Kcentra®, Prothrombin Complex Concentrate (Human), is the only FDA-approved alternative to plasma for urgent warfarin reversal

SUPPORTED BY GUIDELINES

Clinical Practice Guidelines Recommend PCC Over Plasma to Reverse the Effects of Warfarin

Neurocritical Care Society and **Society of Critical Care Medicine** – 2016[1]

"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[2]

"[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 – 2012[3]

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

American Society for Gastrointestinal Endoscopy – 2016[4]

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

American College of Surgeons – 2018[5]

"[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 of Hematology – 2018[6]

"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."

INR, international normalized ratio; PCC, prothrombin complex concentrate; TBI, traumatic brain injury; VKA, vitamin K antagonist.

Indications

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.

Please see Important Safety Information including boxed warning, continued inside, and accompanying full Prescribing Information for Kcentra.

Kcentra®
Prothrombin Complex Concentrate (Human)
Urgent Warfarin Reversal

Administer Kcentra for urgent reversal of warfarin-related acute major bleeding

ASSESS AND IDENTIFY SEVERITY OF BLEED[2]

Bleed is considered major if ≥1 of the following apply:

- Bleeding is at a critical site
- Hemodynamic instability
- Clinically overt bleeding with hemoglobin decrease ≥2 g/dL or administration of ≥2 units of RBCs

Is the bleed at a critical site or is it life-threatening?

NO

Stop warfarin

Initiate appropriate measures to control bleeding

Did the above measures control bleeding?

NO

YES

Stop warfarin

Initiate appropriate measures to control bleeding

Administer Kcentra and vitamin K to control bleeding and stabilize patient

Follow appropriate dosing and administration

Adapted from Tomaselli GF et al (2017).
RBC, red blood cell.

Kcentra dosing is based on pretreatment INR and body weight

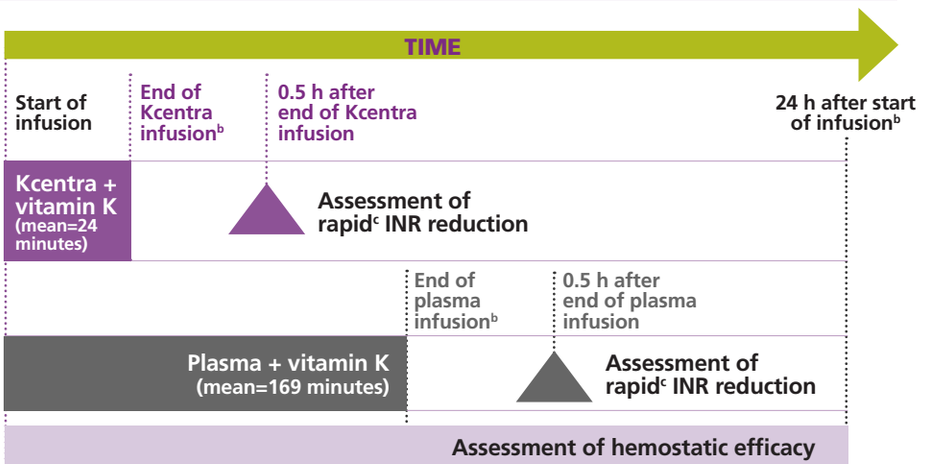
PRETREATMENT INR	2 to <4	4 to 6	>6
Dose[a] of Kcentra (units[b] of factor IX) per kg body weight	25	35	50
Maximum dose[c] (units of factor IX)	Not to exceed 2500	Not to exceed 3500	Not to exceed 5000

[a]Dosing is based on body weight. Dose based on actual potency is stated on the vial, which will vary from 20 to 31 factor IX units/mL after reconstitution. The actual potency for a 500-unit vial ranges from 400 to 620 units/vial. The actual potency for a 1000-unit vial ranges from 800 to 1240 units/vial.

[b]Units refer to international units (IU).

[c]Dose is based on body weight up to but not exceeding 100 kg. For patients who weigh more than 100 kg, the maximum dose should not be exceeded.

Administration of Kcentra according to a prospective, randomized, open-label, active-controlled, multicenter, noninferiority trial[7,a]



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

[a]Two hundred twelve patients ≥18 years of age had acute major bleeding, were receiving warfarin, and had an elevated INR ≥2 within 3 hours before study treatment.

[b]Duration varied between and within treatment groups.

[c]Thirty minutes after end of infusion.

Important Safety Information (cont'd)

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.

Kcentra®
Prothrombin Complex Concentrate (Human)
Urgent Warfarin Reversal

Please see Important Safety Information including boxed warning, continued on the right, and accompanying full Prescribing Information for Kcentra.

Circular of Information recommends against the use of FFP for the correction of coagulopathy associated with warfarin[8]

CIRCULAR OF INFORMATION FOR THE USE OF HUMAN BLOOD AND BLOOD COMPONENTS – 2013

"This *Circular* was prepared jointly by 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."

FFP, fresh frozen plasma.

Important Safety Information (cont'd)

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.

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.

Please see accompanying full Prescribing Information for Kcentra.

References: 1. Frontera JA, Lewin JJ III, Rabinstein AA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage: a statement for healthcare professionals from the Neurocritical Care Society and Society of Critical Care Medicine. *Neurocrit Care.* 2016;24(1):5-46. **2.** Tomaselli GF, Mahaffrey KW, Cuker A, et al. 2017 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol.* 2017;70(24):3042-3067. **3.** Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* 2012;141(2 suppl):e152S-e184S. **4.** American Society for Gastrointestinal Endoscopy (ASGE) Standards of Practice Committee, Acosta RD, Abraham NS, et al. The management of antithrombotic agents for patients undergoing GI endoscopy. *Gastrointest Endosc.* 2016;83(1):3-16. **5.** American College of Surgeons. *Advanced Trauma Life Support (ATLS) Student Course Manual.* 10th ed. Chicago, IL: American College of Surgeons; 2018. **6.** Witt DM, Nieuwlaat R, Clark NP, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. *Blood Adv.* 2018;2(22):3257-3291. **7.** Sarode R, Milling TJ, Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. *Circulation.* 2013;128(11):1234-1243. **8.** American Association of Blood Banks. *Circular of Information for the Use of Human Blood and Blood Components.* Bethesda, MD: American Association of Blood Banks; 2013.

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Biotherapies for Life® **CSL Behring**

Kcentra®
Prothrombin Complex Concentrate (Human)
Urgent Warfarin Reversal

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use KCENTRA safely and effectively. See full prescribing information for KCENTRA.

KCENTRA® (Prothrombin Complex Concentrate (Human))
For Intravenous Use, Lyophilized Powder for Reconstitution
Initial U.S. Approval: 2013

WARNING: ARTERIAL AND VENOUS THROMBOEMBOLIC COMPLICATIONS

Patients being treated with Vitamin K antagonists (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.

- **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. (5.2)**

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.2) 10/2018

----------INDICATIONS AND USAGE----------

Kcentra, Prothrombin Complex Concentrate (Human), is a blood coagulation factor replacement product indicated for the urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients with:

- acute major bleeding or
- need for an urgent surgery/invasive procedure. (1)

----------DOSAGE AND ADMINISTRATION----------

For intravenous use after reconstitution only..

