Biotherapies for Life®

CSL Behring

Urgent warfarin reversal with fast and sustained action*

Kcentra—the only FDA-approved alternative to plasma for urgent warfarin reversal

≥25 years of clinical experience as Beriplex® outside the US

Kcentra is contraindicated in patients with known anaphylactic or severe systemic reactions to Kcentra or any of its components (including heparin, Factors II, VII, IX, X, Proteins C and S, Antithrombin III and human albumin). Kcentra is also contraindicated in patients with disseminated intravascular coagulation. Because Kcentra contains heparin, it is contraindicated in patients with heparin-induced thrombocytopenia (HIT).

Please see full Important Safety Information on page 16.
Please see enclosed full prescribing information, including boxed warning.

*Effective hemostasis measured up to 24 hours for the Acute Major Bleeding trial and until the end of procedure (up to 24 hours) for the Urgent Surgery/Invasive Procedures trial. Rapid INR reduction to ≤1.3 at 0.5 hours after end of infusion.

Kcentra®
Prothrombin Complex Concentrate (Human)
Urgent Warfarin Reversal

When time is of the essence, choose Kcentra

FASTER ACTING* Superior INR reduction at **30 minutes after end of infusion vs plasma**

FASTER ADMINISTRATION, **LOWER** VOLUME Mean infusion time is under 25 minutes **~85% less volume vs plasma**

SUSTAINED INR REDUCTION† Statistically significant INR reduction **sustained ≤1.3 for up to 8 or 12 hours vs plasma**

Efficacy endpoint	Urgent Surgery/ Invasive Procedures trial	Acute Major Bleeding trial
Effective hemostasis	Kcentra ***superior***	Kcentra and plasma ***equally effective***
Early INR reduction	Kcentra ***superior***	Kcentra ***superior***

Effective hemostasis measured up to 24 hours for the Acute Major Bleeding trial and until the end of procedure (up to 24 hours) for the Urgent Surgery/Invasive Procedures trial. Rapid INR reduction to ≤1.3 at 0.5 hours after end of infusion.

- In 2 head-to-head trials, Kcentra demonstrated superiority to plasma in 3 of 4 efficacy endpoints
- The relationship between INR values and clinical hemostasis in patients has not been established

Kcentra was compared with plasma in 2 prospective, randomized, open-label, active-controlled, multicenter, noninferiority trials for urgent warfarin reversal in 388 adult patients with either:

- A need for an urgent surgery/invasive procedure
- Acute major bleeding

*In 2 head-to-head trials, Kcentra demonstrated superiority to plasma in 3 of 4 efficacy endpoints. Superior hemostatic efficacy in the Urgent Surgery/Invasive Procedures trial and equally effective hemostasis efficacy in the Acute Major Bleeding trial. Faster INR reduction (to ≤1.3 at 30 minutes after end of infusion) in both head-to-head trials.

†8 hours for Urgent Surgery/Invasive Procedures trial and 12 hours for Acute Major Bleeding trial. Administer vitamin K concurrently to patients receiving Kcentra. Vitamin K is administered to maintain vitamin K-dependent clotting factor levels once the effects of Kcentra have diminished.

Kcentra replaces only what is needed for urgent warfarin reversal

Factors

II | VII | IX | X

Antithrombotic Proteins

C | S

- Non-activated
- Contains antithrombin III and heparin
- Administer concurrently with vitamin K
- 36-month room-temperature storage prior to reconstitution

Vitamin K-dependent factors	Kcentra	Plasma‡	4F-PCC (FVIII bypassing agent)[1]	3F-PCC[2,3]	rFVIIa[4§]
II	✔	✔	✔	✔	
VII	✔	✔	✔ Activated	Low Levels	✔ Activated
IX	✔	✔	✔	✔	
X	✔	✔	✔	✔	
Protein C	✔	✔			
Protein S	✔	✔			

‡In plasma, total content of factors relative to volume is low; large volumes are required for reversal.
§Off-label use of rFVIIa has been associated with increased thrombotic events.[5-7]

Important Safety Information

WARNING: ARTERIAL AND VENOUS THROMBOEMBOLIC COMPLICATIONS

Patients being treated with Vitamin K antagonist therapy have underlying disease states that predispose them to thromboembolic events. Potential benefits of reversing VKA should be weighed against the risk of thromboembolic events, especially in patients with history of such events. Resumption of anticoagulation therapy should be carefully considered once the risk of thromboembolic events outweighs the risk of acute bleeding. Both fatal and nonfatal arterial and venous thromboembolic complications have been reported in clinical trials and postmarketing surveillance. Monitor patients receiving Kcentra, and inform them of 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 might not be suitable for patients with thromboembolic events in the prior 3 months.

