

## ***Treatment Considerations for Urgent Warfarin Reversal Podcast Transcript***



### ***Announcer:***

You're listening to ReachMD. This medical industry feature, titled "Treatment Considerations for Urgent Warfarin Reversal" is sponsored by CSL Behring. This program is intended for physicians.

Here's your host, Dr. Jennifer Caudle.

### ***Dr. Caudle:***

This is ReachMD, and I'm your host, Dr. Jennifer Caudle. Joining me to walk through a case study highlighting the role of Kcentra® Prothrombin Complex Concentrate (Human) and warfarin-induced acute acquired coagulation deficiencies are Dr. David Janicke and Dr. Michelle Kincaid.

Dr. Janicke is an Associate Professor of Emergency Medicine and is Director of the Emergency Department at Buffalo General Medical Center/Gates Vascular Institute. Dr. Janicke, thanks so much for being here today.

### ***Dr. Janicke:***

Thank you, Dr. Caudle.

### ***Dr. Caudle:***

Excellent. And Dr. Kincaid is a trauma surgeon and Director of Surgical Critical Care at Grant Medical Center in Columbus, Ohio. Dr. Kincaid, it's great to have you with us.

### ***Dr. Kincaid:***

Yeah, so happy to be here. Thank you.

### ***Dr. Caudle:***

Absolutely. Before we begin, let's review some important safety information for Kcentra.

### ***Announcer:***

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—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.

Stay tuned for the complete Important Safety Information for Kcentra throughout this podcast.

**Dr. Caudle:**

Now that we have that understanding, let's dive into our discussion.

So let's start with you, Dr. Kincaid. Before we delve into our patient case, let's cover some foundational aspects of Kcentra. What do we need to know about this treatment option and who would be an appropriate candidate for it?

**Dr. Kincaid:**

So, Kcentra is the only FDA-approved alternative to plasma for the urgent reversal of warfarin-induced coagulopathy. And we really have to focus on the two major indications for Kcentra. Number one would be patients with acute major bleeding such as intracranial hemorrhage, GI bleeding, musculoskeletal bleeding, things like that. The other major indication for Kcentra is patients that need urgent surgery or procedures. And so really there's so many patients that we could talk about for that, but really have to focus on acute major bleeding and the need for urgent surgery.

**Dr. Caudle:**

Excellent, and with that overview in mind, let's consider a case study where a patient was experiencing an intracranial hemorrhage. Turning to you, Dr. Janicke, can you set the stage for us with this patient?

**Dr. Janicke:**

Yes. So, I'm going to start with a case study where we have a 62-year-old female. She was found lying on the floor by her family. EMS was called, and she was transported to the emergency department. When she comes into the emergency department, she's awake and alert but aphasic. She does follow some commands. She's hemiplegic on the right side, and the NIH stroke scale is 12. She has a medical history of hypertension diabetes and atrial fibrillation. Her current medications include lisinopril, insulin and warfarin 7.5 mg once daily. Her vital signs reveal an elevated blood pressure of 205/115. She has a heart rate of 99, a respiratory rate of 12, a temperature of 98.5.

**Dr. Caudle:**

Now staying with you, Dr. Janicke, can you share with us the patient's lab and imaging results?

**Dr. Janicke:**

Yes, absolutely. So, on the top of the differential diagnosis for this particular presentation would be stroke and CNS bleed. This is based on the patient's severe neuro deficit with an NIH stroke scale of 12, and the fact that the patient is on warfarin, for atrial fibrillation. The patient needs stat brain imaging to help discern the diagnosis. Now the lab results we have, the CBC was within normal limits, the INR was 2.3 and that's consistent with the patient being on warfarin. The patient was sent for a non-contrast CAT scan immediately. It did reveal a left basal ganglia distribution CNS bleed with a hematoma of a size of approximately 30 mls. And there was a slight left-to-right shift of the brain.

**Dr. Caudle:**

For those of you who are just joining us, this is ReachMD, and I'm your host, Dr. Jennifer Caudle. Today I'm speaking with emergency medicine specialist, Dr. David Janicke and critical care surgeon, Dr. Michelle Kincaid, about current treatment considerations for acute coagulation factor deficiencies.

