC (Profilnine® SD) with a low-dose rFVIIa (NovoSeven®) as a "cocktail" to rapidly reverse VKA-related intracranial hemorrhage (ICH).[9] Forty-six (46) patients (mean INR 3.4 on admission) were prospectively treated with 4,000 units of Profilnine® SD (approximately 50 units/kg dose for an 80 kg patient) and 1.0 mg of NovoSeven®. Retrospective data analysis showed that patients treated with the Profilnine® and NovoSeven® cocktail achieved a mean INR of 1.0 ($p = 0.0036$ v. FFP; $p = 0.0019$ v. FFP + PCC), which remained normal until discharge or death. The mean time to INR reduction was 179 minutes in the PCC + rFVIIa group, 406 minutes in the FFP alone group, and 217 minutes in the FFP + PCC group. ($p = 0.048$ cocktail v. FFP alone) Four of 11 Profilnine® patients has measureable intraparenchymal expansion at 24 hours after the cocktail. One patient had thrombotic complications 8 hours after the cocktail, and one patient three days after. (Grade 1C)

Safety

The following safety data is based on two RCTs [3,11] of Beriplex® (the product information uses the trade names Beriplex® and Kcentra® interchangeably):[10]

Adverse Reactions
The most common adverse reactions (frequency ≥ 2.8%) observed in patients receiving Kcentra® were headache, nausea/vomiting, arthralgia, and hypotension. Hypersensitivity reactions (≤ 2%) including flushing, urticaria, tachycardia, anxiety, angioedema, wheezing, nausea, vomiting, hypotension, tachypnea, dyspnea, pulmonary edema, and bronchospasm. Because Kcentra® is made from human blood, it may carry a risk of transmitting infectious agents (e.g., viruses), the variant Creutzfeldt-Jakob disease agent, and, theoretically, the Creutzfeldt-Jakob disease agent. The most serious adverse reactions were thromboembolic events including stroke, pulmonary embolism and deep vein thrombosis.Table 4-7 show adverse reactions reported in the literature, product information, and/or information available from the manufacturer in unpublished studies.

Table 4: Adverse Reactions Reported in 3 or more subjects (≥2.8%) following Kcentra® or FFP Administration in Acute Major Bleeding RCT[3]

Adverse Reaction	Kcentra® (n=103)	FFP (n=109)
General disorders and administration site conditions		
Chest pain	1 (1.0%)	3 (2.8%)
Nervous system disorders		
Headache	**8** (7.8%)	2 (1.8%)
Hemorrhage intracranial	3 (2.9%)	0
Respiratory, thoracic, and mediastinal disorders		
Respiratory distress/dyspnea/hypoxia	2 (1.9%)	4 (3.7%)
Breath sounds abnormal/rates	1 (1.0%)	3 (2.8%)
Pulmonary edema	0	4 (3.7%)
Gastrointestinal disorders		
Nausea/vomiting	**4** (3.9%)	1 (0.9%)
Constipation	2 (1.9%)	**6** (5.5%)
Diarrhea	0	3 (2.8%)
Cardiac disorders		
Tachycardia	3 (2.9%)	1 (0.9%)
Investigations		
INR increased	3 (2.9%)	0
Metabolism and nutrition disorders		
Hypokalemia	2 (1.9%)	**5** (4.6%)
Fluid overload	1 (1.0%)	**6** (5.5%)
Hypomagnesemia	0	3 (2.8%)
Psychiatric Disorders		
Mental status changes	3 (2.9%)	0
Insomnia	1 (1.0%)	3 (2.8%)
Musculoskeletal and connective tissue disorders		
Arthralgia	**4** (3.9%)	0
Vascular disorders		
Hypotension	**5** (4.9%)	3 (2.8%)
Blood pressure increased/hypertension	3 (2.9%)	1 (0.9%)
Injury, poisoning, and procedural complications		
Skin laceration/contusion/subcutaneous hematoma	3 (2.9%)	1 (0.9%)
Transfusion reaction	0	**4** (3.7%)
Blood and lymphatic disorders		
Anemia	0	**4** (3.7%)

In the Acute Major Bleeding trial, 6 patients (5.8%) in the Kcentra® group experienced fluid overload versus 14 (12.8%) in the FFP group.[3] A disadvantage of FFP is its fluid volume when used for emergency management of overanticoagulation (4 units of FFP is approximately 1000 mL). Table 5 below compares the incidence of fluid overload in patients with and without history of CHF.