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Kcentra® Prothrombin Complex Concentrate (Human)

Urgent Warfarin Reversal

Choose FDA-approved Kcentra for acute major bleeding or urgent surgery/invasive procedure cases

Acute major bleeding cases

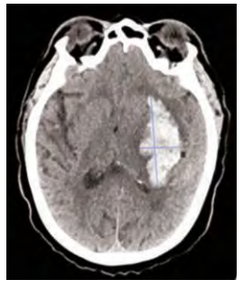
SUSAN, 62*

- Presents with intracranial hemorrhage

Medical history

- Atrial fibrillation
- Chronic kidney disease
- Diabetes mellitus
- Hypertension
- Congestive heart failure

Current medication includes warfarin 7.5 mg once daily, hydralazine, insulin, atorvastatin, and lisinopril.



INR is 2.3

Imaging results

CT results showed a 6.4 x 3 x 3 cm, ~30 cc left basal ganglia hemorrhage.

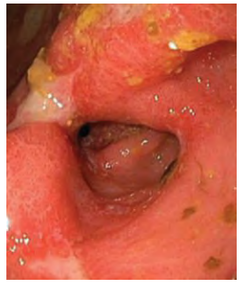
WILLIAM, 72*

- Presents with gastrointestinal bleed

Medical history

- Recurrent unprovoked DVT
- High blood pressure
- No other comorbidities

Current medications include warfarin 5 mg qd and a beta blocker once daily.



INR is 3.4

Imaging results

EGD was positive for residual blood and prepyloric ulcer with oozing visible vessel.

To see what Kcentra can do for acute major bleeding cases like Susan's and William's, g

*Hypothetical patient.

Urgent surgery case

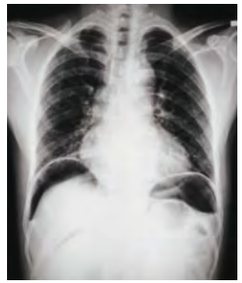
BEN, 62*

- Presents with perforation of the bowel

Medical history

- High blood pressure
- High cholesterol
- Atrial fibrillation

Current medications include warfarin 5 mg once daily, hydrochlorothiazide, and atorvastatin.



INR is 3.5

Imaging results

X-ray of chest shows free air under the right diaphragm, suggesting a perforated viscus.

To see what Kcentra can do for urgent surgery cases like Ben's, go to pages 8-9

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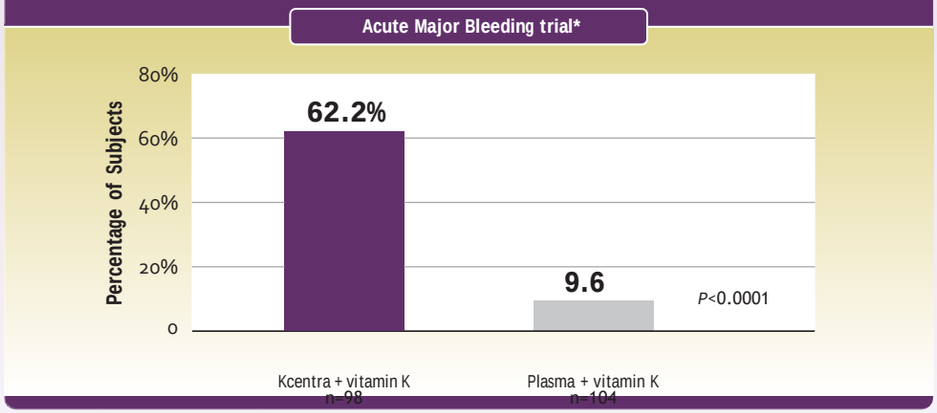
Faster INR reduction vs plasma