Before we examine the case in further detail, let's review some additional important safety information for Kcentra.

**Announcer:**

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.

**Dr. Caudle:**

So doctors, let's pick back up with the case and consider what the next steps in management might be. So coming over to you, Dr. Kincaid, given what we know about this case so far, can you talk us through what your next steps would be in managing this patient?

**Dr. Kincaid:**

Yeah, so it seems like we have a hypertensive stroke, with a pretty significant volume of intracranial hemorrhage. And she is definitely showing the clinical signs with the right hemiparesis and the aphasia. So, in terms of stroke care, we're really worried – you know, time is brain. And so, we have two major goals that we really need to accomplish quite quickly. Number one would be acute blood pressure control, as she is very hypertensive. So, goals would be to get her systolic less than 160, and/or her MAP – mean arterial pressure – less than 110. And number two for this patient, who is on warfarin, and has an INR of 2.3, we really need to reverse that as quickly as possible. The risks of further bleeding and acute hemorrhage are quite high, if we do not control her blood pressure nor reverse her coagulopathy. And so for this patient, she definitely falls into that category of acute major bleeding which is one of the two indications for Kcentra. And, you know, there certainly would be a consideration for surgery in a patient like this, with this significant volume of bleed. She is approaching what we would define as a large volume and when you talk about time to surgery, especially in this situation if you ask our neurosurgeons, they'd want her in the operating room five minutes ago. And so, to be able to get her there safely reversal of her anticoagulation would be definitely one of our key goals for this patient.

**Dr. Caudle:**

And Dr. Janicke, what would your approach be in terms of next steps in treatment?

**Dr. Janicke:**

Yeah, I agree with Dr. Kincaid as far as the control of the blood pressure and reversal of the of the anticoagulation. Kind of an interesting area in the emergency department here, we have a patient that's coming in, and just as Dr. Kincaid said we don't know if the patient's going to go to surgery or have an external ventricular drain placed or have no surgical type of intervention for this CNS bleed. However, we do know that reversal of anticoagulation would be necessary in both situations. One, the patient has life-threatening bleed, and on top of that, the patient may go for a surgical intervention that needs to be done emergently. So, we're kind of thinking we need to reverse that anticoagulation quickly and that's where Kcentra comes into play. The other thing I just wanted to mention is we know that patients can expand that hematoma early on, after it first starts. So again, it's of essence to reverse that coagulation as soon as possible. Other things we would look at is we'd be monitoring the CNS status in case the patient needed further treatment or intervention, or intubation. Watch for hyponatremia, make sure the glucose is not elevated, and also we would place the patient in bed at a 30 degree angle to hopefully decrease intracranial pressure.

**Dr. Caudle:**

And, you know, that's excellent. Staying with you, Dr. Janicke, we're left now with choosing between Kcentra and plasma. Which one would you choose for this patient?

**Dr. Janicke:**

So, a number of national guidelines really help me out on this in that they recommend immediate prothrombin complex concentrate, or Kcentra in this case, used over fresh frozen plasma, to reverse warfarin anti-coagulation in a patient with life-threatening CNS bleed. Now some of the factors that make Kcentra an ideal agent for emergent reversal include, one –the INR can be normalized quickly within 30 minutes after infusion of the Kcentra, and that this effect is sustained for at least 24 hours. Two randomized studies comparing Kcentra to fresh frozen plasma revealed that Kcentra was superior to FFP in INR reduction to less than or equal to 1.3, 30 minutes after the end of infusion.

In addition, the Kcentra dose can be administered seven times faster than fresh frozen plasma, which makes it much better as far as being able to give it expediently. And you do not have to have type and screen, thawing. So, these factors really enable Kcentra to be given expediently for emergency surgery procedures or to be started for life-threatening bleeds, for instance, in outlying emergency departments or institutions that may be sending patients in like this to a tertiary center. There's 85% less volume infused with Kcentra versus fresh frozen plasma, which can decrease the incidence of fluid overload in these severely ill patients. And I think one other important factor is that there has been shown to be no increase in thromboembolic events of Kcentra compared to fresh frozen plasma.