Table 5: Subjects with Fluid Overload Events by Prior History of Congestive Heart Failure in Plasma-Controlled Trial in Subjects with Acute Major Bleeding[3]

Subgroup	Kcentra®		Plasma	
	N	Fluid Overload N (%)	N	Fluid Overload N (%)
All subjects	**103**	**6 (5.8)**	**109**	**14 (12.8)**
With history of CHF	46	4 (8.7)	44	11 (25.0)
Without history of CHF	57	2 (3.5)	65	3 (4.6)

In the Acute Major Bleeding trial, 9 patients (8.7%) in the Kcentra® group experienced a thromboembolic event (TEE) versus 6 patients (5.5%) in the FFP group (see Table 6 below for type of TEE).[3] Additionally, a post-hoc subgroup analysis was conducted to determine if the patients who experienced TEEs had a prior history of TEE (Table 7). Patients with a history of TEE may be at greater risk for a TEE event if administered Kcentra®. This finding is part of the boxed warning in the manufacturer's information for Kcentra®.

Table 6: Adverse Reactions (TEEs only) Following Kcentra® or FFP Administration in the Acute Major Bleeding RCT[3]

System Organ Class	Kcentra® (N=103)	Plasma (N=109)
Any possible TEE	**9 (8.7%)**	**6 (5.5%)**
TEE adverse reactions	**6 (5.5%)**	**4 (3.7%)**
Cardiac disorders		
Myocardial infarction	0	1 (0.9%)
Myocardial ischemia	0	2 (1.8%)
Nervous system disorders		
Ischemic cerebrovascular accident (stroke)	2 (1.9%)	0
Cerebrovascular disorder	0	1 (0.9%)
Vascular disorders		
Venous thrombosis calf	1 (1.0%)	0
Deep vein thrombosis	1 (1.0%)	0
Fistula Clot	1 (1.0%)	0
Unknown cause of death (not confirmed TEE)		
Sudden death	1 (1.0%)	0

Table 7: Subjects with Thromboembolic Events by Prior History of TEE in Plasma-Controlled RCT in Acute Major Bleeding[3]

	Kcentra®		Plasma	
	N	TEEs N (%)	N	TEEs N (%)
All subjects	**103**	**9 (8.7)**	**109**	**6 (5.5)**
With history of TEE	69	8 (11.6)	79	3 (3.8)
Without history of TEE	34	1 (2.9)	30	3 (10.0)

In the Acute Major Bleeding trial, 10 patients (9.7%) died in the Kcentra® group versus 5 patients (4.6%) in the plasma group.[3] In the Surgery/Invasive procedure trial, 3 patients (3.4%) died in Kcentra® group versus 8 (9.1%) in the plasma group. Only 1 death in each trial was considered possibly related to study treatment according to an assessment of masked data by an independent safety adjudication board.

A pharmacovigilance study has been published to report the long-term safety and efficacy of Beriplex®.[12] This study was a retrospective review of CSL Behring's global pharmacovigilance database (included spontaneous reports, case reports from scientific literature, and non-interventional post-authorization studies) between February 1996 and March 2012. The report found 21 thromboembolic events (1 in 31,000) judged to be possibly related to Beriplex®, with no incidences of viral transmission or HIT documented. Table 8 provides a summary of clinical trials included in the pharmacovigilance study reporting the safety and efficacy of four-factor PCC (various formulations: Beriplex® (available in US as Kcentra®), Octaplex® (not available in US), Cofact® (not available in US), and Kaskadil® (not available in US).

Table 8: Summary of Clinical Trials Reporting Four-factor PCC Safety and Efficacy (Adapted[12])

Study Year	Study Design	Indication	Product	n	Primary Outcomes*	Safety Endpoints
Evans et al.[13] 2001	OL, P	Urgent VKA reversal	Beriplex®	10	PCC infusion resulted in a reduction in median INR from >20.0 (range 15.8-20.0) to 1.1 (1.0-1.3)	No thromboembolic or other AEs reported
Preston et al.[6] 2002	OL, P	Urgent VKA reversal	Beriplex®	42	PCC infusion resulted in median INR reduction from 3.98 (range 2.0-27.6) to ≤1.9	No increase in D-dimer concentration No thromboembolic events 7 days post-PCC infusion 1 patient died of thrombotic stroke, PCC could not be ruled out as cause
Lorenz et al.[14] 2003	OL, P	Vitamin K-dependent clotting factor supplementation in severe liver disease	Beriplex®	21	In vivo recovery of vitamin K-dependent clotting factors was 49.7-57.4%. Clinical efficacy was judged 'very good' in 76%, and 'satisfactory' in 24%	No thrombotic events or evidence of pathogen transmission
Lorenz et al.[17] 2007	OL, P	Urgent VKA reversal	Beriplex®	8	Mean INR reduced from 3.4 (±1.2) to <1.3 in 7 pts (clinical efficacy rated 'very good') and <1.4 in 1 pt (clinical efficacy rated 'satisfactory')	No thrombotic events, anaphylactic, or allergic reactions, or other AEs were reported No evidence of viral exposure
Pabinger et al.[5] 2008	P, O	Urgent VKA reversal	Beriplex®	43	INR reduction to ≤1.3 in 93% pts at 30min post-PCC	1 pt had fatal PE, PCC could not be ruled out as a cause
Lubetsky et al.[15] 2004	OL, P	Urgent VKA reversal	Octaplex®	60	Mean INR reduced from 6.1 to 1.5 10 min post-PCC infusion Clinical response to treatment rated 'good' in 85%	2 seroconversion events for parvovirus B19 occurred, possibly related to PCC No thrombotic complications related to PCC
Riess et al.[18] 2007	OL, P	Urgent VKA reversal	Octaplex®	60	Mean INR reduced to <1.4 in 91.5% pts at 60min post-PCC	1 seroconversion event for parvovirus B19 No thrombotic complications
van Aart et al.[16] 2006	P, OL, RC	Urgent VKA reversal	Cofact®	93	Individualized PCC doses achieved target INR 15 min after dosing was significantly higher than those treated with standard dose (89% vs. 43%; p<0.001)	2 cases thrombotic stroke, PCC could not be ruled out as a cause
Vigue et al.[19] 2007	P, O	Immediate VKA reversal	Kaskadil®	18	Mean INR reduced from 4.0 to 1.2	No clinical thrombotic events

