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 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 ischemia, 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)

Dosage and Administration (2.1, 2.2) 2/2017

RECENT MAJOR CHANGES
Dosage and Administration (2.1, 2.2) 2/2017

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)

DOSE 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.

• The safety and effectiveness of repeat dosing have not been established and it is not recommended. (2.1)

ADVERSE REACTIONS

• The most common adverse reactions (ARs) (frequency ≥ 2.8%) observed in subjects receiving Kcentra were headache, nausea/vomiting, hypotension, and anemia. (6.2)

• The most serious ARs were thromboembolic events including stroke, pulmonary embolism, and deep vein thrombosis. (6.2)

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

See 17 for PATIENT COUNSELING INFORMATION

Revised: February 2017

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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 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 predose 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

<table>
<thead>
<tr>
<th>Pre-treatment INR</th>
<th>2–&lt; 4</th>
<th>4–6</th>
<th>&gt; 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose* of Kcentra (units† of Factor IX) / kg body weight</td>
<td>25</td>
<td>35</td>
<td>50</td>
</tr>
<tr>
<td>Maximum dose‡ (units of Factor IX)</td>
<td>Not to exceed 2500</td>
<td>Not to exceed 3500</td>
<td>Not to exceed 5000</td>
</tr>
</tbody>
</table>

*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/ml. The actual potency for 1000 unit vial ranges from 800-1240 units/ml.
† 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 (nominal potency 500 U kit) or 40 mL (nominal potency 1000 U kit) of diluent provided with the kit.
- 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.
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]
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]
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 diluent vial. [Fig. 4] The diluent will automatically transfer into the Kcentra vial.
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.
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]
10. Draw air into an empty, sterile syringe. While the Kcentra vial is upright, screw the syringe onto 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]

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.

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.

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 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 (1.1)].

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 agent. There is also the possibility that unknown infectious agents may be present in such products. Despite the use of two dedicated virus reduction steps in manufacturing to reduce risks, such products may still potentially transmit disease.

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

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

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

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

The following serious adverse reactions are described below and/or elsewhere in the labeling:
- Hypersensitivity Reactions [see Warnings and Precautions (5.1)]
- Arterial and venous thromboembolic complications [see Boxed Warning and Warnings and Precautions (5.2)]
- Possible transmission of infectious agents [see Warnings and Precautions (5.3)]

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

Randomized, Plasma-Controlled Trial in Acute Major Bleeding
In a prospective, randomized, open-label, active-controlled multicenter non-inferiority trial, 212 subjects who required urgent reversal of VKA therapy due to acute major bleeding were enrolled and randomized to treatment; 103 were treated with Kcentra and 109 with plasma. Subjects with a history of a thrombotic event, myocardial infarction, cerebral vascular accident, transient ischemic attack, unstable angina pectoris, severe peripheral vascular disease, or disseminated intravascular coagulation, within the previous 3 months were excluded from participating. Subjects ranged in age from 26 years to 96 years.

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

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

Adverse Reactions are defined as adverse events that began during or within 72 hours of test product infusion plus adverse events considered possibly/probably related or related to study treatment according to the investigator, sponsor, or the blinded safety adjudication board (SAB), and with at least a 1.3-fold difference between treatments.
There were 9 subjects (4.7%, all non-related by investigator assessment) in the Kcentra group who experienced fluid overload in the plasma-controlled RCTs in acute major bleeding and urgent surgery/invasive procedures and 25 (12.7%, 13 events related by investigator assessment) who had fluid overload in the plasma group. The 95% confidence interval for the Kcentra minus Plasma between-group difference in fluid overload event incidence ranged from -14.1% to -2.0%.