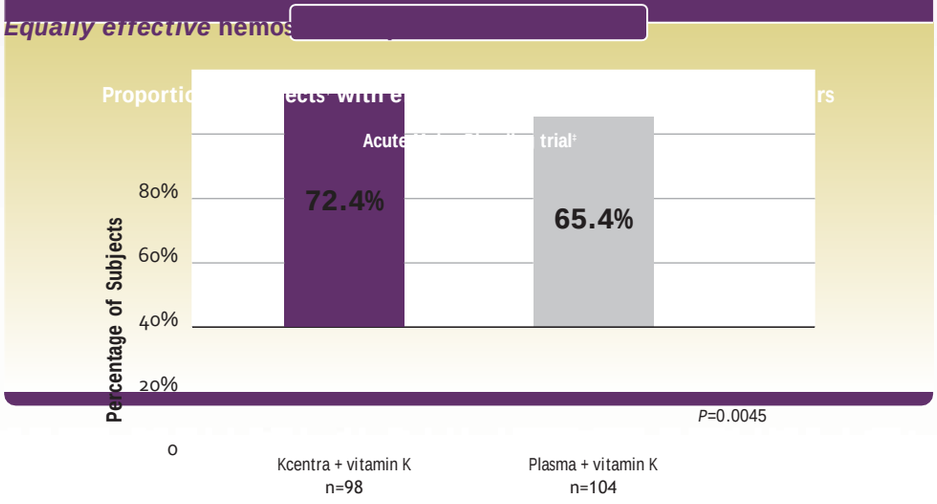
Proportion of subjects experiencing a reduction of INR (≤1.3 at 30 minutes after end of infusion)



The relationship between INR values and clinical hemostasis in patients has not been established.

*Kcentra–plasma (%) [95% CI]=52.6 [39.4, 65.9] for noninferiority (prespecified noninferiority margin >–10%; Kcentra superior to plasma if lower limit 95% CI >0 in the Acute Major Bleeding trial).

Equally effective hemos



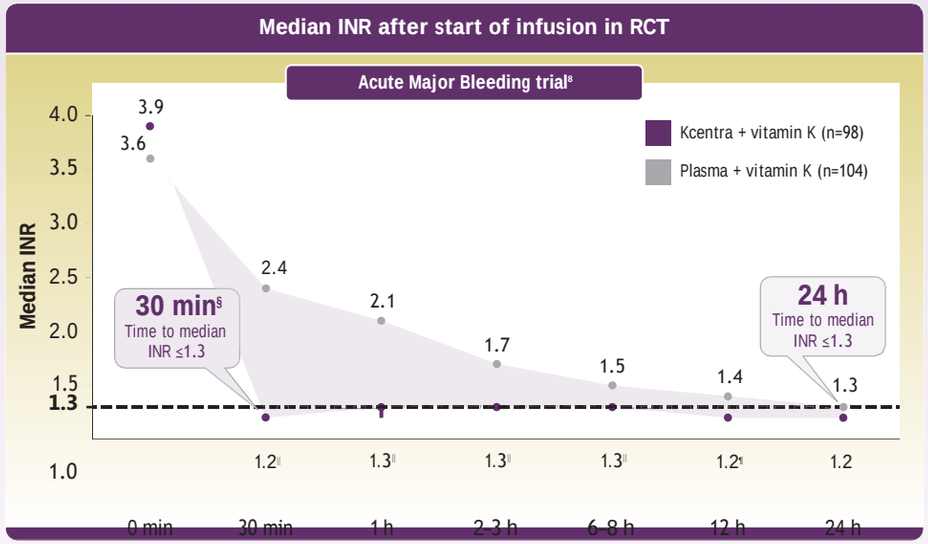
- Efficacy was adjudicated as "effective" or "not effective" by a blinded independent Endpoint Adjudication Board
- Criteria for effective hemostasis were based on standard clinical assessments, including:
  - Vital signs
  - Hemoglobin measurements
  - CT assessments at predefined time points
- Sustained up to 24 hours

†Intent to treat-efficacy (ITT-E) population.

‡Kcentra–plasma (%) [95% CI]=7.1 [–5.8, 19.9] (prespecified noninferiority margin >–10%. Farrington-Manning *P*-value for noninferiority, rejecting null hypothesis of inferiority of 4F-PCC).

Statistically significant INR reduction sustained for up to 12 hours

Median INR after start of infusion in RCT



§30 minutes after start of infusion.

‖Statistically significant difference (*P*<0.0001) compared to plasma by 2-sided Wilcoxon test.
¶*P*=0.0002.