**Dr. Caudle:**

That's very helpful, thank you. And Dr. Kincaid, I'll give you the final word here. You know, what are some takeaways that you'd like to share with our audience regarding this patient case?

**Dr. Janicke:**

Yeah, so kind of building on what Dr. Janicke has already set up, we were able to achieve one goal, which is blood pressure control, with a nicardipine infusion with our – again, goal of systolic less than 160. And then, our second important goal was reversal of her warfarin-induced coagulopathy. She had an INR of 2.3, and so based upon her weight, which was 75 kilograms, and her INR of 2.3 she received 1875 units of Kcentra. And importantly, along with the infusion of Kcentra, we also have to give the patient Vitamin K, and that helps to replace the patient’s own coagulation factors after ongoing from here on out. This patient potentially could also be a candidate for surgery. They had a pretty sizable volume of intraparenchymal hemorrhage, which certainly could be a high risk for secondary damage to the surrounding brain tissue. So, if that patient would be a candidate for surgery or an intracranial monitor, then the benefits of Kcentra – the rapid administration, the rapid reduction in INR the getting the patient to surgery faster compared to plasma – would definitely be a benefit. But this patient, for our case study, you know, she actually did quite well. She was admitted to the ICU, she had her serial neuro exams, her neuro deficits stayed the same, which is a great outcome for this acute stroke. Her repeat head CT did show that her intracranial hemorrhage volume was stable. And ultimately, this patient was able to go home, with those stable neuro deficits, with just some home health care. And really, this is, I would say, one of the best possible outcomes for what could be quite devastating to a patient, and that this case is really an important one to demonstrate the role that Kcentra has, as really a vital tool for these very time-sensitive and critical patients.

**Dr. Caudle:**

Well, that’s a great way to wrap up our case study examining Kcentra, for urgent warfarin reversal. I’d like to thank my guests for helping us better understand this treatment option and its role in coagulation factor replacement for acute deficiencies. Dr. Janicke and Dr. Kincaid, it was great speaking with you both today.

**Dr. Kincaid:**

Yeah, thank you so much.

**Dr. Janicke:**

Thank you, Dr. Caudle. I appreciate your time in discussing this important area.

**Dr. Caudle:**

Thank you. I’m your host, Dr. Jennifer Caudle, and please stay tuned for additional important safety information.

**Announcer:**

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 ( $\geq 2.8\%$ ) 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.

**Announcer:**

This program was sponsored by CSL Behring. If you missed any part of this discussion, visit [ReachMD.com/industry-feature](http://ReachMD.com/industry-feature). This is ReachMD. Be Part of the Knowledge.

**References:**

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## 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 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-dose 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](http://www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION

Revised: July 2020

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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 after reconstitution 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 <sup>†</sup> of Factor IX) / kg body weight	25	35	50
Maximum dose <sup>‡</sup> (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.

<sup>†</sup> Units refer to International Units.

<sup>‡</sup> 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:

$$35 \text{ units of Factor IX/kg} \times 80 \text{ kg} = 2,800 \text{ units of Factor IX required}^*$$

\* 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  $\leq 1.3$  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-dose only. Contains no preservatives. Discard partially used vials.

### 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.



Fig. 4

**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. 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 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.

### 3 DOSAGE FORMS AND STRENGTHS

- KCENTRA is available as a white or slightly colored lyophilized concentrate in a single-dose 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](http://www.fda.gov/medwatch).

## 6 ADVERSE REACTIONS

The most common adverse reactions (ARs) (frequency  $\geq 2.8\%$ ) 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 2).

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 2: Adverse Reactions Reported in more than 5 Subjects ( $\geq 2.8\%$ ) Following KCENTRA or Plasma Administration in RCTs**

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

<sup>†</sup> Includes fluid overload and cardiac failure congestive

<sup>‡</sup> Includes orthostatic hypotension, hypotension, and hemorrhagic shock

<sup>‡</sup> 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 3.