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

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

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Acute Major Bleeding Study</th>
<th>Urgent Surgery/Invasive Procedures Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Kcentra</td>
<td>Plasma</td>
</tr>
<tr>
<td>N Fluid Overload</td>
<td>103</td>
<td>109</td>
</tr>
<tr>
<td>Overload N (%)</td>
<td>6 (5.8)</td>
<td>14 (12.8)</td>
</tr>
<tr>
<td>All subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With history of CHF</td>
<td>46</td>
<td>44</td>
</tr>
<tr>
<td>Hypotension†</td>
<td>14 (7.3)</td>
<td>10 (5.1)</td>
</tr>
<tr>
<td>Without history of CHF</td>
<td>57</td>
<td>65</td>
</tr>
</tbody>
</table>

**Thromboembolic Events**

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

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

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

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>No. (%) of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Kcentra (N = 103)</td>
</tr>
<tr>
<td></td>
<td>Kcentra (N = 88)</td>
</tr>
<tr>
<td>Any possible TEE*</td>
<td>9 (8.7%)</td>
</tr>
<tr>
<td>TEE Adverse reactions</td>
<td>6 (5.5%)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0 (1.0%)</td>
</tr>
<tr>
<td>Myocardial ischemia</td>
<td>0 (2.3%)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Ischemic cerebrovascular accident (stroke)</td>
<td>2 (1.9%)</td>
</tr>
<tr>
<td>Embolic cerebral infarction</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Cerebrovascular disorder</td>
<td>0 (1.1%)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
</tr>
<tr>
<td>Venous thrombosis calf</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Venous thrombosis radial vein</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Thrombosis (microthrombosis of toes)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Deep vein thrombosis (DVT)</td>
<td>1 (1.0%)</td>
</tr>
<tr>
<td>Fistula Clot</td>
<td>1 (1.0%)</td>
</tr>
</tbody>
</table>

**Unknown Cause of Death (not confirmed TEE)**

Sudden death 1 (1.0%) 0 (0.0%)

* The tabulation of possible TEEs includes subjects with confirmed TEEs as well as 9 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.

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

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th>No. (%) of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kcentra (N = 191)</td>
<td>Plasma (N = 197)</td>
</tr>
<tr>
<td>Headache</td>
<td>14 (7.3%)</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>8 (4.2%)</td>
</tr>
<tr>
<td>Respiratory distress/dyspnea/hypoxia</td>
<td>7 (3.7%)</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>3 (1.6%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>12 (6.3%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (2.1%)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>9 (4.7%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>8 (4.2%)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
</tr>
<tr>
<td>Fluid overload‡</td>
<td>5 (2.6%)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>9 (4.7%)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>9 (4.7%)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
</tr>
<tr>
<td>Hypotension†</td>
<td>14 (7.3%)</td>
</tr>
<tr>
<td>Injury, poisoning, and procedural complications</td>
<td></td>
</tr>
<tr>
<td>Skin laceration/contusion/subcutaneous hematoma</td>
<td>8 (4.2%)</td>
</tr>
<tr>
<td>Blood and lymphatic disorders</td>
<td></td>
</tr>
<tr>
<td>Anemia‡</td>
<td>11 (5.8%)</td>
</tr>
</tbody>
</table>

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

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

There were a total of 10 subjects (9.7%) who died in the Kcentra group (1 additional death occurred on day 46 just after completion of the study reporting period) and 5 (4.6%) who died in the plasma group in the plasma-controlled RCT in acute major bleeding. The 95% confidence interval for the Kcentra minus plasma between-group difference in deaths ranged from -2.7% to 13.5%. From the plasma-controlled RCT in urgent surgery/invasive procedures, there were a total of 3 subjects (3.4%) who died in the Kcentra group (1 additional death occurred on day 48 after completion of the study reporting period) and 8 (9.1%) who died in the Plasma group. The 95% confidence interval for the Kcentra minus plasma between-group difference in deaths in this trial ranged from -14.6% to 12.5%.

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 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 supernormal laboratory factor levels did not have a mortality rate out of proportion to the overall population.
The safety and efficacy of Kcentra in the pediatric population has not been studied. A postmarketing use of Kcentra outside the US since 1996. Precautions (5) and Adverse Reactions (6) have been observed in the
No adverse reactions other than those addressed [See Warnings And
factors.