- Kcentra dosing should be individualized based on the patient's baseline International Normalized Ratio (INR) value, and body weight. (2.1)
- Administer Vitamin K concurrently to patients receiving Kcentra to maintain factor levels once the effects of Kcentra have diminished.
- The safety and effectiveness of repeat dosing have not been established and it is not recommended. (2.1)
- Administer reconstituted Kcentra at a rate of 0.12 mL/kg/min (~3 units/kg/min) up to a maximum rate of 8.4 mL/min (~210 units/min). (2.3)

Pre-treatment INR	2–< 4	4–6	> 6
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.

----------DOSAGE FORMS AND STRENGTHS----------

- Kcentra is available as a white or slightly colored lyophilized concentrate in a single-use vial containing coagulation Factors II, VII, IX and X, and antithrombotic Proteins C and S. (3)

----------CONTRAINDICATIONS ----------

Kcentra is contraindicated in patients with:

- Known anaphylactic or severe systemic reactions to Kcentra or any components in Kcentra including heparin, Factors II, VII, IX, X, Proteins C and S, Antithrombin III and human albumin. (4)
- Disseminated intravascular coagulation. (4)
- Known heparin-induced thrombocytopenia. Kcentra contains heparin. (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity reactions may occur. If necessary, discontinue administration and institute appropriate treatment. (5.1)
- Arterial and venous thromboembolic complications have been reported in patients receiving Kcentra. Monitor patients receiving Kcentra for signs and symptoms of thromboembolic events. Kcentra was not studied in subjects who had a thrombotic or thromboembolic (TE) event within the prior 3 months. Kcentra may not be suitable in patients with thromboembolic events in the prior 3 months. (5.2)
- Kcentra is made from human blood and may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. (5.3)

----------ADVERSE REACTIONS----------

- The most common adverse reactions (ARs) (frequency ≥ 2.8%) observed in subjects receiving Kcentra were headache, nausea/vomiting, hypotension, and anemia. (6)
- The most serious ARs were thromboembolic events including stroke, pulmonary embolism, and deep vein thrombosis. (6)

To report SUSPECTED ADVERSE REACTIONS, contact CSL Behring at 1-866-915-6958 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

See 17 for PATIENT COUNSELING INFORMATION

Revised: October 2018

FULL PRESCRIBING INFORMATION: CONTENTS*

***** Sections or subsections omitted from the full prescribing information are not listed.

CSL Behring

FULL PRESCRIBING INFORMATION

Kcentra® Prothrombin Complex Concentrate (Human)

WARNING: ARTERIAL AND VENOUS THROMBOEMBOLIC COMPLICATIONS

Patients being treated with Vitamin K antagonists (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 (TE), 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.

- **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. (5.2)**
- **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. (5.2)**

1 INDICATIONS AND USAGE

Kcentra®, (Prothrombin Complex Concentrate (Human)), is a blood coagulation factor replacement product indicated for the urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients with:

- acute major bleeding or
- need for an urgent surgery/invasive procedure.

2 DOSAGE AND ADMINISTRATION

For intravenous use only.

2.1 Dosage

- Measurement of INR prior to treatment and close to the time of dosing is important because coagulation factors may be unstable in patients with acute major bleeding or an urgent need for surgery and other invasive procedures.
- Individualize Kcentra dosing based on the patient's current pre-dose International Normalized Ratio (INR) value, and body weight (*see Table 1*).
- The actual potency per vial of Factors II, VII, IX and X, Proteins C and S is stated on the carton.
- 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.
- The safety and effectiveness of repeat dosing have not been established and it is not recommended.
- Dose ranging within pre-treatment INR groups has not been studied in randomized clinical trials of Kcentra.

Table 1: Dosage Required for Reversal of VKA Anticoagulation in Patients with acute major bleeding or need for an urgent surgery/invasive procedure

Pre-treatment INR	2–< 4	4–6	> 6
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.

Example dosing calculation for 80 kg patient

For example, an 80 kg patient with a baseline of INR of 5.0, the dose would be 2,800 Factor IX units of Kcentra, calculated as follows based on INR range of 4-6, see *Table 1*:

35 units of Factor IX/kg x 80 kg = 2,800 units of Factor IX required*

* For a vial with an actual potency of 30 units/mL Factor IX, 93 mL would be given (2,800 U/30 U per mL = 93 mL).

Monitor INR and clinical response during and after treatment. In clinical trials, Kcentra decreased the INR to ≤ 1.3 within 30 minutes in most subjects. The relationship between this or other INR values and clinical hemostasis in patients has not been established *[see Clinical Studies (14)]*.

2.2 Preparation and Reconstitution

- Reconstitute Kcentra using aseptic technique with 20 mL (nominal potency 500 U kit) or 40 mL (nominal potency 1000 U kit) of Sterile Water for Injection (diluent) provided in the kit.
- Do not use Kcentra beyond the expiration date on the vial label and carton.
- Kcentra is for single use only. Contains no preservatives. Discard partially used vials.

Table 2: Kcentra Reconstitution Instructions

1. Ensure that the Kcentra vial and diluent vial are at room temperature.	
2. Remove flip caps from the Kcentra and diluent vials.	
3. Wipe the stoppers with the alcohol swab provided and allow to dry prior to opening the Mix2Vial package.	
4. Open the Mix2Vial package by peeling off the lid. [*Fig. 1*] Do **not** remove the Mix2Vial from the blister package.	 Fig. 1
5. Place the diluent vial on an even, clean surface and hold the vial tight. Take the Mix2Vial together with the blister package and push the spike of the **blue** adapter end **straight down** through the diluent vial stopper. [*Fig. 2*]	 Fig. 2
6. Carefully remove the blister package from the Mix2Vial set by holding at the rim, and pulling **vertically** upwards. Make sure that you only pull away the blister package and not the Mix2Vial set. [*Fig. 3*]	 Fig. 3
7. Place the **Kcentra vial** on an even and firm surface. Invert the diluent vial with the Mix2Vial set attached and push the spike of the **transparent** adapter end **straight down** through the Kcentra vial stopper. [*Fig. 4*] The diluent will automatically flow into the Kcentra vial. **Note:** If the vacuum in the Kcentra vial is accidentally lost during reconstitution with the Mix2Vial device, the transfer with the Mix2Vial will not work. In this case, separate the set into two pieces as illustrated in Fig. 6 below; do not discard the diluent vial. Place the Kcentra vial aside on a flat surface. Remove the blue adapter end from the diluent vial of the Mix2Vial set (Fig. 5) by lifting and bending the blue adapter to the side until it disconnects from the diluent vial. For reconstitution: • Using a separate sterile needle and syringe, withdraw the remaining diluent. Remove the needle from the syringe. • Attach the syringe to the transparent adapter of the Kcentra vial as illustrated in Fig. 8 below, and transfer the entire diluent volume into the Kcentra vial. Remove syringe. • Gently swirl the Kcentra vial to ensure the product is fully dissolved. Do not shake. • Proceed to step 10.	 Fig. 4  Fig. 5
8. With one hand, grasp the Kcentra-side of the Mix2Vial set and with the other hand grasp the diluent-side and unscrew the set carefully counterclockwise into two pieces (Fig. 6). Discard the diluent vial with the blue Mix2Vial adapter attached.	 Fig. 6

9. Gently swirl the Kcentra vial with the transparent adapter attached until the substance is fully dissolved (Fig. 7). Do not shake.	 Fig. 7
10. Draw air into an empty, sterile syringe. While the Kcentra vial is upright, connect the syringe to the Mix2Vial's Luer Lock fitting by screwing clockwise. Inject air into the Kcentra vial (Fig. 8).	 Fig. 8
11. While keeping the syringe plunger pressed, turn the system upside down and draw the solution into the syringe by pulling the plunger back slowly (Fig. 9).	 Fig. 9
12. Now that the solution has been transferred into the syringe, firmly hold on to the barrel of the syringe (keeping the syringe plunger facing down) and disconnect the transparent Mix2Vial adapter from the syringe by unscrewing counterclockwise (Fig. 10). Attach the syringe to a suitable intravenous administration set.	 Fig. 10
13. After reconstitution, administration should begin promptly or within 4 hours.	
14. If the same patient is to receive more than one vial, you may pool the contents of multiple vials. Use a separate unused Mix2Vial transfer set for each product vial.	