- Administer vitamin K concurrently to patients receiving Kcentra. Vitamin K is administered to maintain vitamin K–dependent clotting factor levels once the effects of Kcentra have diminished

Important Safety Information

Kcentra is a blood coagulation factor replacement product indicated for the urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA—eg, warfarin) therapy in adult patients with acute major bleeding or the need for urgent surgery or other invasive procedure. Kcentra is for intravenous use only.

Kcentra is contraindicated in patients with known anaphylactic or severe systemic reactions to Kcentra or any of its components (including heparin, Factors II, VII, IX, X, Proteins C and S, Antithrombin III and human albumin). Kcentra is also contraindicated in patients with disseminated intravascular coagulation. Because Kcentra contains heparin, it is contraindicated in patients with heparin-induced thrombocytopenia (HIT).

Hypersensitivity reactions to Kcentra may occur. If patient experiences severe allergic or anaphylactic type reactions, discontinue administration and institute appropriate treatment.

In clinical trials, the most frequent (≥2.8%) adverse reactions observed in subjects receiving Kcentra were headache, nausea/vomiting, hypotension, and anemia. The most serious adverse reactions were thromboembolic events, including stroke, pulmonary embolism and deep vein thrombosis.

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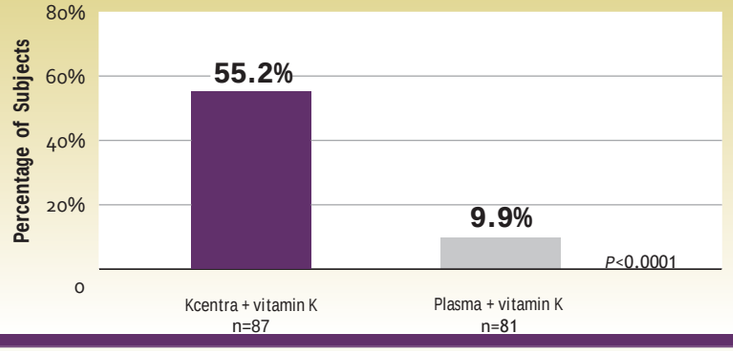
Faster INR reduction vs plasma

Proportion of subjects experiencing a reduction of INR (≤1.3 at 30 minutes after end of infusion)

Urgent Surgery/Invasive Procedures trial*



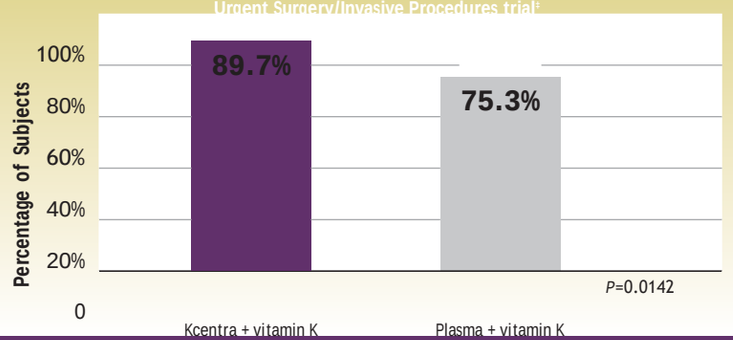
The relationship between INR values and clinical hemostasis in patients has not been established.

*Kcentra–plasma (%) [95% CI]=45.3 [31.9, 56.4] for noninferiority (prespecified noninferiority margin >–10% in the Urgent Surgery/Invasive Procedures trial; Kcentra superior to plasma if lower limit 95% CI >0).

Superior hemostasis vs plasma

Proportion of subjects† with effective hemostasis at end of procedure

Urgent Surgery/Invasive Procedures trial‡



- Criteria for effective hemostasis were based on:
  - The difference between predicted and actual blood losses
  - Subjective hemostasis rating
  - The need for additional blood products containing coagulation factors
- Sustained until end of urgent procedure

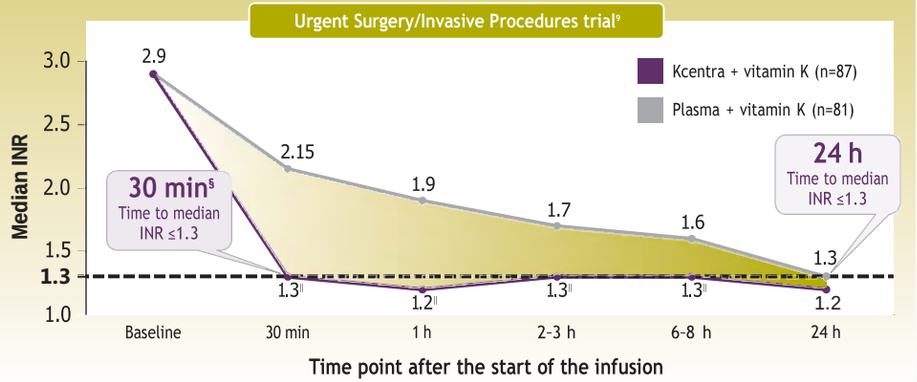
†Intent-to-treat efficacy (ITT-E) population.

