Faculty Presenter

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Important Safety Information

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.

WARNING: ARTERIAL AND VENOUS THROMBOEMBOLIC COMPLICATIONS

Patients being treated with Vitamin K antagonist therapy have underlying disease states that predispose them to thromboembolic events. Potential benefits of reversing VKA should be weighed against the risk of thromboembolic events, especially in patients with history of such events. Resumption of anticoagulation therapy should be carefully considered once the risk of thromboembolic events outweighs the risk of acute bleeding. Both fatal and nonfatal arterial and venous thromboembolic complications have been reported in clinical trials and postmarketing surveillance. Monitor patients receiving Kcentra, and inform them of signs and symptoms of thromboembolic events. Kcentra was not studied in subjects who had a thromboembolic event, myocardial infarction, disseminated intravascular coagulation, cerebral vascular accident, transient ischemic attack, unstable angina pectoris, or severe peripheral vascular disease within the prior 3 months. Kcentra might not be suitable for patients with thromboembolic events in the prior 3 months.

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

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

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

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

The safety and efficacy of Kcentra in pediatric use have not been studied, and Kcentra should be used in women who are pregnant or nursing only if clearly needed.

Please see accompanying full prescribing information for Kcentra.

Kcentra® is a registered trademark of CSL Behring GmbH.

Kcentra® Educational Programs

Treatment Options for Your Patients Requiring Urgent Warfarin Reversal: A Case-Based Presentation

December 8, 2016

6:30 PM - Dinner and Presentation
Metropolitan Grill
2931 East Battlefield Street
Springfield, MO

This presentation will discuss:

• Important considerations for the management of patients requiring urgent warfarin reversal
• Product information and clinical trial data for Kcentra, the first and only FDA-approved 4F-PCC indicated for urgent warfarin reversal in adult patients with:
  - Acute major bleeding or
  - Need for urgent surgery/invasive procedure
• Important Safety Information for Kcentra

3 ways to register for this program:

1. Please visit www.kcentraprograms.com and complete the online registration form.
2. Call 1-877-732-7033.
3. Send an email to kprogramsupport@mei-nyc.com. Please be sure to include your full name and contact information so that we may call you back to complete your registration.

Would you like more information about this program?

Please contact Medical Exchange International at 1-877-732-7033 or at kprogramsupport@mei-nyc.com, or contact your local Kcentra representative, Robert Kish at 913-909-6644.

Space is limited and we request that you complete your registration by December 5, 2016.

This program is intended for US healthcare providers only. A meal will be provided during this educational program. In accordance with the Federal Physician Payment Sunshine Statute and any applicable state reporting laws, the value of the food and beverage provided and your national provider identity will be disclosed to CMS and any applicable state agencies.

Kcentra® Prothrombin Complex Concentrate (Human)
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

WARNINGS: 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 pectoris, or severe peripheral vascular disease within the prior 3 months. Kcentra may not be suitable in patients with thromboembolic events in the prior 3 months. (5.2)

RECENT MAJOR CHANGES
Indications and Usage (1) 12/2013
Dosage and Administration (2.1) 11/2013
Warnings and Precautions (5.2) 12/2013

INDICATIONS AND USAGE
Kcentra, Prothrombin Complex Concentrate (Human), is a blood coagulation factor replacement product indicated for the urgent reversal of acquired coagulation factor deficiencies induced by Vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients. Kcentra is available as a single-use vial containing coagulation Factors II, VII, IX, and X, and antithrombotic Proteins C and S as a lyophilized concentrate. (3)

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

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

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

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

See 17 for PATIENT COUNSELING INFORMATION

Revised: September 2014

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Kcentra®
Prothrombin Complex Concentrate (Human)

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

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.
- Individually kcentra is dosed 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, Prothrombin Complex Concentrate (Human), 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>Dose1 of Kcentra (units1 of Factor IX) / kg body weight</td>
<td>25</td>
<td>35</td>
<td>50</td>
</tr>
<tr>
<td>Maximum dose2 (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>