2.3 Administration

- Do not mix Kcentra with other medicinal products; administer through a separate infusion line.
- Visually inspect the reconstituted solution for particulate matter and discoloration prior to administration whenever solution and container permit. Reconstituted Kcentra solution should be colorless, clear to slightly opalescent, and free from visible particles. Do not use if the solution is cloudy, discolored, or contains particulates.
- Use aseptic technique when adminstering Kcentra.
- Administer at room temperature.
- Administer 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 (~210 units/min).
- No blood should enter the syringe, as there is a possibility of fibrin clot formation.

3 DOSAGE FORMS AND STRENGTHS

- Kcentra is available as a white or slightly colored lyophilized concentrate in a single use vial containing coagulation Factors II, VII, IX and X, and antithrombotic Proteins C and S.
- Kcentra potency (units) is defined by Factor IX content. The actual potency for 500 unit vial ranges from 400-620 Factor IX units/vial. The actual potency for 1000 unit vial ranges from 800-1240 Factor IX units/vial. The actual content of Factor IX as measured in units of potency for the vial before reconstitution is stated by the expiration date. When reconstituted, the final concentration of drug product in Factor IX units will be in a range from 20-31 units/mL.
- The actual units of potency for each coagulation factor (Factors II, VII, IX and X), and Proteins C and S are stated on the carton.

4 CONTRAINDICATIONS

Kcentra is contraindicated in:

- Patients with known anaphylactic or severe systemic reactions to Kcentra or any components in Kcentra 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). Kcentra contains heparin *[see Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions including flushing, urticaria, tachycardia, anxiety, angioedema, wheezing, nausea, vomiting, hypotension, tachypnea, dyspnea, pulmonary edema, and bronchospasm have been observed with Kcentra.

If severe allergic reaction or anaphylactic type reactions occur, immediately discontinue administration, and institute appropriate treatment.

5.2 Thromboembolic Risk/Complications

Both fatal and non-fatal arterial thromboembolic events (including acute myocardial infarction and arterial thrombosis), and venous thromboembolic events (including pulmonary embolism and venous thrombosis) and disseminated intravascular coagulation have been reported with Kcentra in clinical trials and post marketing surveillance *[see Adverse Reactions (6) and Clinical Studies (14)]*. Patients being treated with VKA therapy have underlying disease states that predispose them to thromboembolic events. Reversing VKA therapy exposes patients to the thromboembolic risk of their underlying disease. Resumption of anticoagulation should be carefully considered following administration of Kcentra and Vitamin K once the risk of thromboembolic events outweighs the risk of bleeding.

Thromboembolic events occurred more frequently following Kcentra compared to plasma in a randomized, plasma controlled trial in subjects requiring urgent reversal of VKA anticoagulation due to acute major bleeding, and the excess in thromboembolic events was more pronounced among subjects who had a history of prior thromboembolic event, although these differences were not statistically significant *[see Adverse Reactions (6.1) and Clinical Studies (14)]*. Potential benefits of treatment with Kcentra should be weighed against the potential risks of thromboembolic events *[see Adverse Reactions (6)]*. 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 RCT. Kcentra may not be suitable in patients with thromboembolic events in the prior 3 months. Because of the risk of thromboembolism associated with reversal of VKA, closely monitor patients for signs and symptoms of thromboembolism during and after administration of Kcentra. *[see 17 Patient Counseling Information]*

5.3 Transmissible Infectious Agents

Because Kcentra is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. There is also the possibility that unknown infectious agents may be present in such products. Despite the use of two dedicated virus reduction steps in manufacturing to reduce risks, such products may still potentially transmit disease.

Reports of suspected virus transmission of hepatitis A, B, C, and HIV were generally confounded by concomitant administration of blood/blood components and/or other plasma-derived products. No causal relationship to Kcentra administration was established for any of these reports since introduction of a virus filtration step in 1996.

All infections thought by a physician to have been possibly transmitted by Kcentra should be reported by the physician or other healthcare provider to the CSL Behring Pharmacovigilance Department at 1-866-915-6958 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

6 ADVERSE REACTIONS

The most common adverse reactions (ARs) (frequency ≥ 2.8%) observed in subjects receiving Kcentra were headache, nausea/vomiting, hypotension, and anemia.

The most serious ARs were thromboembolic events including stroke, pulmonary embolism, and deep vein thrombosis.

The following serious adverse reactions are described below and/or elsewhere in the labeling:

- Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*
- Arterial and venous thromboembolic complications *[see Boxed Warning and Warnings and Precautions (5.2)]*
- Possible transmission of infectious agents *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Randomized, Plasma-Controlled Trial in Acute Major Bleeding

In a prospective, randomized, open-label, active-controlled multicenter non-inferiority trial, 212 subjects who required urgent reversal of VKA therapy due to acute major bleeding were enrolled and randomized to treatment; 103 were treated with Kcentra and 109 with plasma. Subjects with a history of a thrombotic event, 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. Subjects ranged in age from 26 years to 96 years.

Randomized, Plasma-Controlled Trial in Urgent Surgery/Invasive Procedures

In a prospective, randomized, open-label, active-controlled, multicenter non-inferiority trial, 176 subjects who required urgent reversal of VKA therapy due to the need for an urgent surgical or urgent invasive procedure were enrolled; 88 were treated with Kcentra and 88 with plasma. Subjects ranged in age from 27 years to 94 years.

Adverse reactions are summarized for Kcentra and plasma in the Acute Major Bleeding and Urgent Surgery/Invasive Procedures RCTs (*see Table 3*).

Adverse Reactions are defined as adverse events that began during or within 72 hours of test product infusion plus adverse events considered possibly/probably related or related to study treatment according to the investigator, sponsor, or the blinded safety adjudication board (SAB), and with at least a 1.3-fold difference between treatments.

Table 3: Adverse Reactions Reported in more than 5 Subjects (≥ 2.8%) Following Kcentra or Plasma Administration in RCTs

	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

Serious adverse reactions in subjects receiving Kcentra in both RCTs included ischemic cerebrovascular accident (stroke), DVT, thrombosis, and venous insufficiency. Serious adverse reactions in both RCTs for plasma included myocardial ischemia, myocardial infarction, fluid overload, embolic cerebral infarction, pulmonary edema, respiratory failure, and DVT.