‡Kcentra–plasma (%) [95% CI]=14.3 [2.8, 25.8] (prespecified noninferiority margin >–10%; Kcentra superior to plasma as lower limit of 95% CI >0).

Statistically significant INR reduction sustained for up to 8 hours

Median INR after start of infusion in RCT

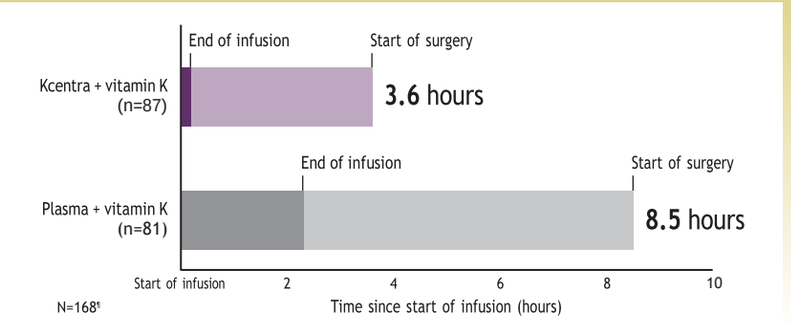
Urgent Surgery/Invasive Procedures trial[9]



§30 minutes after start of infusion.
‖Statistically significant difference compared to plasma by 2-sided Wilcoxon test.

- Administer vitamin K concurrently to patients receiving Kcentra. Vitamin K is administered to maintain vitamin K-dependent clotting factor levels once the effects of Kcentra have diminished

Median time to surgery was *~5 hours faster with Kcentra*[9]



¶ITT-E population.

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intravascular

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Kcentra®
Prothrombin Complex Concentrate (Human)

Faster administration and lower volume with Kcentra

Kcentra is ~25x more concentrated than plasma[6]

- 3 vials of Kcentra (an average volume of 2500 IU administered as a single dose) are equal to 10–12 units of plasma

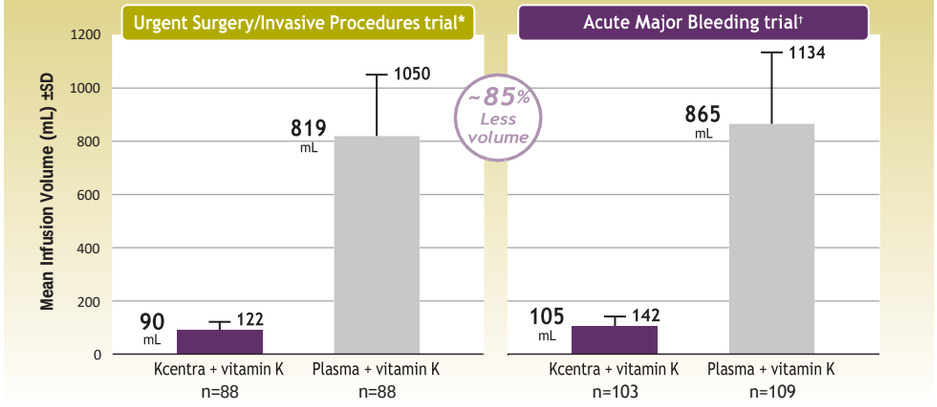
Kcentra

100 mL

Plasma

250 mL/bag

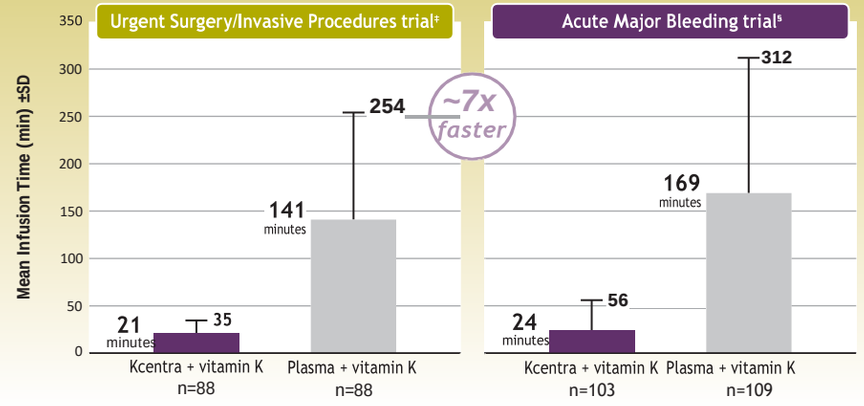
Kcentra requires *~85% less volume vs plasma*