The product contents are shown in Table 7 and listed as ranges for the blood coagulation
preparation as stated on the vial label. The excipients are human antithrombin
and the antithrombotic Proteins C and S. Factor IX is the lead factor for the potency of the
CFR 640.60). It contains the Vitamin K dependent Coagulation Factors
11
Congenital F

Heparin
Antithrombin III
Human albumin
Sodium chloride
Sodium citrate
HCl
NaOH

substances considered possibly related to Kcentra included a suspected pulmonary

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 nonreactive (negative), and the plasma is also tested by NAT for human
parvovirus B19 (B19V) in order to exclude donations with high tilters. The limit for B19V
in the fractionation pool is set not to exceed 10^1 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
minutes at 60°C, precipitated, adsorbed to calcium phosphate, virus filtered, and lyophilized.
Manufacturing steps were independently validated in a series of in vitro experiments for their virus inactivation / reduction capacity for both enveloped and non-enveloped viruses. Table 8 shows the virus clearance during the manufacturing process for Kcentra, expressed as the mean log_{10} reduction factor.

<table>
<thead>
<tr>
<th>Virus Studied</th>
<th>Manufacturing Steps</th>
<th>Ammonium sulphate precipitation followed by Ca Phosphate adsorption</th>
<th>2 x 20 nm Virus Filtration</th>
<th>Overall Virus Reduction [log_{10}]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enveloped Viruses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>≥ 5.9</td>
<td>≥ 5.9</td>
<td>≥ 6.6</td>
<td>≥ 18.4</td>
</tr>
<tr>
<td>BVDV</td>
<td>≥ 8.5</td>
<td>2.2</td>
<td>≥ 6.0</td>
<td>≥ 16.7</td>
</tr>
<tr>
<td>PRV</td>
<td>3.8</td>
<td>7.2</td>
<td>≥ 6.6</td>
<td>≥ 17.6</td>
</tr>
<tr>
<td>WNV</td>
<td>≥ 7.4</td>
<td>n.d.</td>
<td>≥ 8.1</td>
<td>≥ 15.5</td>
</tr>
<tr>
<td>Non-Envelope Viruses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAV</td>
<td>4.0</td>
<td>1.8</td>
<td>≥ 6.1</td>
<td>≥ 11.9</td>
</tr>
<tr>
<td>CPV</td>
<td>[0.5]^*</td>
<td>1.5</td>
<td>6.5</td>
<td>8.0</td>
</tr>
</tbody>
</table>

Reduction factors 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.

HI: Human immunodeficiency virus, a model for HIV-1 and HIV-2
BVDV: Bovine viral diathesis 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

### Table 7: Composition per Vial of Kcentra *

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Potency Range for 500 units</th>
<th>Potency Range for 1000 units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total protein</td>
<td>120–280 mg</td>
<td>240–560 mg</td>
</tr>
<tr>
<td>Factor II</td>
<td>380–800 units</td>
<td>760–1600 units</td>
</tr>
<tr>
<td>Factor VII</td>
<td>200–500 units</td>
<td>400–1000 units</td>
</tr>
<tr>
<td>Factor IX</td>
<td>400–620 units</td>
<td>800–1240 units</td>
</tr>
<tr>
<td>Factor X</td>
<td>500–1020 units</td>
<td>1000–2040 units</td>
</tr>
<tr>
<td>Protein C</td>
<td>420–820 units</td>
<td>840–1640 units</td>
</tr>
<tr>
<td>Protein S</td>
<td>240–680 units</td>
<td>480–1360 units</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Acute Major Bleeding Study</th>
<th>Urgent Surgery/Invasive Procedures Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kcentra</td>
<td>Plasma</td>
</tr>
<tr>
<td>N</td>
<td>TE Events*</td>
</tr>
<tr>
<td>---</td>
<td>-------------</td>
</tr>
<tr>
<td>103</td>
<td>9 (8.7)</td>
</tr>
</tbody>
</table>

* 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/VF filter insertion).