There were a total of 10 subjects (9.7%) who died in the Kcentra group (1 additional death occurred on day 46 just after completion of the study reporting period) and 5 (4.6%) who died in the plasma group in the plasma-controlled RCT in acute major bleeding. The 95% confidence interval for the Kcentra minus plasma between-group difference in deaths ranged from -2.7% to 13.5%. From the plasma-controlled RCT in urgent surgery/invasive procedures, there were a total of 3 subjects (3.4%) who died in the Kcentra group (1 additional death occurred on day 48 after completion of the study reporting period) and 8 (9.1%) who died in the Plasma group. The 95% confidence interval for the Kcentra minus plasma between-group difference in deaths in this trial ranged from -14.6% to 2.7%. One death in the Kcentra group in the RCT in Acute Major Bleeding and one death in the plasma group in the RCT in urgent surgery/invasive procedures were considered possibly related to study treatment according to an assessment of masked data by an independent safety adjudication board. No factors common to all deaths were identified, except for the frequent findings of a high comorbidity burden, advanced age, and death after being placed on comfort care. Although, a greater proportion of subjects in the RCT in acute major bleeding than in the RCT in surgery/invasive procedure received the highest two recommended doses of Kcentra because more subjects in the trial in acute major bleeding had a baseline INR in the ranges of 4-6 and > 6.0, an analysis of deaths and factor levels in subjects with major bleeding revealed that subjects who died had similar median factor levels to subjects that did not die. Additionally, outliers with supraphysiologic factor levels did not have a mortality rate out of proportion to the overall population.

Fluid Overload

There were 9 subjects (4.7%, all non-related by investigator assessment) in the Kcentra group who experienced fluid overload in the plasma-controlled RCTs in acute major bleeding and urgent surgery/invasive procedures and 25 (12.7%, 13 events related by investigator assessment) who had fluid overload in the plasma group. The 95% confidence interval for the Kcentra minus Plasma between-group difference in fluid overload event incidence ranged from -14.1% to -2.0%.

Subgroup analyses of the RCTs in acute major bleeding and urgent surgery/invasive procedures according to whether subjects with fluid overload events had a prior history of congestive heart failure are presented in Table 4.

Table 4: Subjects with Fluid Overload Events by Prior History of Congestive Heart Failure in RCTs

Subgroup	**Acute Major Bleeding Study**				**Urgent Surgery/Invasive Procedures Study**			
	Kcentra		**Plasma**		**Kcentra**		**Plasma**	
	N	**Fluid Overload N (%)**	**N**	**Fluid Overload N (%)**	**N**	**Fluid Overload N (%)**	**N**	**Fluid Overload N (%)**
All subjects	**103**	**6 (5.8)**	**109**	**14 (12.8)**	**88**	**3 (3.4)**	**88**	**11 (12.5)**
With history of CHF	46	4 (8.7)	44	11 (25.0)	24	1 (4.2)	36	6 (16.7)
Without history of CHF	57	2 (3.5)	65	3 (4.6)	64	2 (3.1)	52	5 (9.6)

Thromboembolic Events

In RCTs, there were 13 subjects (6.8%) in the Kcentra group who experienced possible thromboembolic events (TEEs) and 14 (7.1%) who had TEEs in the plasma group. The incidence of thromboembolic (TE) adverse reactions assessed as at least possibly related to study treatment by the Investigator or, in the case of serious thromboembolic events, the blinded safety adjudication board (SAB) was 9 (4.7%) in the Kcentra group and 7 (3.6%) in the plasma group. When also considering the events which began during or within 72 hours of test product infusion, the incidence was 9 (4.7%) in the Kcentra group and 8 (4.1%) in the plasma group.

TE events observed in the acute major bleeding and the urgent surgery/invasive procedures RCTs are shown in Table 5.

Table 5: Adverse Reactions (TEEs only) Following Kcentra or Plasma Administration in RCTs

System Organ Class	No. (%) of subjects			
	Acute Major Bleeding Study		Urgent Surgery/ Invasive Procedures Study	
	Kcentra (N = 103)	Plasma (N = 109)	Kcentra (N = 88)	Plasma (N = 88)
Any possible TEE*	**9 (8.7%)**	**6 (5.5%)**	**4 (4.5)**	**8 (9.1)**
TEE Adverse reactions	**6 (5.5%)**	**4 (3.7%)**	**4 (4.5)**	**4 (4.5)**
Cardiac disorders				
Myocardial infarction	0	1 (0.9%)	0	2 (2.3)
Myocardial ischemia	0	2 (1.8%)	0	0
Nervous system disorders				
Ischemic cerebrovascular accident (stroke)	2 (1.9%)	0	1 (1.1)	0
Embolic cerebral infarction	0	0	0	1 (1.1)
Cerebrovascular disorder	0	1 (0.9%)	0	0
Vascular disorders				
Venous thrombosis calf	1 (1.0%)	0	0	0
Venous thrombosis radial vein	0	0	1 (1.1)	0
Thrombosis (microthrombosis of toes)	0	0	1 (1.1)	0
Deep vein thrombosis (DVT)	1 (1.0%)	0	1 (1.1)	1 (1.1)
Fistula Clot	1 (1.0%)	0	0	0
Unknown Cause of Death (not confirmed TEE)				
Sudden death	1 (1.0%)	0	0	0

* The tabulation of possible TEEs includes subjects with confirmed TEEs as well as 3 subjects in the Acute Major Bleeding RCT Kcentra group that died of unknown causes on days 7, 31, and 38 and 1 subject in the Urgent Surgery/Invasive Procedures RCT plasma group that died of unknown causes on day 18. The death on day 7 was considered possibly related to study product by the SAB and is tabulated as an adverse reaction.

Subgroup analyses of the RCTs according to whether subjects with thromboembolic events had a prior history of a thromboembolic event are presented in Table 6.

Table 6: Subjects with Thromboembolic Events by Prior History of TE Event in RCTs

	Acute Major Bleeding Study				Urgent Surgery/Invasive Procedures Study			
	Kcentra		Plasma		Kcentra		Plasma	
	N	TE Events* N (%)	N	TE Events N (%)	N	TE Events* N (%)	N	TE Events N (%)
All subjects	**103**	**9 (8.7)**	**109**	**6 (5.5)**	**88**	**4 (4.5)**	**88**	**8 (9.1)**
With history of TE event†	69	8 (11.6)	79	3 (3.8)	55	3 (5.5)	62	5 (8.1)
Without history of TE event	34	1 (2.9)	30	3 (10.0)	33	1 (3.0)	26	3 (11.5)

* One additional subject in the Acute Major Bleeding RCT who had received Kcentra, not listed in the table, had an upper extremity venous thrombosis in association with an indwelling catheter. Two additional subjects in the Urgent Surgery/Invasive Procedures RCT who had received Kcentra, not listed in the table, had non-intravascular events (catheter-related/IVC filter insertion).

† History of prior TE event greater than 3 months from study entry (TE event within 3 months not studied).

The European Bleeding and Surgical Study:

In a prospective, open label, single-arm, multicenter safety and efficacy trial, 17 subjects who required urgent reversal of VKA due to acute bleeding were enrolled and 26 subjects who required urgent reversal of Vitamin K antagonist due to the need for an urgent surgical/invasive procedure were enrolled, all were treated with Kcentra. Subjects ranged in age from 22 years to 85 years. Serious adverse reactions considered possibly related to Kcentra included a suspected pulmonary embolism which occurred in one subject following a second dose of Kcentra. A single non-fatal TE event occurred in another Kcentra-treated subject in that trial.