1 Dosing is based on body weight. Dose based on actual potency as stated on the carton, which will vary from 20-31 units/mL after reconstitution. Nominal potency is 500 or 1000 units per vial, approximately 25 units per mL after reconstitution.
2 Units refer to International Units.
3 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 dosage 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 (500 U kit) or 40 mL (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. Place the Kcentra vial and diluent vial 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. Open the Mix2Vial transfer set package by peeling away the lid. [Fig. 1] Leave the Mix2Vial transfer set in the clear package.
4. 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]
5. 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]
6. With the Kcentra vial placed firmly on a flat surface, invert the diluent vial with the Mix2Vial transfer set attached and push the plastic spike of the transparent adapter firmly through the center of the stopper of the Kcentra vial. [Fig. 4] The diluent will automatically transfer into the Kcentra vial.
7. 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] Do not shake the 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]

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Fig. 1
Fig. 2
Fig. 3
Fig. 4
Fig. 5
Fig. 6
10. Draw air into an empty, sterile syringe. While the Kcentra vial is upright, screw the syringe to the Mix2Vial transfer set. Inject air into the Kcentra vial. While keeping the syringe plunger pressed, invert the system upside down and draw the concentrate into the syringe by pulling the plunger back slowly. [Fig. 7]

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 range of Factor IX units per vial is 400-620 units for the 500 U kit and 800-1240 units for the 1000 U kit. When reconstituted, the final concentration of drug product in Factor IX units will be in a range from 20-31 units/mL.
- The actual content of Factor IX as measured in units of potency is stated on the vial.
- The actual units of potency for each coagulation factor (Factors II, VII, IX and X), and Proteins C and S are stated on the carton.

### 4 CONTRAINDICATIONS
Kcentra is contraindicated in:
- Patients with known anaphylactic or severe systemic reactions to Kcentra or any components in Kcentra including heparin, Factor 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), Clinical Studies (14)]. Potential benefits of treatment with Kcentra should be weighed against the potential risks of thromboembolic events [see Adverse Reactions (6)].

#### 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 to be transmitted from 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, myoccardial 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.
Levels did not have a mortality rate out of proportion to the overall population. Additional serious adverse reactions in subjects receiving Kcentra included ischemic cerebrovascular accident (stroke), DVT, thrombosis, and venous insufficiency.

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

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Reaction</th>
<th>Kcentra (N = 191)</th>
<th>Plasma (N = 197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (% of subjects)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>14 (7.3%)</td>
<td>7 (3.6%)</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>Pleural effusion</td>
<td>8 (4.2%)</td>
<td>3 (1.5%)</td>
</tr>
<tr>
<td></td>
<td>Respiratory distress/dyspnea/hypoxia</td>
<td>7 (3.7%)</td>
<td>10 (5.1%)</td>
</tr>
<tr>
<td></td>
<td>Pulmonary edema</td>
<td>3 (1.6%)</td>
<td>10 (5.1%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea/vomiting</td>
<td>12 (6.3%)</td>
<td>8 (4.1%)</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>4 (2.1%)</td>
<td>7 (3.6%)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Tachycardia</td>
<td>9 (4.7%)</td>
<td>2 (1.0%)</td>
</tr>
<tr>
<td></td>
<td>Atrial fibrillation</td>
<td>8 (4.2%)</td>
<td>6 (3.0%)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Fluid overload†</td>
<td>5 (2.6%)</td>
<td>16 (8.1%)</td>
</tr>
<tr>
<td></td>
<td>Hypokalemia</td>
<td>9 (4.7%)</td>
<td>14 (7.1%)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Insomnia</td>
<td>9 (4.7%)</td>
<td>6 (3.0%)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypotension‡</td>
<td>14 (7.3%)</td>
<td>10 (5.1%)</td>
</tr>
<tr>
<td>Injury, poisoning, and procedural complications</td>
<td>Skin laceration/contusion/subcutaneous hematoma</td>
<td>8 (4.2%)</td>
<td>5 (2.5%)</td>
</tr>
<tr>
<td>Blood and lymphatic disorders</td>
<td>Anemia‡</td>
<td>11 (5.8%)</td>
<td>16 (8.1%)</td>
</tr>
</tbody>
</table>

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

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 46 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 -2.0%.

