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)**

----------INDICATIONS AND USAGE----------
Kcentra, Prothrombin Complex Concentrate (Human), is 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.

Kcentra is not indicated for urgent reversal of VKA anticoagulation in patients without acute major bleeding. (1)

----------DOSAGE AND ADMINISTRATION----------
For intravenous use 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.
- **Repeat dosing with Kcentra is not supported by clinical data and 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

* Base dosing on actual potency, which is stated on the carton and will vary from 20-31 Factor IX units/mL. Nominal potency is 500 units per vial, approximately 25 units per mL after reconstitution.
† Units refer to International Units.
‡ Dose is based on body weight up to but not exceeding 100 kg. Do not exceed stated maximum dose for patients weighing more than 100 kg.

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

- Kcentra is available as a single-use vial containing coagulation Factors II, VII, IX and X, and antithrombotic Proteins C and S as a lyophilized concentrate. (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, arthralgia, and hypotension. (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*.

----------USE IN SPECIFIC POPULATIONS----------
Pregnancy: No human or animal data. Use only if clearly needed. (8.1)

See 17 for PATIENT COUNSELING INFORMATION

Issued: XX/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

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 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.

Kcentra is not indicated for urgent reversal of VKA anticoagulation in patients without acute major bleeding.

2 DOSAGE AND ADMINISTRATION

For intravenous use only.

2.1 Dosage

- The actual potency per vial of Factors II, VII, IX and X, Proteins C and S is stated on the carton.
- Individualize Kcentra dosing based on the patient's current pre-dose International Normalized Ratio (INR) value, and body weight.
- 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.
- **Repeat dosing with Kcentra is not supported by clinical data and is not recommended.**

- Dose ranging other than what is recommended has not been studied in randomized clinical trials of Kcentra.

Dosage Required for Reversal of VKA Anticoagulation in Patients with Acute Major Bleeding
Reconstitute Kcentra with 20 mL of diluent (Sterile Water for Injection, USP) provided with the kit *[see Dosage and Administration (2.2)]*. When reconstituted, the final concentration of drug product in Factor IX units will be in a range from 20-31 units/mL, depending on the actual potency, which is listed on the carton.

Coagulation factor levels may be unstable in patients with acute major bleeding who are receiving Vitamin K. Measure INR prior to treatment close to the time of dosing, then individualize dosage based on the INR value and the subject's body weight (kg) as shown in *Table 1* below.

Table 1: Dosing Guideline

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 as stated on the carton, which will vary from 20-31 Factor IX units/mL. Nominal potency is 500 units per vial, approximately 25 units per mL after reconstitution.
† 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 using aseptic technique with 20 mL of diluent provided with the kit.
- Do not use Kcentra beyond the expiration date on the vial label and carton.

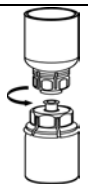
- Visually inspect parenteral drug products for particulate matter and discoloration prior to administration whenever solution and container permit. Reconstituted Kcentra solution should be colorless, clear to slightly opalescent, and free from visible particles. Do not use solutions that are cloudy or have deposits.
- Kcentra is for single use only. Contains no preservatives. Discard partially used vials.

The procedures provided in *Table 2* are general guidelines for the preparation and reconstitution of Kcentra.

Reconstitute at room temperature as follows:

Table 2: Kcentra Reconstitution Instructions

1. Ensure that the Kcentra vial and diluent vial are at room temperature. Prepare and administer using aseptic technique.	
2. Place the Kcentra vial, diluent vial, and Mix2Vial® transfer set on a flat surface.	
3. Remove Kcentra and diluent vial flip caps. Wipe the stoppers with the alcohol swab provided and allow to dry prior to opening the Mix2Vial transfer set package.	
4. Open the Mix2Vial transfer set package by peeling away the lid. [*Fig. 1*] Leave the Mix2Vial transfer set in the clear package.	 Fig. 1
5. Place the diluent vial on a flat surface and hold the vial tightly. Grip the Mix2Vial transfer set together with the clear package and push the plastic spike at the blue end of the Mix2Vial transfer set firmly through the center of the stopper of the diluent vial. [*Fig. 2*]	 Fig. 2
6. Carefully remove the clear package from the Mix2Vial transfer set. Make sure that you pull up only the clear package, not the Mix2Vial transfer set. [*Fig. 3*]	 Fig. 3
7. With the Kcentra vial placed firmly on a flat surface, invert the diluent vial with the Mix2Vial transfer set attached and push the plastic spike of the transparent adapter firmly through the center of the stopper of the Kcentra vial. [*Fig. 4*] The diluent will automatically transfer into the Kcentra vial.	 Fig. 4
8. With the diluent and Kcentra vial still attached to the Mix2Vial transfer set, gently swirl the Kcentra vial to ensure that the Kcentra is fully dissolved. [*Fig. 5*] Do not shake the vial.	 Fig. 5