*Mean infusion volume was 90 mL (±32 mL) for Kcentra and 819 mL (±231 mL) for plasma.
†Mean infusion volume was 105 mL (±37 mL) for Kcentra and 865 mL (±269 mL) for plasma.

Faster mean infusion time with Kcentra vs plasma

Mean infusion time with Kcentra is *~7x faster* vs plasma



‡Mean infusion time was 21 min (±14 min) for Kcentra and 141 min (±113 min) for plasma.
§Mean infusion time was 24 min (±32 min) for Kcentra and 169 min (±143 min) for plasma.

- No need for thawing or ABO typing

Important Safety Information

Hypersensitivity reactions to Kcentra may occur. If patient experiences severe allergic or anaphylactic type reactions, discontinue administration and institute appropriate treatment.

In clinical trials, the most frequent (≥2.8%) adverse reactions observed in subjects receiving Kcentra were headache, nausea/vomiting, hypotension, and anemia. The most serious adverse reactions were thromboembolic events, including stroke, pulmonary embolism and deep vein thrombosis.

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Single-dose administration

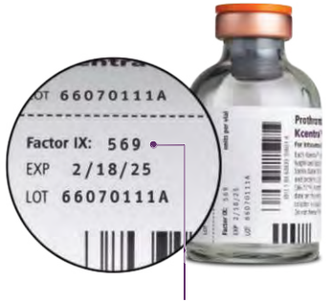
Patient's pretreatment INR and body weight determine dose

Dose* of Kcentra (units† of Factor IX)/kg body weight	25	35	50
Maximum dose‡ (units of Factor IX)	Not to exceed 2500	Not to exceed 3500	Not to exceed 5000

*Dosing is based on body weight. Dose based on actual potency is stated on the vial, which will vary from 20–31 Factor IX units/mL after reconstitution. The actual potency for 500 unit vial ranges from 400–620 units/vial. The actual potency for 1000 unit vial ranges from 800–1240 units/vial.
†Units refer to international units.
‡Dose is based on body weight up to but not exceeding 100 kg. For patients weighing more than 100 kg, maximum dose should not be exceeded.

- Repeat dosing is not supported by clinical data and is not recommended
- Administer Kcentra:
  - By intravenous infusion at a rate of 0.12 mL/kg/min (~3 units/kg/min) up to a maximum rate of 8.4 mL/min
  - Concurrently with vitamin K
  - Through a separate infusion line

Kcentra dose is calculated using Factor IX content



Actual Factor IX content (units) is printed on each vial

Visit Kcentra.com to access the Dosing Calculator and download the Quick Guide

Guidelines recommend 4F-PCC for urgent warfarin reversal

- **Neurocritical Care Society (NCS) and Society of Critical Care Medicine (SCCM)—2016[10]**

"Benefits of PCC include its fast preparation and reconstitution time, rapid INR reversal, small volume, and lower risk of infection as compared to [plasma]."

"PCC use in VKA-associated intracranial hemorrhage leads to faster INR reversal, less hematoma expansion, and similar or better mortality rates and functional outcomes compared to [plasma]."

- **American College of Cardiology—2017[11]**

"[For patients with VKA-associated major bleeding], administration [of vitamin K] must be accompanied by a repletion strategy (PCCs or plasma only if 4-factor PCC…is unavailable)…PCC can be given in a much smaller volume and at a much faster infusion rate…compared with plasma and is preferred."

- **American College of Chest Physicians (ACCP)—2012[12]**

"For patients with VKA-associated major bleeding, we suggest rapid reversal of anticoagulation with [4-factor PCC] rather than with plasma."

- **American College of Surgeons (ACS)—2018[13]**

"[For elderly patients with TBI,] aggressive and early reversal of anticoagulant therapy may improve outcome. This result may be accomplished rapidly with the use of [PCC], plasma and vitamin K."