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 (N = 103)</td>
<td>Plasma (N = 109)</td>
</tr>
<tr>
<td>N (%)</td>
<td>Fluid Overload</td>
<td>N (%)</td>
</tr>
<tr>
<td>All subjects</td>
<td>103 (6.6%)</td>
<td>109 (6.3%)</td>
</tr>
<tr>
<td>With history of CHF</td>
<td>9 (8.2%)</td>
<td>11 (9.1%)</td>
</tr>
<tr>
<td>Without history of CHF</td>
<td>64 (6.0%)</td>
<td>75 (6.8%)</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>Adverse Reaction</th>
<th>Kcentra (N = 103)</th>
<th>Plasma (N = 109)</th>
<th>Kcentra (N = 88)</th>
<th>Plasma (N = 88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (% of subjects)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any possible TEE*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEE Adverse reactions</td>
<td>Myocardial infarction</td>
<td>0 (1.0%)</td>
<td>0 (0.9%)</td>
<td>0 (2.3%)</td>
<td>0 (0.9%)</td>
</tr>
<tr>
<td></td>
<td>Myocardial ischemia</td>
<td>0 (2.1%)</td>
<td>0 (2.3%)</td>
<td>0 (2.3%)</td>
<td>0 (2.3%)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Ischemic cerebrovascular accident (stroke)</td>
<td>2 (1.9%)</td>
<td>0 (0.9%)</td>
<td>0 (0.9%)</td>
<td>0 (0.9%)</td>
</tr>
<tr>
<td></td>
<td>Embolic cerebral infarction</td>
<td>0 (0.9%)</td>
<td>0 (0.9%)</td>
<td>1 (1.1%)</td>
<td>0 (0.9%)</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular disorder</td>
<td>0 (0.9%)</td>
<td>0 (0.9%)</td>
<td>0 (0.9%)</td>
<td>0 (0.9%)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Venous thrombosis calf</td>
<td>1 (1.0%)</td>
<td>0 (0.9%)</td>
<td>0 (0.9%)</td>
<td>0 (0.9%)</td>
</tr>
<tr>
<td></td>
<td>Venous thrombosis radial vein</td>
<td>0 (0.9%)</td>
<td>1 (1.0%)</td>
<td>0 (0.9%)</td>
<td>1 (1.0%)</td>
</tr>
<tr>
<td></td>
<td>Thrombosis (microthrombosis of toes)</td>
<td>0 (0.9%)</td>
<td>0 (0.9%)</td>
<td>1 (1.1%)</td>
<td>0 (0.9%)</td>
</tr>
<tr>
<td></td>
<td>Deep vein thrombosis (DVT)</td>
<td>1 (1.0%)</td>
<td>1 (1.1%)</td>
<td>1 (1.1%)</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td></td>
<td>Fistula Clot</td>
<td>1 (1.0%)</td>
<td>0 (0.9%)</td>
<td>0 (0.9%)</td>
<td>0 (0.9%)</td>
</tr>
<tr>
<td>Unknown Cause of Death (not confirmed TEE)</td>
<td>Sudden death</td>
<td>1 (1.0%)</td>
<td>0 (0.9%)</td>
<td>0 (0.9%)</td>
<td>0 (0.9%)</td>
</tr>
</tbody>
</table>

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

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.

These serious adverse reactions 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 occurring during or within 72 hours of test product infusion.
Subgroup analyses of the RCTs according to whether subjects with thromboembolic events had a prior history of a thromboembolic event are presented in Table 6.

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

<table>
<thead>
<tr>
<th></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><strong>N TE Events</strong></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>All subjects</td>
<td>103 (8.7)</td>
<td>109 (6.5)</td>
</tr>
<tr>
<td>With history of TE event*</td>
<td>69 (8.1)</td>
<td>79 (3.8)</td>
</tr>
<tr>
<td>Without history of TE event</td>
<td>34 (2.9)</td>
<td>30 (10.0)</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 VVC, 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 in 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

Pregnancy Category C. Animal reproduction studies have not been conducted with Kcentra. It is also not known whether Kcentra can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Kcentra should be prescribed for a pregnant woman only if clearly needed.