9. With one hand, grasp the Kcentra side of the Mix2Vial transfer set and with the other hand grasp the blue diluent-side of the Mix2Vial transfer set, and unscrew the set into two pieces. [*Fig. 6*]	 Fig. 6
10. Draw air into an empty, sterile syringe. While the Kcentra vial is upright, screw the syringe to the Mix2Vial transfer set. Inject air into the Kcentra vial. While keeping the syringe plunger pressed, invert the system upside down and draw the concentrate into the syringe by pulling the plunger back slowly. [*Fig. 7*]	 Fig. 7
11. Now that the concentrate has been transferred into the syringe, firmly grasp the barrel of the syringe (keeping the plunger facing down) and unscrew the syringe from the Mix2Vial transfer set. [*Fig. 8*] Attach the syringe to a suitable intravenous administration set.	 Fig. 8
12. After reconstitution, administration should begin promptly or within 4 hours.	
13. 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.
- Use aseptic technique when administering 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.
- Record the lot number of the product in the patient's medical record when Kcentra is administered to the patient.

3 DOSAGE FORMS AND STRENGTHS

- Kcentra is available as a single use vial containing coagulation Factors II, VII, IX and X, antithrombotic Proteins C and S as a lyophilized concentrate.
- Kcentra potency (units) is defined by Factor IX content. The range of Factor IX units per vial is 400-620 units. When reconstituted using 20 mL of diluent, the final

concentration of drug product in Factor IX units will be in a range from 20-31 units/mL.
- The actual content of Factor IX as measured in units of potency is stated on the vial.
- 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 *[see Adverse Reactions (6.2)]*.

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 and venous thromboembolic complications have been reported with Kcentra in clinical trials and post marketing surveillance *[see Adverse Reactions (6.1), (6.2), 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 acute 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), Clinical Studies (14)]*. Potential benefits of treatment with Kcentra should be weighed against the potential risks of thromboembolic events *[*see *Adverse Reactions (6, 6.1, 6.2)]*. 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 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, arthralgia, and hypotension.

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 RCT (*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 3 or more Subjects (≥2.8%) Following Kcentra or Plasma Administration in Acute Major Bleeding RCT

	No. (%) of subjects	
	Kcentra (N = 103)	**Plasma (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		
International normalized ratio 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%)	0
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%)

* Two subjects experienced an INR correction that was not sustained past 3 hours; One subject received a lower than protocol specified Kcentra dose.
† Includes fluid overload and cardiac failure congestive
‡ Includes orthostatic hypotension, hypotension, and hemorrhagic shock
§ Includes transfusion reaction, allergic transfusion reaction
‖ 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%. In a preliminary analysis of data 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 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 6 subjects (5.8%, all non-related by investigator assessment) in the Kcentra group who experienced fluid overload in the plasma-controlled RCT in acute major bleeding and 14 (12.8%, 7 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 -15.8% to 1.8%.

Post-hoc subgroup analyses of the RCT in acute major bleeding were conducted according to whether subjects had a prior history of congestive heart failure *(Table 4)*. The incidence of fluid overload events was 8.7% in the Kcentra group and 25% in the plasma group in the subgroup of subjects with a history of prior congestive heart failure. The 95% confidence interval (CI) for the Kcentra minus Plasma between-group difference in fluid overload in subjects with a prior history of congestive heart failure ranged from -33.0% to 0.9%. In subjects without a history of congestive heart failure, the Kcentra minus Plasma between-group difference in fluid overload was – 1.1% (95% CI -10.7 to 9.1%).