6.2 Postmarketing Experience

No adverse reactions other than those addressed *[see Warnings and Precautions (5)* and *Adverse Reactions (6)]* have been observed in the postmarketing use of Kcentra outside the US since 1996.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data with Kcentra use in pregnancy to inform on drug-associated risk. Animal reproduction studies have not been conducted with Kcentra. It is not known whether Kcentra can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Kcentra should be prescribed for a pregnant woman only if clearly needed.

In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the excretion of Kcentra in human milk, the effect on the breastfed infant, or the effects on milk production. Because many drugs are excreted in human milk, use Kcentra only if clearly needed when treating a nursing woman.

8.4 Pediatric Use

The safety and efficacy of Kcentra in the pediatric population has not been studied.

8.5 Geriatric Use

Of the total number of subjects (431) with acute major bleeding or with the need for an urgent surgery/invasive procedure treated to reverse VKA anticoagulation in three clinical studies, 66% were 65 years old or greater and 39% were 75 years old or greater. There were no clinically significant differences between the safety profile of Kcentra and plasma in any age group.

8.6 Congenital Factor Deficiencies

Kcentra has not been studied in patients with congenital factor deficiencies.

11 DESCRIPTION

Kcentra is a purified, heat-treated, nanofiltered and lyophilized non-activated four-factor Prothrombin Complex Concentrate (Human) prepared from human U.S. Source Plasma (21 CFR 640.60). It contains the Vitamin K dependent Coagulation Factors II, VII, IX and X, and the antithrombotic Proteins C and S. Factor IX is the lead factor for the potency of the preparation as stated on the vial label. The excipients are human antithrombin III, heparin, human albumin, sodium chloride, and sodium citrate. Kcentra is sterile, pyrogen-free, and does not contain preservatives.

The product contents are shown in Table 7 and listed as ranges for the blood coagulation factors.

Table 7: Composition per Vial of Kcentra *

Ingredient	Potency Range for 500 units	Potency Range for 1000 units
Total protein	120–280 mg	240–560 mg
Factor II	380–800 units	760–1600 units
Factor VII	200–500 units	400–1000 units
Factor IX	400–620 units	800–1240 units
Factor X	500–1020 units	1000–2040 units
Protein C	420–820 units	840–1640 units
Protein S	240–680 units	480–1360 units
Heparin	8–40 units	16–80 units
Antithrombin III	4–30 units	8–60 units
Human albumin	40–80 mg	80–160 mg
Sodium chloride	60–120 mg	120–240 mg
Sodium citrate	40–80 mg	80–160 mg
HCl	Small amounts	Small amounts
NaOH	Small amounts	Small amounts

* Exact potency of coagulant and antithrombotic proteins are listed on the carton

All plasma used in the manufacture of Kcentra is obtained from US donors and is tested using serological assays for hepatitis B surface antigen and antibodies to HIV-1/2 and HCV. The plasma is tested with Nucleic Acid Testing (NAT) for HCV, HIV-1, HAV, and HBV, and found to be non-reactive (negative), and the plasma is also tested by NAT for human parvovirus B19 (B19V) in order to exclude donations with high titers. The limit for B19V in the fractionation pool is set not to exceed 10^4 units of B19V DNA per mL. Only plasma that passed virus screening is used for production.

The Kcentra manufacturing process includes various steps, which contribute towards the reduction/ inactivation of viruses. Kcentra is manufactured from cryo-depleted plasma that is adsorbed via ion exchange chromatography, heat treated in aqueous solution for 10 hours at 60°C, precipitated, adsorbed to calcium phosphate, virus filtered, and lyophilized.

Manufacturing steps were independently validated in a series of in vitro experiments for their virus inactivation / reduction capacity for both enveloped and non-enveloped viruses. Table 8 shows the virus clearance during the manufacturing process for Kcentra, expressed as the mean $\log_{10}$ reduction factor.

Table 8: Mean Virus Reduction Factors [$\log_{10}$] of Kcentra

Virus Studied	Manufacturing Steps			Overall Virus Reduction [$\log_{10}$]
	Heat treatment ("Pasteurization")	Ammonium sulphate precipitation followed by Ca Phosphate adsorption	2 x 20 nm Virus Filtration	
Enveloped Viruses				
HIV	≥ 5.9	≥ 5.9	≥ 6.6	≥ 18.4
BVDV	≥ 8.5	2.2	≥ 6.0	≥ 16.7
PRV	3.8	7.2	≥ 6.6	≥ 17.6
WNV	≥ 7.4	n.d.	≥ 8.1	≥ 15.5
Non-Enveloped Viruses				
HAV	4.0	1.8	≥ 6.1	≥ 11.9
CPV	[0.5]*	1.5	6.5	8.0

* Reduction factor below 1 $\log_{10}$ was not considered in calculating the overall virus reduction. Studies using human parvovirus B19, which are considered experimental in nature, have demonstrated a virus reduction factor of 3.5 $\log_{10}$ by heat treatment.

HIV Human immunodeficiency virus, a model for HIV-1 and HIV-2
BVDV Bovine viral diarrhea virus, model for HCV
PRV Pseudorabies virus, a model for large enveloped DNA viruses
WNV West Nile virus
HAV Hepatitis A virus
CPV Canine parvovirus, model for B19V
n.d. not determined

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Kcentra contains the Vitamin K-dependent coagulation Factors II (FII), VII (FVII), IX (FIX), and X (FX), together known as the Prothrombin Complex, and the antithrombotic Protein C and Protein S.

A dose-dependent acquired deficiency of the Vitamin K-dependent coagulation factors occurs during Vitamin K antagonist treatment. Vitamin K antagonists exert anticoagulant effects by blocking 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.

Coagulation Factor II

Factor II (prothrombin) is converted to thrombin by activated FX (FXa) in the presence of Ca^{2+}, FV, and phospholipids.

Coagulation Factor VII

Factor VII (proconvertin) is converted to the activated form (FVIIa) by splitting of an internal peptide link. The FVIIa-TF complex activates Factor IX and initiates the primary coagulation pathway by activating FX in the presence of phospholipids and calcium ions.

Coagulation Factor IX

Factor IX (antihemophilic globulin B, or Christmas factor) is activated by the FVIIa-TF complex and by FXIa. Factor IXa in the presence of FVIIIa activates FX to FXa.

Coagulation Factor X

Factor X (Stuart-Prower factor) activation involves the cleavage of a peptide bond by the FVIIIa-Factor IXa complex or the TF-FVIIa complex. Factor Xa forms a complex with activated FV (FVa) that converts prothrombin to thrombin in the presence of phospholipids and calcium ions.

Protein C

Protein C, when activated by thrombin, exerts an antithrombotic effect by inhibiting FVa and FVIIIa leading to a decrease in thrombin formation, and has indirect profibrinolytic activity by inhibiting plasminogen activator inhibitor-1.

Protein S

Protein S exists in a free form (40%) and in a complex with C4b-binding protein (60%). Protein S (free form) functions as a cofactor for activated Protein C in the inactivation of FVa and FVIIIa, leading to antithrombotic activity.