**Table 3: 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 (%)
<b>All subjects</b>	<b>103</b>	<b>6 (5.8)</b>	<b>109</b>	<b>14 (12.8)</b>	<b>88</b>	<b>3 (3.4)</b>	<b>88</b>	<b>11 (12.5)</b>
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 4.

**Table 4: 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)
<b>Any possible TEE*</b>	<b>9 (8.7%)</b>	<b>6 (5.5%)</b>	<b>4 (4.5)</b>	<b>8 (9.1)</b>
<b>TEE Adverse reactions</b>	<b>6 (5.5%)</b>	<b>4 (3.7%)</b>	<b>4 (4.5)</b>	<b>4 (4.5)</b>
<b>Cardiac disorders</b>				
Myocardial infarction	0	1 (0.9%)	0	2 (2.3)
Myocardial ischemia	0	2 (1.8%)	0	0

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)
<b>Nervous system disorders</b>				
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
<b>Vascular disorders</b>				
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
<b>Unknown Cause of Death (not confirmed TEE)</b>				
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 5.

**Table 5: 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 (%)
<b>All subjects</b>	<b>103</b>	<b>9 (8.7)</b>	<b>109</b>	<b>6 (5.5)</b>	<b>88</b>	<b>4 (4.5)</b>	<b>88</b>	<b>8 (9.1)</b>
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 6 and listed as ranges for the blood coagulation factors.

**Table 6: 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<sup>4</sup> 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 7 shows the virus clearance during the manufacturing process for KCENTRA, expressed as the mean log<sub>10</sub> reduction factor.

**Table 7: Mean Virus Reduction Factors [log<sub>10</sub>] of KCENTRA**

Virus Studied	Manufacturing Steps			Overall Virus Reduction [log <sub>10</sub> ]
	Heat treatment ("Pasteurization")	Ammonium sulphate precipitation followed by Ca Phosphate adsorption	2 x 20 nm Virus Filtration	
<b>Enveloped Viruses</b>				
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
<b>Non-Enveloped Viruses</b>				
HAV	4.0	1.8	≥ 6.1	≥ 11.9
CPV	[0.5]*	1.5	6.5	8.0

\* Reduction factor below 1 log<sub>10</sub> 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<sub>10</sub> by heat treatment.

HIV<sup>1</sup> Human immunodeficiency virus, a model for HIV-1 and HIV-2  
 BVDV<sup>2</sup> Bovine viral diarrhea virus, model for HCV  
 PRV<sup>3</sup> Pseudorabies virus, a model for large enveloped DNA viruses  
 WNV<sup>4</sup> West Nile virus  
 HAV<sup>5</sup> Hepatitis A virus  
 CPV<sup>6</sup> 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<sup>2+</sup>, 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 8].

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

**Table 8: Median INR (Min-Max) after Start of Infusion in RCTs**

Study	Treatment	Base-line	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 9] 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 9: 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) <sup>†</sup>	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 <sub>ss</sub> (mL/kg) <sup>‡</sup>	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

<sup>†</sup> MRT: Mean Residence Time

<sup>‡</sup> Vd<sub>ss</sub>: 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 10].

**Table 10: 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 <sup>†</sup>	Mean (SD)	95% CI <sup>†</sup>
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

<sup>†</sup> 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 11]. 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 11: Rating of Hemostatic Efficacy in Subjects with Acute Major Bleeding**

Rating	No. (%) of subjects [95% CI]		Difference KCENTRA – Plasma (%) [95% CI] <sup>*</sup>
	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]

<sup>\*</sup> 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 12.

**Table 12: 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 <sup>*</sup>	(4.4%)	(11.6%)	(7.9%)
95% CI K-P	-13.2-21.9	-17.4-40.6	-17.0-32.9

<sup>\*</sup> 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 13].