Table 4: Subjects with Fluid Overload Events by Prior History of Congestive Heart Failure in Plasma-Controlled Trial in Subjects with Acute Major Bleeding

Subgroup	Major Bleeding Study			
	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)

Thromboembolic Events

There were 9 subjects (8.7%) in the Kcentra group who experienced possible thromboembolic events (TEEs) in the plasma-controlled RCT in acute major bleeding and 6 (5.5%) who had TEEs in the plasma group. The 95% confidence interval for the Kcentra minus Plasma between-group difference in possible TEE incidence ranged from -4.7% to 11.5%. 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 5 (4.9%) in the Kcentra group and 3 (2.8%) in the plasma group. When also considering the events which began during or within 72 hours of test product infusion, the incidence was 5 (4.9%) in the Kcentra group and 4 (3.7%) in the plasma group (95% confidence interval) for the Kcentra minus plasma difference ranged from -5.6% to 8.3%. TE events observed in the major bleeding study are shown in *Table 5*.

Table 5: Adverse Reactions (TEEs only) Following Kcentra or Plasma Administration in the Acute Major Bleeding RCT

System Organ Class	No. (%) of subjects	
	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 (DVT)‖	1 (1.0%)	0
Fistula Clot	1 (1.0%)	0
Unknown Cause of Death (not confirmed TEE)		
Sudden death	1 (1.0%)	0

* The tabulation of possible TEEs includes subjects with confirmed TEEs as well as 3 subjects in the Kcentra group that died of unknown causes on days 7, 31, and 38. The death on day 7 was considered possibly related to study product by the SAB and is tabulated as an adverse reaction. One additional subject who had received Kcentra, not listed in the table, had an upper extremity venous thrombosis in association with an indwelling catheter.

† One subject who had received plasma had an acute myocardial infarction (d1) rated moderate in severity, not considered serious.

‡ One subject, included in the tabulation, had an ischemic cerebrovascular accident on day 43 that was considered unrelated by the SAB.

§ One subject who had received plasma had a cerebrovascular disorder (d1) not considered serious, and

‖ One Kcentra subject had two DVTs, both considered related by SAB.

Post-hoc subgroup analyses of the RCT in acute major bleeding were conducted according to whether subjects had a prior history of a thromboembolic event. Among subjects who received Kcentra, the incidence of TE events was 11.6% (95% confidence interval 6.0 –21.2%) in the subgroup of subjects with a history of prior TE event compared to 2.9% (95% confidence interval 0.5 – 14.9%) in the subgroup without such history. The incidence of TE events in the plasma group was 3.8% (95% confidence interval 1.3 – 10.6%) in the subgroup of subjects with a history of prior TE event compared to 10.0% (95% confidence interval 3.5 – 25.6%) in the subgroup without such history.

Table 6 shows treatment-emergent TE events by randomized treatment subgroup according to whether subjects had a prior history of TE event.

Table 6: Subjects with Thromboembolic Events by Prior History of TE Event in Plasma-Controlled RCT in Acute Major Bleeding

	Acute Major Bleeding Study			
	Kcentra		Plasma	
	N	TE Events† N (%)	N	TE Events N (%)
All subjects	**103**	**9 (8.7)**	**109**	**6 (5.5)**
With history of TE event*	69	8 (11.6)	79	3 (3.8)
Without history of TE event	34	1 (2.9)	30	3 (10.0)

* History of prior TE event.
† One additional subject who had received Kcentra, not listed in the table, had an upper extremity venous thrombosis in association with an indwelling catheter.

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 events 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

Because postmarketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.

The following adverse reactions have been identified and reported during postmarketing use of Kcentra outside the US since 1996.

- *Hypersensitivity or Allergic reactions:* flushing, urticaria, tachycardia, anxiety, angioedema, wheezing, nausea, vomiting, hypotension, tachypnea, dyspnea, pulmonary edema, and bronchospasm.
- *Thromboembolic complications:* arterial thromboembolic events (including acute myocardial infarction and arterial thrombosis), venous thromboembolic events (including pulmonary embolism and venous thrombosis), and disseminated intravascular coagulation.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Kcentra. It is also 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.

8.2 Labor and Delivery
Kcentra has not been studied for use during labor and delivery. Safety and effectiveness in labor and delivery have not been established.

8.3 Nursing Mothers
It is not known whether Kcentra is excreted in human milk. 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 (229) with acute major bleeding treated to reverse VKA anticoagulation in two clinical studies, 71% were 65 years old or greater and 43% were 75 years old or greater. There were no clinically significant differences between the safety profile of Kcentra and plasma in any age group.

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 500 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 – 1020 units
Protein C	420 – 820 units
Protein S	240 – 680 units
Heparin	8 – 40 units
Antithrombin III	4 – 30 units
Human albumin	40 – 80 mg
Sodium chloride	60 – 120 mg
Sodium citrate	40 – 80 mg
HCl	Small amounts
NaOH	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.