12.2 Pharmacodynamics

International Normalized Ratio (INR)

In the plasma-controlled RCT in acute major bleeding, the INR was determined at varying time points after the start or end of infusion, depending upon study design. The median INR was above 3.0 prior to the infusion and dropped to a median value of 1.20 by the 30 minute time point after start of Kcentra infusion. By contrast, the median value for plasma was 2.4 at 30 minutes after the start of infusion. The INR differences between Kcentra and plasma were statistically significant in randomized plasma-controlled trial in bleeding up to 12 hours after start of infusion [*see Table 9*].

The relationship between these or other INR values and clinical hemostasis in patients has not been established *[see Clinical Studies (14)]*.

Table 9: Median INR (Min-Max) after Start of Infusion in RCTs

Study	Treatment	Baseline	30 min	1 hr	2-3 hr	6-8 hr	12 hr	24 hr
Acute Major Bleeding Study	Kcentra (N = 98)	3.90 (1.8–20.0)	1.20* (0.9–6.7)	1.30* (0.9–5.4)	1.30* (0.9–2.5)	1.30* (0.9–2.1)	1.20* (0.9–2.2)	1.20 (0.9–3.8)
	Plasma (N = 104)	3.60 (1.9–38.9)	2.4 (1.4–11.4)	2.1 (1.0–11.4)	1.7 (1.1–4.1)	1.5 (1.0–3.0)	1.4 (1.0–3.0)	1.3 (1.0–2.9)
Urgent Surgery/ Invasive Procedures Study	Kcentra (N = 87)	2.90 (2.0–17.0)	1.30* (0.9–7.0)	1.20* (0.9–2.5)	1.30* (0.9–39.2)	1.30* (1.0–10.3)	NC	1.20 (0.9–2.7)
	Plasma (N = 81)	2.90 (2.0–26.7)	2.15 (1.4–5.4)	1.90 (1.3–5.7)	1.70 (1.1–3.7)	1.60 (1.0–5.8)	NC	1.30 (1.0–2.7)

* Statistically significant difference compared to plasma by 2-sided Wilcoxon test
INR = international normalized ratio; NC = not collected.

12.3 Pharmacokinetics

Fifteen healthy subjects received 50 units/kg of Kcentra. No subjects were receiving VKA therapy or were experiencing acute bleeding. A single intravenous Kcentra infusion produced a rapid and sustained increase in plasma concentration of Factors II, VII, IX and X as well as Proteins C and S. The PK analysis *[see Table 10]* shows that factor II had the longest half-life (59.7 hours) and factor VII the shortest (4.2 hours) in healthy subjects. PK parameters obtained from data derived from the study of healthy subjects may not be directly applicable to patients with INR elevation due to VKA anticoagulation therapy.

Table 10: Vitamin K-Dependent Coagulation Factor Pharmacokinetics after a Single Kcentra Infusion in Healthy Subjects (n=15) Mean (SD)*

Parameter	Factor IX	Factor II	Factor VII	Factor X	Protein C	Protein S
Terminal half-life (h)	42.4 (41.6)	60.4 (25.5)	5.0 (1.9)	31.8 (8.7)	49.6 (32.7)	50.4 (13.4)
IVR (%/ units/kg bw)*	1.6 (0.4)	2.2 (0.3)	2.5 (0.4)	2.2 (0.4)	2.9 (0.3)	2.0 (0.3)
AUC (IU/dL x h)	1850.8 (1001.4)	7282.2 (2324.9)	512.9 (250.1)	6921.5 (1730.5)	5397.5 (2613.9)	3651.6 (916.3)
Clearance (mL/ kg x h)	3.7 (1.6)	1.0 (0.3)	7.4 (4.1)	1.3 (0.3)	1.5 (0.9)	1.2 (0.3)
MRT (h)†	47.3 (49.5)	82.0 (34.2)	7.1 (2.7)	45.9 (12.6)	62.4 (42.1)	70.3 (18.3)
Vd_{ss} (mL/kg)‡	114.3 (54.6)	71.4 (13.7)	45.0 (10.7)	55.5 (6.7)	62.2 (17.4)	78.8 (11.6)

* IVR: In Vivo Recovery
† MRT: Mean Residence Time
‡ Vd_{ss}: Volume of Distribution at steady state

The mean in vivo recovery (IVR) of infused factors was calculated in subjects who received Kcentra. The IVR is the increase in measurable factor levels in plasma (units/dL) that may be expected following an infusion of factors (units/kg) administered as a dose of Kcentra. The in vivo recovery ranged from 1.15 (Factor IX) to 2.81 (Protein S) *[see Table 11]*.

Table 11: In vivo Recovery in RCTs*

Parameter	Incremental (units/dL per units/kg b.w.)			
	Acute Major Bleeding Study (N = 98)		Urgent Surgery/Invasive Procedures Study (N = 87)	
	Mean (SD)	95% CI†	Mean (SD)	95% CI†
Factor IX	1.29 (0.71)	(1.14–1.43)	1.15 (0.57)	(1.03–1.28)
Factor II	2.00 (0.88)	(1.82–2.18)	2.14 (0.74)	(1.98–2.31)
Factor VII	2.15 (2.96)	(1.55–2.75)	1.90 (4.50)	(0.92–2.88)
Factor X	1.96 (0.87)	(1.79–2.14)	1.94 (0.69)	(1.79–2.09)
Protein C	2.04 (0.96)	(1.85–2.23)	1.88 (0.68)	(1.73–2.02)
Protein S	2.17 (1.66)	(1.83–2.50)	2.81 (1.95)	(2.38–3.23)

* ITT-E: Intention to Treat – Efficacy Population
† CI: Confidence Interval

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of Kcentra, or studies to determine the effects of Kcentra on genotoxicity or fertility have not been performed. An assessment of the carcinogenic potential of Kcentra was completed and suggests minimal carcinogenic risk from product use.

14 CLINICAL STUDIES

Acute Major Bleeding RCT

The efficacy of Kcentra has been evaluated in a prospective, open-label, (blinded assessor), active-controlled, non-inferiority, multicenter RCT in subjects who had been treated with VKA therapy and who required urgent replacement of their Vitamin K-dependent clotting factors to treat acute major bleeding. A total of 216 subjects with acquired coagulation factor deficiency due to oral Vitamin K antagonist therapy were randomized to a single dose of Kcentra or plasma. Two hundred twelve (212) subjects received Kcentra or plasma for acute major bleeding in the setting of a baseline INR ≥ 2.0 and recent use of a VKA anticoagulant. The doses of Kcentra (25 units/kg, 35 units/kg, or 50 units/kg) based on nominal Factor IX content and plasma (10 mL/kg, 12 mL/kg, or 15 mL/kg) were calculated according to the subject's baseline INR (2-< 4, 4-6, > 6, respectively). The observation period lasted for 90 days after the infusion of Kcentra or plasma. The modified efficacy (ITT-E) population for Kcentra included 98 subjects and for plasma included 104 subjects. Additionally, intravenous Vitamin K was administered.