**Table 13: 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] <sup>*</sup>
	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]

<sup>\*</sup> 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 14]. 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 14: Rating of Hemostatic Efficacy in Urgent Surgery/Invasive Procedure RCT**

Rating	No. (%) of subjects [95% CI]		Difference KCENTRA – Plasma (%) [95% CI] <sup>*</sup>
	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]

<sup>\*</sup> 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 15.

**Table 15: 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 <sup>*</sup>	(13.9%)	(10.0%)	(20.8%)
95% CI K-P	1.4-26.6	-26.5-43.5	-19.8-53.7

<sup>\*</sup> 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 16]. The relationship between a decrease in INR to less than or equal to 1.3 and clinical hemostatic efficacy has not been established.

**Table 16: 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 – Plasma (%) [95% CI] <sup>*</sup>
	KCENTRA (N = 87)	Plasma (N = 81)	
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]

<sup>\*</sup> 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

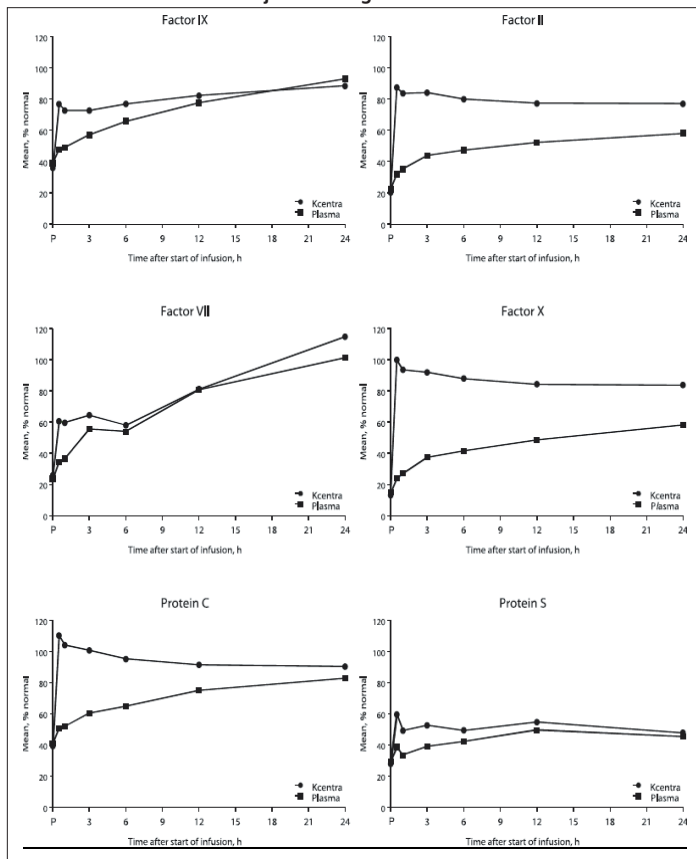
The European Bleeding and Surgical Study was an open-label, single-arm, multicenter study.<sup>1</sup> Forty-three (43) subjects who were receiving VKA were treated with KCENTRA, because they either (1) required a surgical or an invasive diagnostic intervention (26 subjects), or (2) experienced an acute 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**

- KCENTRA is supplied in a single-dose 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.

**Table 17. How Supplied**

Each kit consists of the following:

Carton NDC Number	Components
63833-386-02	<ul style="list-style-type: none"> <li>• Nominal potency 500 (range 400-620) units KCENTRA in a single-dose vial [NDC 63833-396-01]</li> <li>• 20 mL vial of Sterile Water for Injection, USP [NDC 63833-761-20]</li> <li>• Mix2Vial filter transfer set</li> <li>• Alcohol swab</li> </ul>
63833-387-02	<ul style="list-style-type: none"> <li>• Nominal potency 1000 (range 800-1240) units KCENTRA in a single-dose vial [NDC 63833-397-01]</li> <li>• 40 mL vial of Sterile Water for Injection, USP [NDC 63833-761-40]</li> <li>• Mix2Vial filter transfer set</li> <li>• Alcohol swab</li> </ul>

**Storage and Handling**

**Prior to Reconstitution**

- KCENTRA is for single-dose 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* (1.1)].

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