These 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: Virus Reduction Factors [log_{10}] of Kcentra

Virus Studied	Manufacturing Steps						Overall Virus Reduction [log_{10}]
	Cryo-precipi-tation	DEAE-Adsorption (Ion Exchange Chroma-tography)	Heat treatment ("Pasteuri-zation")	Ammonium sulphate precipitation followed by Ca Phosphate adsorption	75/35 nm Filtration	Lyophili-zation	
Enveloped Viruses							
HIV	n.d.	n.d	≥ 6.9	≥ 5.9	≥ 7.3	n.d.	≥ 20.1
BVDV	n.d.	n.d	≥ 8.5	2.2	4.2	n.d.	≥ 14.9
PRV	n.d.	n.d	4.1	7.2	≥ 6.8	n.d.	≥ 18.1
WNV	n.d.	n.d.	≥ 7.4	n.d.	n.d.	n.d.	≥ 7.4
Non-Enveloped Viruses							
HAV	n.d	n.d	4.0	1.8	n.d.	2.2	8.0
CPV	1.3		[0.5]*	1.5	n.d.	n.d.	2.8

* 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

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

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. If the patient has an acquired coagulation factor deficiency where one or more of the Vitamin K-dependent coagulation factors are deficient, bleeding may occur.

The coagulation cascade is a series of pro-coagulant and antithrombotic reactions involving the activation of zymogens. The vascular endothelium provides a protective barrier separating blood cells and plasma factors from subendothelial vessel wall reactive adhesive proteins and tissue factor (TF). The latter proteins trigger blood coagulation. Thrombin converts fibrinogen to fibrin for clot formation.

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 anti-thrombotic 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 after Start of Infusion

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)

* Statistically significant difference compared to plasma by 2-sided Wilcoxon test in Study 3002
INR = international normalized ratio.

12.3 Pharmacokinetics

Pharmacokinetic (PK) parameters were obtained in healthy subjects. PK parameters obtained from data derived from the study of healthy subjects may not be directly applicable to those with acute major bleeding and INR elevation due to VKA anticoagulation therapy.

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. Concentrations of Proteins C and S also increased rapidly and substantially. The PK analysis *[see Table 10 and Table 11]* shows that factor II had the longest half-life (59.7 hours) and factor VII the shortest (4.2 hours) in healthy subjects. The mean residence time (MRT) was longest for factor II (81.7 hours) and shortest for factor VII (6.1 hours).

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

Parameter	Factor IX	Factor II	Factor VII	Factor X
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)
IVR (%/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)
AUC (IU/dL x h)	1490 (1153-2376)	6577 (5870-7912)	424 (331-742)	6707 (5234-8577)
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)
MRT (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)
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)

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

Table 11: Antithrombotic Proteins C and S Pharmacokinetics after a Single Kcentra Infusion in Healthy Subjects- PK Study in Healthy Subjects (n=15) Median (Min – Max)