8.2 Labor and Delivery

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

8.3 Nursing Mothers

It is not known whether Kcentra is excreted in human milk. Because many drugs are excreted in human milk, use Kcentra only if clearly needed when treating a nursing woman.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the total number of subjects (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 excipients are human antithrombin III, heparin, human albumin, sodium chloride, and sodium citrate. Kcentra is sterile, pyrogen-free, and does not contain preservatives.

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

12.1 Mechanism of Action

Kentra 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 Kentra 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 phospholipids and calcium ions.

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 Fxa. 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-FXa complex or the TF-FVIIa complex. Factor Xa forms a complex with phospholipids and calcium ions.

Protein C

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

Protein S

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

12.2 Pharmacodynamics

International Normalized Ratio (INR)

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

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

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

<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>Acute Major Bleeding Study</td>
<td>Kentra (N = 98)</td>
<td>3.90 (1.8–20.0)</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 (0.9–2.2)</td>
<td>1.20 (0.9–3.8)</td>
</tr>
<tr>
<td></td>
<td>Plasma (N = 104)</td>
<td>2.6 (1.4–11.4)</td>
<td>2.1 (1.0–3.0)</td>
<td>1.7 (1.0–4.1)</td>
<td>1.5 (1.0–3.0)</td>
<td>1.4 (1.0–3.0)</td>
<td>1.3 (1.0–2.9)</td>
<td></td>
</tr>
<tr>
<td>Urgent Surgery/Invasive Procedures Study</td>
<td>Kentra (N = 87)</td>
<td>2.90 (2.0–17.0)</td>
<td>1.20 (0.9–7.0)</td>
<td>1.20 (0.9–2.5)</td>
<td>1.20 (0.9–3.9)</td>
<td>1.30 (1.0–3.0)</td>
<td>NC</td>
<td>1.20 (0.9–2.7)</td>
</tr>
<tr>
<td></td>
<td>Plasma (N = 87)</td>
<td>2.20 (1.4–5.4)</td>
<td>1.90 (1.0–5.8)</td>
<td>1.70 (1.1–3.7)</td>
<td>1.60 (1.0–4.9)</td>
<td>1.30 (1.0–2.7)</td>
<td>NC</td>
<td></td>
</tr>
</tbody>
</table>

Table 10: Vitamin K-Dependent Coagulation Factor Pharmacokinetics after a Single Kcentra 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>Terminal half-life (h)</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>49.3 (26.7)</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>Vdss (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>

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>Acute Major Bleeding Study</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 (0.96)</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>

12.3 Pharmacokinetics

Fifteen healthy subjects received 50 units/kg of Kentra. No subjects were receiving VKA therapy or were experiencing acute bleeding. A single intravenous Kentra infusion produced a rapid and sustained increase in plasma concentration of Factors II, VII, IX and X as well as Proteins C and S. The PK analysis [see Table 10] shows that Factor II had the longest half-life (59.7 hours) and factor VII the shortest (4.2 hours) in healthy subjects. PK parameters obtained from data derived from the study of healthy subjects may not be directly applicable to patients with INR elevation due to VKA anticoagulation therapy.
received study product. Criteria for effective hemostasis were based upon standard clinical assessments including vital signs, hemoglobin measurements, and CT assessments at pre-defined time points, as relevant to the type of bleeding (i.e., gastrointestinal, intracranial hemorrhage, visible, musculoskeletal, etc.). The proportion of subjects with effective hemostasis was 72.4% in the Kcentra group and 65.4% in the plasma group. The lower limit of the 95% confidence interval (CI) for the difference in proportions of Kcentra minus plasma was -5.8%, which exceeded -10% and thereby demonstrated the non-inferiority of Kcentra versus plasma (the study’s primary objective) [see Table 12]. Because the lower limit of the CI was not greater than zero, the prospectively defined criterion for superiority of Kcentra for hemostatic efficacy (a secondary objective) was not met.

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 39.6% to 65.9%. The lower limit of the 95% CI of 39.6% demonstrated superiority of Kcentra versus plasma for this endpoint [see Table 14].