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

<table>
<thead>
<tr>
<th>Acute Major Bleeding Study</th>
<th>Urgent Surgery/Invasive Procedures Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kcentra</td>
<td>Plasma</td>
</tr>
<tr>
<td>N</td>
<td>TE Events*</td>
</tr>
<tr>
<td>---</td>
<td>-------------</td>
</tr>
<tr>
<td>103</td>
<td>9 (8.7)</td>
</tr>
</tbody>
</table>

### 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 nonactivated 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 expiants 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.
12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Kcntra 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 Kcntra 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 Ca²⁺, 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 Fxla. 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 FVIIa-TF-Xa complex to form 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 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 FVIIa, leading to antithrombotic activity.

12.2 Pharmacodynamics

International Normalized Ratio (INR)

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 Kcntra infusion. By contrast, the median value for plasma was 2.4 at 30 minutes after the start of infusion. The INR differences between Kcntra and plasma were statistically significant in randomized plasma-controlled trial in bleeding up to 12 hours after start of infusion [see Table 9].

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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Baseline</th>
<th>30 min</th>
<th>1 hr</th>
<th>2-3 hr</th>
<th>6-8 hr</th>
<th>12 hr</th>
<th>24 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Major Bleeding Study</strong></td>
<td>Kcntra (N = 98)</td>
<td>3.90 (2.0–20.0)</td>
<td>1.20* (0.9–6.7)</td>
<td>1.30* (0.9–5.4)</td>
<td>1.30* (0.9–2.5)</td>
<td>1.30* (0.9–2.1)</td>
<td>1.20* (0.9–3.8)</td>
<td>1.20</td>
</tr>
<tr>
<td></td>
<td>Plasma (N = 104)</td>
<td>3.60 (1.9–38.9)</td>
<td>2.4 (1.4–11.4)</td>
<td>2.1 (1.0–11.4)</td>
<td>1.7 (1.0–14.1)</td>
<td>1.5 (1.0–3.0)</td>
<td>1.5 (1.0–2.9)</td>
<td>1.20</td>
</tr>
<tr>
<td><strong>Urgent Surgery/Invasive Procedures Study</strong></td>
<td>Kcntra (N = 87)</td>
<td>2.90 (2.0–17.0)</td>
<td>1.30* (0.9–7.0)</td>
<td>1.30* (0.9–2.5)</td>
<td>1.30* (0.9–3.9)</td>
<td>1.30* (1.0–10.3)</td>
<td>NC 1.20</td>
<td>1.20 (0.9–2.7)</td>
</tr>
<tr>
<td></td>
<td>Plasma (N = 87)</td>
<td>2.90 (2.0–26.7)</td>
<td>2.15 (1.4–5.4)</td>
<td>1.90 (1.3–5.7)</td>
<td>1.90 (1.3–5.7)</td>
<td>1.70 (1.0–5.8)</td>
<td>1.60 NC 1.30</td>
<td>1.30 (1.0–2.7)</td>
</tr>
</tbody>
</table>

Statistically significant difference compared to plasma by 2-sided Wilcoxon test CI = confidence interval.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

14 CLINICAL STUDIES

Kcntra has been evaluated in a prospective, open-label, blinded assessor, active-controlled, noninferiority, 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 included in this RCT. The study was randomized to a single dose of Kcntra or plasma.

The efficacy endpoint was hemostatic efficacy for the time period from the start of infusion to 24 hours after the start of infusion. The IVR was the increase in measurable factor levels in plasma (units/dL) that may be attributed to Kcntra. The IVR is calculated as the median increase in the procoagulant factors in plasma from baseline to 24 hours after the start of infusion.

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

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

* IVR: In Vivo Recovery
† MRT: Mean Residence Time
‡ Vd∞: Volume of Distribution at steady state

Table 11: In vivo Recovery in RCTs’

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Incremental (units/dL per units/kg b.w.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Major Bleeding Study</strong></td>
<td>(N = 98)</td>
</tr>
<tr>
<td>Factor IX</td>
<td>1.29 (0.71)</td>
</tr>
<tr>
<td>Factor II</td>
<td>2.00 (0.88)</td>
</tr>
<tr>
<td>Factor VII</td>
<td>2.15 (2.96)</td>
</tr>
<tr>
<td>Factor X</td>
<td>1.96 (0.87)</td>
</tr>
<tr>
<td>Protein C</td>
<td>2.04 (0.96)</td>
</tr>
<tr>
<td>Protein S</td>
<td>2.17 (1.66)</td>
</tr>
</tbody>
</table>