- **American Society for Gastrointestinal Endoscopy (ASGE)—2016[14]**

"For warfarin…reversal, the 4-factor PCC is the appropriate reversal agent."

- **American Society of Hematology—2018[15]**

"For life-threatening bleeding during VKA treatment for VTE with an elevated INR, ASH suggests using 4-factor PCC and IV vitamin K rather than FFP."

- **Circular of Information for the Use of Human Blood Components—2013[16]**

"This Circular was prepared jointly by the AABB, the American Red Cross, America's Blood Centers, and the Armed Services Blood Program. The Food and Drug Administration recognizes this Circular of Information as an acceptable extension of container labels."

"Do not use [FFP] when coagulopathy can be corrected more effectively with specific therapy, such as vitamin K, cryoprecipitated AHF (antihemophilic factor), [PCCs] used to reverse warfarin, or specific coagulation factor concentrates."

- **American College of Emergency—2019[17]**

The ACEP expert panel on anticoagulation reversal recommends 4-factor PCC and vitamin K as a tier 1 recommendation for the reversal of vitamin K antagonists (warfarin) for anticoagulated patients with a life threatening/critical site bleed or need for emergency surgery/urgent procedure.

Visit Kcentra.com to download guidelines

Important Safety Information

Kcentra is derived from human plasma. The risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent and its variant (vCJD), cannot be completely eliminated.

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Safety profile of Kcentra is *comparable to plasma*

Adverse reactions reported in more than 5 subjects (≥2.8%) following Kcentra or plasma administration in both randomized, controlled trials

Adverse reactions	No. (%) of subjects	
	Kcentra (N=191)	**Plasma** (N=197)
Nervous system disorders		
Headache	14 (7.3%)	7 (3.6%)
Respiratory, thoracic, and mediastinal disorders		
Pleural effusion	8 (4.2%)	3 (1.5%)
Respiratory distress/dyspnea/hypoxia	7 (3.7%)	10 (5.1%)
Pulmonary edema	3 (1.6%)	10 (5.1%)
Gastrointestinal disorders		
Nausea/vomiting	12 (6.3%)	8 (4.1%)
Diarrhea	4 (2.1%)	7 (3.6%)
Cardiac disorders		
Tachycardia	9 (4.7%)	2 (1.0%)
Atrial fibrillation	8 (4.2%)	6 (3.0%)
Metabolism and nutrition disorders		
Fluid overload*	5 (2.6%)	16 (8.1%)
Hypokalemia	9 (4.7%)	14 (7.1%)
Psychiatric disorders		
Insomnia	9 (4.7%)	6 (3.0%)
Vascular disorders		
Hypotension†	14 (7.3%)	10 (5.1%)
Injury, poisoning, and procedural complications		
Skin laceration/contusion/subcutaneous hematoma	8 (4.2%)	5 (2.5%)
Blood and lymphatic disorders		
Anemia‡	11 (5.8%)	16 (8.1%)

*Includes fluid overload and cardiac failure congestive.
†Includes orthostatic hypotension, hypotension, and hemorrhagic shock.
‡Includes anemia, hemoglobin decreased, and hematocrit decreased.

Kcentra *did not increase* the risk of thromboembolic (TE) events vs plasma

Serious events occurring in both RCTs		
Serious adverse reactions	**No. (%) of subjects**	
	Kcentra (N=191)	**Plasma** (N=197)
TE events§	13 (6.8%)	14 (7.1%)
Fluid overload events‖	9 (4.7%)	25 (12.7%)
Deaths	13 (6.8%)	13 (6.6%)

§Includes deep-vein thrombosis, thrombosis, ischemic stroke, vena cava filter insertion, catheter-related complication, acute myocardial infarction, pulmonary embolism, and transient ischemic attack.[1]
‖Includes fluid overload and cardiac failure congestive.

- One death in the Kcentra group was considered possibly related to study treatment in the Acute Major Bleeding trial
- One death in the plasma group was considered possibly related to study treatment in the Urgent Surgery/Invasive Procedures trial
- No factors common to all deaths were identified, except the frequent findings of high comorbidity burden, advanced age, and death after being placed on comfort care
- Outliers with supraphysiologic factor levels did not have a mortality rate out of proportion to the overall population
- Patients were monitored for serious adverse reactions, including TE events, for 45 days postinfusion

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