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

<table>
<thead>
<tr>
<th>Rating</th>
<th>Kcentra (N = 87)</th>
<th>Plasma (N = 81)</th>
<th>Difference Kcentra – Plasma (% [95% CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Effective” hemostasis</td>
<td>78 (89.7%)</td>
<td>61 (75.3%)</td>
<td>14.3%  [2.8, 25.8]</td>
</tr>
<tr>
<td></td>
<td>[83.3; 96.1]</td>
<td>[65.9; 84.7]</td>
<td></td>
</tr>
</tbody>
</table>

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

CI = confidence interval; N = number of subjects

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

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

<table>
<thead>
<tr>
<th>Rating of Hemostatic Efficacy Stratifed by Actual Dose</th>
<th>Kcentra (N = 104)</th>
<th>Plasma (N = 99)</th>
<th>Difference Kcentra – Plasma (% [95% CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Dose</td>
<td>N = 49 (K)</td>
<td>N = 22 (P)</td>
<td>24.1%  [10.1, 38.1]</td>
</tr>
<tr>
<td>Mid Dose</td>
<td>N = 55 (P)</td>
<td>N = 31 (P)</td>
<td>23.6%  [9.1, 38.0]</td>
</tr>
<tr>
<td>High Dose</td>
<td>N = 61 (K)</td>
<td>N = 46 (P)</td>
<td>16.5%  [4.2, 28.8]</td>
</tr>
</tbody>
</table>

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

CI = confidence interval; N = total subjects

**Urgent Surgery/Invasive Procedure RCT:** The efficacy of Kcentra has been evaluated in a prospective, open-label, 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 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 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 Vitamin K antagonist therapy were randomized to a single dose of Kcentra or 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. In the Kcentra group, 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), respectively. The observation period lasted for 90 days after the infusion of Kcentra or plasma. The modified efficacy (ITE-E) population for Kcentra included 87 subjects and for plasma included 81 subjects. Additionally, oral or intravenous Vitamin K was administered.

Effective hemostasis was based upon the difference between predicted and actual blood losses, subjective hemostasis rating, and the need for additional blood products containing coagulation factors. The proportion of subjects with effective hemostasis was 89.7% in the Kcentra group and 75.3% in the plasma group. The lower limit of the 95% confidence interval (CI) for the difference in proportions of Kcentra minus plasma was 2.8%, which exceeded -10% and thereby demonstrated the non-inferiority of Kcentra versus plasma (the study’s primary objective) [see Table 15]. Because the lower limit of the CI was greater than 0, the prospectively defined criterion for superiority of Kcentra for hemostatic efficacy (a secondary objective) was also met.

Table 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>Kcentra (N = 98)</th>
<th>Plasma (N = 104)</th>
<th>Difference Kcentra – Plasma (% [95% CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease of INR to ≤ 1.3 at 30 min</td>
<td>61 (62.2%)</td>
<td>10 (9.6%)</td>
<td>51.6%  [39.4, 65.9]</td>
</tr>
<tr>
<td></td>
<td>[52.6; 71.8]</td>
<td>[3.9; 15.3]</td>
<td></td>
</tr>
</tbody>
</table>

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

CI = confidence interval; N = total subjects

**The European Bleeding and Surgical Study:** The 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 ≤ 1.3 within 30 minutes after end of Kcentra infusion in subjects who received any portion of study product. Of 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 Antithrombotics 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


16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

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

Each kit consists of the following:

<table>
<thead>
<tr>
<th>Carton NDC Number</th>
<th>Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>63833-386-02</td>
<td>• 500 units Kcentra in a single-use vial [NDC 63833-396-01]</td>
</tr>
<tr>
<td></td>
<td>• 20 mL vial of Sterile Water for Injection, USP [NDC 63833-761-20]</td>
</tr>
<tr>
<td></td>
<td>• Mix2Vial filter transfer set</td>
</tr>
<tr>
<td></td>
<td>• Alcohol swab</td>
</tr>
<tr>
<td>63833-387-02</td>
<td>• 1000 units Kcentra in a single-use vial [NDC 63833-397-01]</td>
</tr>
<tr>
<td></td>
<td>• 40 mL vial of Sterile Water for Injection, USP [NDC 63833-761-40]</td>
</tr>
<tr>
<td></td>
<td>• Mix2Vial filter transfer set</td>
</tr>
<tr>
<td></td>
<td>• Alcohol swab</td>
</tr>
</tbody>
</table>

16.2 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)].

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