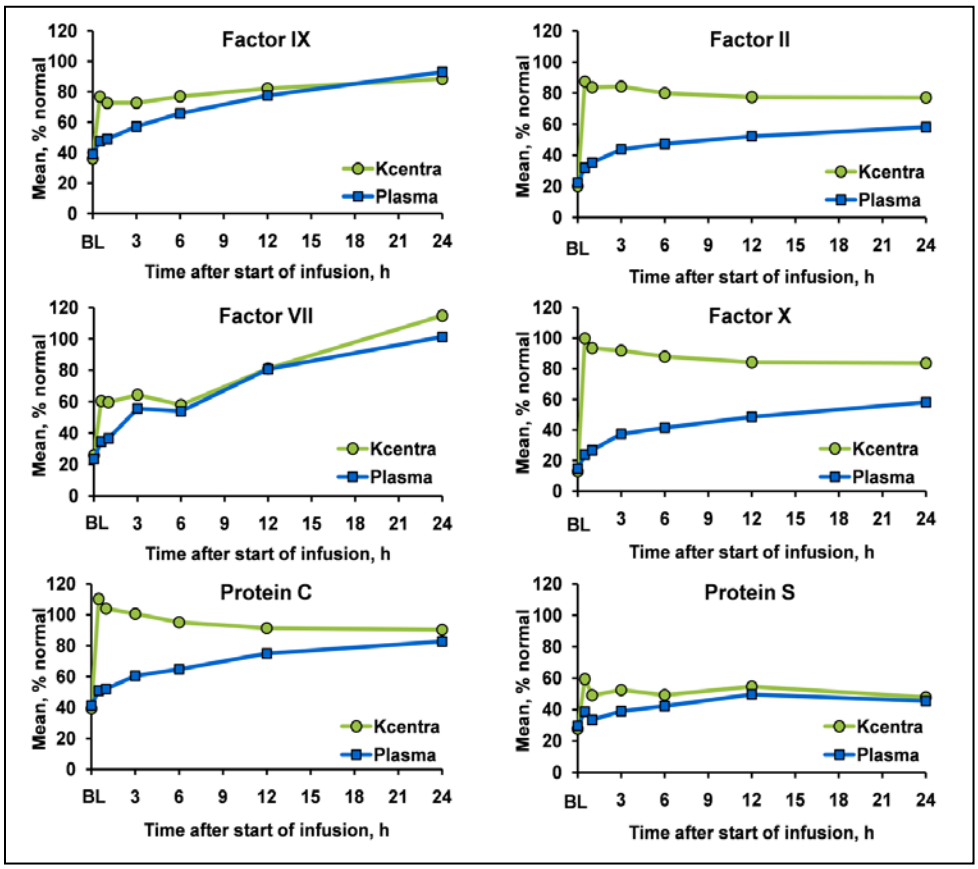
Parameter	Protein C	Protein S
Terminal half-life (h)	47.2 (9.3-121.7)	49.1 (33.1-83.3)
IVR (%/units/kg bw)*	2.76 (2.16–3.31)	2.02(1.46–2.70)
AUC (IU/dL x h)	5,276 (1,772–10,444)	3,667 (2,218–3,667)
Clearance (mL/ kg x h)	1.1 (0.6-3.3)	1.1 (0.7-1.8)
MRT (h)†	57.0-13.4-161.4)	69.2 (45.3-113.5)
Vd_{ss} (mL/kg)‡	62.9 (43.9-109.3)	76.6 (61.9-105.0)

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

Plasma levels of Coagulation Factors II, VII, IX, X, and Antithrombotic Proteins C and S were measured after the infusion of Kcentra or plasma in studies of subjects requiring urgent reversal due to acquired deficiency of Vitamin K-dependent coagulation factors. In randomized, plasma-controlled study 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.

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. 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



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

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 1.29 (Factor IX) to 2.4 (Protein S) *[see Table 12 and Table 13]*.

Table 12: In vivo Recovery (Single-Arm European Study in Bleeding and Surgery, ITT*, N=43)

Analyte	Incremental (units/dL per units/kg b.w.)	
	Mean (SD)	**95% CI†**
Factor IX	1.37 (0.50)	(1.21–1.53)
Factor II	1.91 (0.52)	(1.75–2.08)
Factor VII	1.60 (0.54)	(1.43–1.77)
Factor X	1.93 (0.47)	(1.78–2.07)
Protein C	2.07 (0.44)	(1.94–2.21)
Protein S	2.44 (0.82)	(2.18–2.69)

* ITT: Intention to Treat
† CI: Confidence Interval

Table 13: In vivo Recovery (Plasma-Controlled RCT in Acute Major Bleeding, Kcentra, N=98*)

Parameter	Incremental (units/dL per units/kg b.w.)	
	Mean (SD)	**95% CI†**
Factor IX	1.29 (0.71)	(1.14-1.43)
Factor II	2.00 (0.88)	(1.82-2.18)
Factor VII	2.15 (2.96)	(1.55-2.75)
Factor X	1.96 (0.87)	(1.79-2.14)
Protein C	2.04 (0.96)	(1.85-2.23)
Protein S	2.17 (1.66)	(1.83-2.50)

* 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

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 $\geq$ 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 14]*. 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 14: 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 are presented in *Table 15*.

Table 15: Primary 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
	N = 55 (P)	N = 18 (P)	N = 31
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 16]*.

Table 16: Decrease of INR (1.3 or Less at 30 Minutes after End of Infusion)

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

The Bleeding and Surgical Study – European 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.

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

16.1 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:

NDC Number	Components
63833-386-02	• 500 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

16.2 Storage and Handling

16.2.1 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 beyond the expiration date on the carton and the vial label.
- Store the vial in the original carton to protect it from light.

16.2.2 After Reconstitution

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