OL=Open-Label, P=Prospective, RC=Randomized Control, O=Observational
*Studies of Kcentra®/Beriplex® with >10 patients also included in Table 3 [5,6]

Contraindications[10]

- Patients with known anaphylactic or severe systemic reactions to Kcentra® or any components in Kcentra® including **heparin**, FII, FVII, FIX, FX, Protein C and S, Antithrombin III, and human albumin.
- Patients with disseminated intravascular coagulation (DIC).
- Patients with known heparin-induced thrombocytopenia (HIT).

Warnings and Precautions[10]

The following **boxed warning** is included in the package literature for Kcentra®:

WARNING: ARTERIAL AND VENOUS THROMBOEMBOLIC COMPLICATIONS

Patients treated with Vitamin K antagonist (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 a 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.

- Both fatal and non-fatal arterial and venous thromboembolic complications have been reported with Kcentra® in clinical trials and post marketing surveillance. Monitor patients receiving Kcentra® for signs and symptoms of thromboembolic events.
- Kcentra® 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. Kcentra® may not be suitable in patients with thromboembolic events in the prior 3 months.

Drug Interactions

There are currently no significant drug-drug interactions reported with Kcentra®.[10]

Risk Evaluation and Mitigation Strategy (REMS)

There is currently no REMS program for KCentra®.

Dosage and Administration

Kcentra® is for intravenous use only. Kcentra® is supplied as a 500-unit single dose vial. Kcentra® is dosed according to Factor IX potency and is individualized based on the patient's baseline International Normalized Ratio (INR) and body weight. Kcentra® is supplied as a kit containing: one Kcentra® vial, one vial containing 20 mL of diluent (Sterile Water for Injection, USP), and one Mix2Vial®. After preparing and reconstituting Kcentra® with the kit and instructions provided, the final concentration of drug product in Factor IX units will range from 20-31 units/mL (approximately 400-620 units per vial) depending on the actual potency, which is listed on the carton. he actual potency per vial of Factors II, VII, IX, and X and Proteins C and S is stated on each individual carton. Once reconstituted, the Kcentra® must be used immediately, or the infusion started within four hours. The relative potency of coagulant and antithrombotic proteins in a typical 500-unit vial of Kcentra® is listed in Table 9 below.

Table 9: Composition per Vial of Kcentra® 500 International Units

Ingredient	Kcentra® 500 units
Total protein	120-280 mg
Factor II	380-800 units
Factor VII	200-500 units
Factor IX	400-620 units
Factor X	500-1,020 units
Protein C	420-820 units
Protein S	240-680 units
Heparin	8-40 units
Antithrombin III	4-30 units

Dosing to reverse coagulation factor deficiency induced by VKA:

Vitamin K is to be administered concurrently to patients receiving Kcentra®. Kcentra® is dosed according to Factor IX potency (units) and is individualized based on the patient's pre-dose INR and body weight (kg), as shown in Table 10 below. Repeat dosing with Kcentra® is not supported by clinical data and is not recommended.

Table 10: Dosing Guideline of Kcentra®
Dose is based on actual body weight up to but not exceeding 100 kg.
For patient weight > 100 kg, maximum dose should not be exceeded.