The efficacy endpoint was hemostatic efficacy for the time period from the start of infusion of Kcentra or plasma until 24 hours. Efficacy was adjudicated as "effective" or "not effective" by a blinded, independent Endpoint Adjudication Board for all subjects who received study product. Criteria for effective hemostasis were based upon standard clinical assessments including vital signs, hemoglobin measurements, and CT assessments at pre-defined time points, as relevant to the type of bleeding (i.e., gastrointestinal, intracranial hemorrhage, visible, musculoskeletal, etc.). The proportion of subjects with effective hemostasis was 72.4% in the Kcentra group and 65.4% in the plasma group. The lower limit of the 95% confidence interval (CI) for the difference in proportions of Kcentra minus plasma was -5.8%, which exceeded -10% and thereby demonstrated the non-inferiority of Kcentra versus plasma (the study's primary objective) *[see Table 12]*. Because the lower limit of the CI was not greater than zero, the prospectively defined criterion for superiority of Kcentra for hemostatic efficacy (a secondary objective) was not met.

Table 12: Rating of Hemostatic Efficacy in Subjects with Acute Major Bleeding

Rating	No. (%) of subjects [95% CI]		Difference Kcentra – Plasma (%) [95% CI]*
	Kcentra (N = 98)	Plasma (N = 104)	
"Effective" hemostasis	71 (72.4%) [62.3; 82.6]	68 (65.4%) [54.9; 75.8]	(7.1%) [-5.8; 19.9]

* Kcentra non-inferior to plasma if lower limit of 95% CI > –10%; Kcentra superior to plasma if lower limit of 95% CI > 0.
CI = confidence interval; N = number of subjects

Results of a post-hoc analysis of hemostatic efficacy stratified by actual dose of Kcentra or plasma administered in the acute major bleeding RCT are presented in Table 13.

Table 13: Rating of Hemostatic Efficacy Stratified by Actual Dose of Kcentra or Plasma (Number and % of Subjects rated "Effective" in Acute Major Bleeding RCT

	Low Dose	Mid Dose	High Dose
	N = 49 (K)	N = 22 (K)	N = 26 (K)
	N = 55 (P)	N = 18 (P)	N = 31 (P)
Kcentra	36 (74.5%)	16 (72.7%)	18 (69.2%)
Plasma	38 (69.1%)	11 (61.1%)	19 (61.3%)
Difference*	(4.4%)	(11.6%)	(7.9%)
95% CI K– P	-13.2–21.9	-17.4–40.6	-17.0–32.9

* Kcentra minus Plasma

An additional endpoint was the reduction of INR to ≤ 1.3 at 30 minutes after the end of infusion of Kcentra or plasma for all subjects that received study product. The proportion of subjects with this decrease in INR was 62.2% in the Kcentra group and 9.6% in the plasma group. The 95% confidence interval for the difference in proportions of Kcentra minus plasma was 39.4% to 65.9%. The lower limit of the 95% CI of 39.4% demonstrated superiority of Kcentra versus plasma for this endpoint *[see Table 14]*.

Table 14: Decrease of INR (1.3 or Less at 30 Minutes after End of Infusion) in Acute Major Bleeding RCT

Rating	No. (%) of subjects [95% CI]		Difference Kcentra – Plasma (%) [95% CI]*
	Kcentra (N = 98)	Plasma (N = 104)	
Decrease of INR to ≤ 1.3 at 30 min	61 (62.2%) [52.6; 71.8]	10 (9.6%) [3.9; 15.3]	(52.6%) [39.4; 65.9]

* Kcentra non-inferior to plasma if lower limit of 95% CI > –10%; Kcentra superior to plasma if lower limit of 95% CI > 0.
CI = confidence interval; INR = international normalized ratio; N = total subjects

Urgent Surgery/Invasive Procedure RCT

The efficacy of Kcentra has been evaluated in a prospective, open-label, active-controlled, non-inferiority, multicenter RCT in subjects who had been treated with VKA therapy and who required urgent replacement of their Vitamin K-dependent clotting factors because of their need for an urgent surgery/ invasive procedure. A total of 181 subjects with acquired coagulation factor deficiency due to oral Vitamin K antagonist therapy were randomized to a single dose of Kcentra or plasma. One hundred seventy-six (176) subjects received Kcentra or plasma because of their need for an urgent surgery/ invasive procedure in the setting of a baseline INR ≥ 2.0 and recent use of a VKA anticoagulant. The doses of Kcentra (25 units/kg, 35 units/kg, or 50 units/kg) based on nominal Factor IX content and plasma (10 mL/kg, 12 mL/kg, or 15 mL/kg) were calculated according to the subject's baseline INR (2-< 4, 4-6, > 6, respectively). The observation period lasted for 90 days after the infusion of Kcentra or plasma. The modified efficacy (ITT-E) population for Kcentra included 87 subjects and for plasma included 81 subjects. Additionally, oral or intravenous Vitamin K was administered.

The efficacy endpoint was hemostatic efficacy for the time period from the start of infusion of Kcentra or plasma until the end of the urgent surgery/invasive procedure. Criteria for effective hemostasis were based upon the difference between predicted and actual blood losses, subjective hemostasis rating, and the need for additional blood products containing coagulation factors. The proportion of subjects with effective hemostasis was 89.7% in the Kcentra group and 75.3% in the plasma group. The lower limit of the 95% confidence interval (CI) for the difference in proportions of Kcentra minus plasma was 2.8%, which exceeded -10% and thereby demonstrated the non-inferiority of Kcentra versus plasma (the study's primary objective) *[see Table 15]*. Because the lower limit of the CI was greater than 0, the prospectively defined criterion for superiority of Kcentra for hemostatic efficacy (a secondary objective) was also met.

Table 15: Rating of Hemostatic Efficacy in Urgent Surgery/Invasive Procedure RCT

Rating	No. (%) of subjects [95% CI]		Difference Kcentra – Plasma (%) [95% CI]*
	Kcentra (N = 87)	Plasma (N = 81)	
"Effective" hemostasis	78 (89.7%) [83.3; 96.1]	61 (75.3%) [65.9; 84.7]	(14.3%) [2.8; 25.8]

* Kcentra non-inferior to plasma if lower limit of 95% CI > –10%; Kcentra superior to plasma if lower limit of 95% CI > 0.
CI = confidence interval; N = number of subjects
Results of a post-hoc analysis of hemostatic efficacy stratified by actual dose of Kcentra or plasma administered in the urgent surgery/invasive procedure RCT are presented in Table 16.

Table 16: Rating of Hemostatic Efficacy Stratified by Actual Dose of Kcentra or Plasma (Number and % of Subjects Rated "Effective" in Urgent Surgery/Invasive Procedure RCT)

	Low Dose	Mid Dose	High Dose
	N = 69 (K)	N = 10 (K)	N = 8 (K)
	N = 62 (P)	N = 10 (P)	N = 9 (P)
Kcentra	63 (91.3%)	8 (80.0%)	7 (87.5%)
Plasma	48 (77.4%)	7 (70.0%)	6 (66.7%)
Difference*	(13.9%)	(10.0%)	(20.8%)
95% CI K–P	1.4-26.6	-26.5-43.5	-19.8-53.7

* Kcentra minus Plasma

An additional endpoint was the reduction of INR to ≤ 1.3 at 30 minutes after the end of infusion of Kcentra or plasma for all subjects that received study product. The proportion of subjects with this decrease in INR was 55.2% in the Kcentra group and 9.9% in the plasma

group. The 95% confidence interval for the difference in proportions of Kcentra minus plasma was 31.9% to 56.4%. The lower limit of the 95% CI of 31.9% demonstrated superiority of Kcentra versus plasma for this endpoint *[see Table 17]*. The relationship between a decrease in INR to less than or equal to 1.3 and clinical hemostatic efficacy has not been established.