**Urgent Surgery/Invasive Procedures Study** | (N = 87) |
| Factor IX | 1.15 (0.57) | 1.03 (1.28) |
| Factor II | 2.14 (0.74) | 1.98 (2.31) |
| Factor VII | 1.90 (4.50) | 0.92 (2.88) |
| Factor X | 1.79 (2.09) | 1.73 (2.02) |
| Protein C | 1.88 (6.88) | 1.73 (2.02) |
| Protein S | 2.81 (1.95) | 2.38 (3.23) |

ITT-E: Intention to Treat – Efficacy Population CI: Confidence Interval
received study product. Criteria for effective hemostasis were based upon standard clinical assessments including vital signs, hemoglobin measurements, and CT assessments at predefined time points, as relevant to the type of bleeding (i.e., gastrointestinal, intracranial hemorrhage, visible, musculoskeletal, etc.). The proportion of subjects with effective hemostasis was 72.4% in the Kcentra group and 65.4% in the plasma group. The lower limit of the 95% confidence interval (CI) for the difference in proportions of Kcentra minus plasma was -5.8%, which exceeded -10% and thereby demonstrated the non-inferiority of Kcentra versus plasma (the study’s primary objective) [see Table 12]. Because the lower limit of the CI was not greater than zero, the prospectively defined criterion for superiority of Kcentra for hemostatic efficacy (a secondary objective) was not met.

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

<table>
<thead>
<tr>
<th>Rating</th>
<th>No. (%) of subjects [95% CI]</th>
<th>Difference Kcentra – Plasma [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kcentra (N = 98)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma (N = 104)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot;Effective&quot; hemostasis</td>
<td>71 (72.4%) [63.8; 82.6]</td>
<td>13.5% [5.5; 21.5]</td>
</tr>
<tr>
<td></td>
<td>68 (65.4%) [54.9; 75.8]</td>
<td>12% [4.0; 20.0]</td>
</tr>
<tr>
<td></td>
<td>72.4% (71.1%)</td>
<td>12.4% (11.1%)</td>
</tr>
</tbody>
</table>

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 59.4% to 65.9%. The lower limit of the 95% CI of 59.4% demonstrated superiority of Kcentra versus plasma for this endpoint [see Table 14].

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

<table>
<thead>
<tr>
<th>Rating</th>
<th>No. (%) of subjects [95% CI]</th>
<th>Difference Kcentra – Plasma [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kcentra (N = 98)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma (N = 104)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease of INR to ≤1.3 at 30 min</td>
<td>61 (62.2%) [52.6; 71.8]</td>
<td>29.6% [18.0; 41.3]</td>
</tr>
<tr>
<td></td>
<td>10 (9.6%) [3.9; 15.3]</td>
<td>30.7% [24.4; 37.1]</td>
</tr>
<tr>
<td></td>
<td>61.2% (52.6%)</td>
<td>30.7% (24.4%)</td>
</tr>
</tbody>
</table>

The European Bleeding and Surgical Study was an open-label, single-arm, multicenter study. 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. The 17 eligible 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 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


16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Kcentra is supplied in a single-use vial.

The actual units of potency of all coagulation factors (Factors II, VII, IX and X), Proteins C and S in units are stated on each Kcentra carton.

The Kcentra packaging components are not made with natural rubber latex.

Each kit consists of the following:

<table>
<thead>
<tr>
<th>Carton NDC Number</th>
<th>Components</th>
</tr>
</thead>
</table>
| 63833-386-02      | • Nominal potency 500 (range 400-620) units Kcentra in a single-use vial [NDC 63833-396-01]  
|                   | • 20 mL vial of Sterile Water for Injection, USP [NDC 63833-761-20]  
|                   | • Mix2Vial filter transfer set  
|                   | • Alcohol swab |

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

Storage and Handling

Prior to Reconstitution

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

After Reconstitution

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)].