Pre-treatment INR	**2.0 - < 4.0**	**4.0 – 6.0**	**> 6.0**
Dose[*] of Kcentra® (units[†] of FIX / kg body weight)	25	35	50
Maximum dose (units of FIX)	Not to exceed 2,500	Not to exceed 3,500	Not to exceed 5,000

[*] Dosing is based on actual body weight. Dose based on actual potency as stated on the carton, which will vary from 20-31 FIX units/mL.
Nominal potency is 500 units per vial, approximately 25 units/mL after reconstitution.
[†] Units refer to International Units

Kcentra® is to be administered by intravenous infusion at a rate of 0.12 mL/kg/min. (approximately 3 units/kg/min), up to a maximum rate of 8.4 mL/min (approximately 210 units/min). Duration of infusion to complete a single dose has ranged from 12 minutes to 24 minutes across available studies.

Dosing to reverse rivaroxaban (new oral anticoagulant)
Dose is 50 units/kg. (single dose) [2]

Special Populations [10]
KCentra® is Pregnancy Category C, and it has not been studied for use during labor and delivery, in nursing mothers, or in pediatrics. In the adult clinical trials, there were no clinically significant differences between safety profile of Kcentra® and FFP in any group (patients all aged > 18 years).

Storage:
Kcentra® must be administered through a separate infusion line and should not be mixed with other medicinal products, including blood products. Kcentra® is to be stored, reconstituted, and administered at room temperature.

Cost

In Table 11, the cost of Kcentra® is compared to other treatment modalities used for immediate VKA anticoagulation reversal.

Table 11: Cost Comparison of Various Agents Implicated in Emergent VKA Anticoagulation Reversal

Reversal Agent(s)	**Unit Cost**	**Dose**	**Cost per Dose***
FFP	$75 per 250mL unit	4 units	$300
3-Factor PCC (Bebulin®)	$0.92 per unit	50 units/kg	$3,680
3-Factor PCC + FFP	$0.92 per unit + $75 per unit	50 units/kg + 4 units	$3,980
rFVIIa (NovoSeven®)	$1.46/mcg	40mcg/kg~	$4,672
rFVIIa (NovoSeven®) + FFP	$1.46/mcg + $75 per unit	90mcg/kg + 4 units	$4,972
3 Factor PCC + rFVIIa (NovoSeven®)	$0.92/unit + $1.46/mcg	50 units/kg + 1.0 mg†	$5,140
Kcentra®	**$1.27/unit**	**50 units/kg**	**$5,080**

*Based on 80 kg patient with INR > 6.0
†Based on dosing used in Sarode et al. *J Neurosurg* 2012
~ approved UPMC reversal protocol dosing

Place in Therapy

The most recent *CHEST* guidelines suggest that four-factor PCC is preferred over FFP for the urgent reversal of VKA anticoagulation.[1] This recommendation is a 2C, which is defined as a weak recommendation (2 = weak; 1 = strong) with low-quality evidence (C = low quality; B = moderate quality; A = high quality). Moreover, FFP transfusion has several disadvantages: 1) a delay in therapeutic effect because of the time required to thaw and transfuse FFP; 2) the risk of transfusion-associated circulatory overload due to the large volume that must be administered; 3) the risk of allergic reactions; 4) the risk of infection from exposure to multiple donors; and 5) transfusion-related acute lung injury. There is paucity of evidence to suggest superiority of comparative therapies over Kcentra® for this indication and the costs are similar among agents. Therefore, the use of Kcentra®, given the available evidence at this time, should be restricted to the urgent reversal of VKA anticoagulation for acute bleeding or emergency surgery when FFP is contraindicated because of cardiovascular compromise. KCentra® is currently the only available four-factor PCC in the U.S.

There does not appear to be a role for Kcentra® in reversal of dabigatran-related bleeding. The data for rivaroxaban reversal are not compelling with respect to hemostasis. Further studies are necessary to clarify the possible role of Kcentra® in the reversal of bleeding associated with the newer oral anticoagulants.

Prepared by: Laura Guido, PharmD, PGY1 Resident, UPMC Mercy and Robert Simonelli, PharmD, UPMC Mercy
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<table>
<tr><th colspan="2">Grade of Recommendation</th></tr>
<tr><th>Methodologic Strength of Supporting Evidence</th><th>Clarity of Risk/Benefit</th></tr>
<tr><td>A
(Clinical trials without important limitations)</td><td>1
No change OR clear improvement in risk/benefit ratio
(clear = strong study conclusion, clinically relevant outcomes, large treatment effect)</td></tr>
<tr><td>B
(Clinical trials with important limitations)</td><td rowspan="2">2
Decrease OR unclear risk/benefit ratio
(unclear = weak study conclusion, surrogate outcomes, small treatment effect, higher risk of therapy, higher cost, varying values)</td></tr>
<tr><td>C
(Clinical trials with significant flaws, or data available only in abstract form)</td></tr>
</table>