Table 17: Decrease of INR (1.3 or Less at 30 Minutes after End of Infusion) in Urgent Surgery/Invasive Procedure RCT

Rating	No. (%) of subjects [95% CI]		Difference
	Kcentra (N = 87)	Plasma (N = 81)	Kcentra – Plasma (%) [95% CI]*
Decrease of INR to ≤ 1.3 at 30 min	48 (55.2%) [44.7; 65.6]	8 (9.9%) [3.4; 16.4]	(45.3%) [31.9; 56.4]

* Kcentra non-inferior to plasma if lower limit of 95% CI > -10%; Kcentra superior to plasma if lower limit of 95% CI > 0.

CI = confidence interval; INR = international normalized ratio; N = total subjects

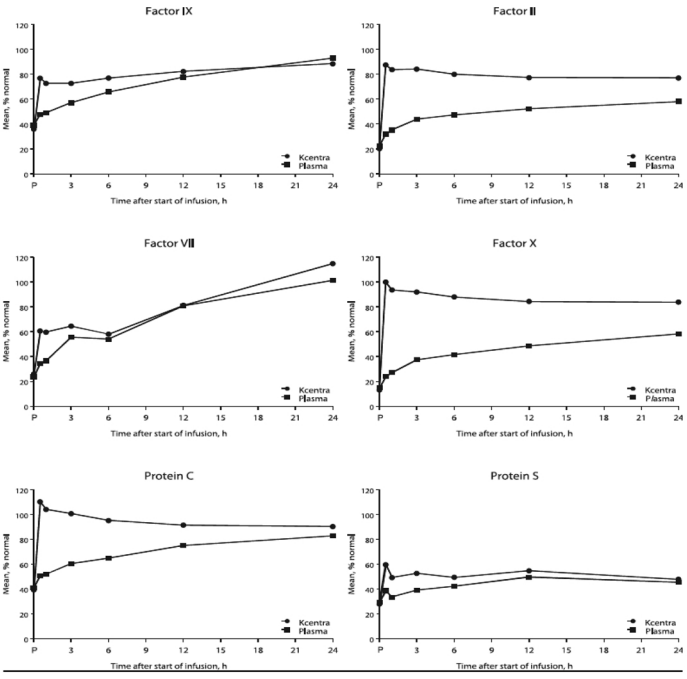
The European Bleeding and Surgical Study was an open-label, single-arm, multicenter study.[1] Forty-three (43) subjects who were receiving VKA were treated with Kcentra, because they either (1) required a surgical or an invasive diagnostic intervention (26 subjects), or (2) experienced an acute bleeding event (17 subjects). The dose of Kcentra (25 units/kg, 35 units/kg, or 50 units/kg) based on nominal Factor IX content was calculated according to the subject's baseline INR value (2–< 4, 4-6, > 6). The endpoint was the decrease of the INR to ≤ 1.3 within 30 minutes after end of Kcentra infusion in subjects who received any portion of study product.

Of the 17 evaluable subjects receiving Kcentra for acute bleeding, 16 subjects (94%) experienced a decrease in INR to ≤ 1.3 within 30 minutes after the end of the Kcentra infusion.

In RCTs, levels of Coagulation Factors II, VII, IX, X, and Antithrombotic Proteins C and S were measured after the infusion of Kcentra or plasma and the results were similar for subjects with acute major bleeding or subjects requiring an urgent surgery or invasive procedure. In the plasma-controlled RCT in acute major bleeding, the mean duration of Kcentra infusion was 24 minutes (± 32 minutes) and the mean duration of infusion for plasma was 169 minutes (± 143 minutes). The mean infusion volume of Kcentra was 105 mL ± 37 mL and the mean infusion volume of plasma was 865 mL ± 269 mL. In the plasma-controlled RCT for patients needing urgent surgery/invasive procedures, the mean duration of Kcentra infusion was 21 minutes (± 14 minutes) and the mean duration of infusion for plasma was 141 minutes (± 113 minutes). The mean infusion volume of Kcentra was 90 mL ± 32 mL and the mean infusion volume of plasma was 819 mL ± 231 mL.

The increase in mean factor levels over time following Kcentra and plasma administration in the plasma-controlled RCT in acute major bleeding is shown in *Figure 9* below (the mean factor levels over time following Kcentra and plasma administration in the plasma-controlled RCT for patients needing urgent surgery/invasive procedures are not shown, but showed similar profiles). Levels of some factors continued to increase at later time points, consistent with the effect of concomitant Vitamin K treatment. Formal pharmacokinetic parameters were not derived because of the effect of Vitamin K on factor levels at time points required for pharmacokinetic profiling.

Figure 9: Mean Factor Levels (Factors II, VII, IX, X, Proteins C & S) over 24 hours in Acute Major Bleeding RCT



Time axis is scheduled measuring time: hours after start of infusion (P=pre-infusion)

15 REFERENCES

1. Pabinger I, Brenner B, Kalina U, *et al*. Prothrombin complex concentrate (Beriplex P/N) for emergency anticoagulation reversal: a prospective multinational clinical trial. *Journal of Thrombosis and Haemostasis* 2008; 6: 622-631.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

- Kcentra is supplied in a single-use vial.
- The actual units of potency of all coagulation factors (Factors II, VII, IX and X), Proteins C and S in units are stated on each Kcentra carton.
- The Kcentra packaging components are not made with natural rubber latex.

Each kit consists of the following:

Carton NDC Number	Components
63833-386-02	• Nominal potency 500 (range 400-620) units Kcentra in a single-use vial [NDC 63833-396-01] • 20 mL vial of Sterile Water for Injection, USP [NDC 63833-761-20] • Mix2Vial filter transfer set • Alcohol swab
63833-387-02	• Nominal potency 1000 (range 800-1240) units Kcentra in a single-use vial [NDC 63833-397-01] • 40 mL vial of Sterile Water for Injection, USP [NDC 63833-761-40] • Mix2Vial filter transfer set • Alcohol swab

Storage and Handling

Prior to Reconstitution

- Kcentra is for single use only. Contains no preservatives.
- Store Kcentra between 2-25°C (36-77°F), this includes room temperature, not to exceed 25°C (77°F). Do not freeze.
- Kcentra is stable for 36 months from the date of manufacture, up to the expiration date on the carton and vial labels.
- Do not use Kcentra beyond the expiration date on the vial label and carton.
- Store the vial in the original carton to protect it from light.

After Reconstitution

Kcentra must be used within 4 hours following reconstitution. Reconstituted Kcentra can be stored at 2-25°C. If cooled, the solution should be warmed to 20-25°C prior to administration. Do not freeze. Discard partially used vials.

17 PATIENT COUNSELING INFORMATION

- Inform patients of the signs and symptoms of allergic hypersensitivity reactions, such as urticaria, rash, tightness of the chest, wheezing, hypotension and/or anaphylaxis experienced during or after injection of Kcentra *[see Warnings and Precautions (5.1)]*.
- Inform patients of signs and symptoms of thrombosis, such as limb or abdomen swelling and/or pain, chest pain or pressure, shortness of breath, loss of sensation or motor power, altered consciousness, vision, or speech *[see Warnings and Precautions (5.2)]*.
- Inform patients that, because Kcentra is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent *[see Warnings and Precautions (5.3) and Description (11)]*.

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