KCENTRA- prothrombin, coagulation factor vii human, coagulation factor ix human, coagulation factor x human, protein c, protein s human, and water
CSL Behring GmbH

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

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

WARNING: ARTERIAL AND VENOUS THROMBOEMBOLIC COMPLICATIONS

Patients being treated with Vitamin K antagonists (VKA) therapy have underlying disease states that predispose them to thromboembolic events. Potential benefits of reversing VKA should be weighed against the potential risks of thromboembolic events, especially in patients with the history of a thromboembolic event. Resumption of anticoagulation should be carefully considered as soon as the risk of thromboembolic events outweighs the risk of acute bleeding.

- **Both fatal and non-fatal arterial and venous thromboembolic complications have been reported with Kcentra in clinical trials and post marketing surveillance. Monitor patients receiving Kcentra for signs and symptoms of thromboembolic events.**
- **Kcentra was not studied in subjects who had a thromboembolic event, myocardial infarction, disseminated intravascular coagulation, cerebral vascular accident, transient ischemic attack, unstable angina pectoris, or severe peripheral vascular disease within the prior 3 months. Kcentra may not be suitable in patients with thromboembolic events in the prior 3 months. (5.2)**

RECENT MAJOR CHANGES

Dosage and Administration (2.1, 2.2)	02/2017

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)

DOSAGE AND ADMINISTRATION

For intravenous use only.

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

Pre-treatment INR	**2–< 4**	**4–6**	**> 6**
Dose* of Kcentra (units† of Factor IX) / kg body weight	25	35	50
Maximum dose‡ (units of Factor IX)	Not to exceed 2500	Not to exceed 3500	Not to exceed 5000

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

† Units refer to International Units.

‡ Dose is based on body weight up to but not exceeding 100 kg. For patients weighing more than 100 kg, maximum dose should not be exceeded.

DOSAGE FORMS AND STRENGTHS

- Kcentra is available as a 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.*
See 17 for PATIENT COUNSELING INFORMATION.

Revised: 2/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: ARTERIAL AND VENOUS THROMBOEMBOLIC COMPLICATIONS

Patients being treated with Vitamin K antagonists (VKA) therapy have underlying disease states that predispose them to thromboembolic events. Potential benefits of reversing VKA should be weighed against the potential risks of thromboembolic events (TE), especially in patients with the history of a thromboembolic event. Resumption of anticoagulation should be carefully considered as soon as the risk of thromboembolic events outweighs the risk of acute bleeding.

- **Both fatal and non-fatal arterial and venous thromboembolic complications have been reported with Kcentra in clinical trials and post marketing surveillance. Monitor patients receiving Kcentra for signs and symptoms of thromboembolic events. (5.2)**
- **Kcentra was not studied in subjects who had a thromboembolic event, myocardial infarction, disseminated intravascular coagulation, cerebral vascular accident, transient ischemic attack, unstable angina pectoris, or severe peripheral vascular disease within the prior 3 months. Kcentra may not be suitable in patients with thromboembolic events in the prior 3 months. (5.2)**

1 INDICATIONS AND USAGE

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

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

2 DOSAGE AND ADMINISTRATION

For intravenous use only.

2.1 Dosage

- Measurement of INR prior to treatment and close to the time of dosing is important because coagulation factors may be unstable in patients with acute major bleeding or an urgent need for surgery and other invasive procedures.

- Individualize Kcentra dosing based on the patient's current pre-dose International Normalized Ratio (INR) value, and body weight (*see Table 1*).
- The actual potency per vial of Factors II, VII, IX and X, Proteins C and S is stated on the carton.
- Administer Vitamin K concurrently to patients receiving Kcentra. Vitamin K is administered to maintain Vitamin K-dependent clotting factor levels once the effects of Kcentra have diminished.
- The safety and effectiveness of repeat dosing have not been established and it is not recommended.
- Dose ranging within pre-treatment INR groups has not been studied in randomized clinical trials of Kcentra.

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

Pre-treatment INR	**2–< 4**	**4–6**	**> 6**
Dose* of Kcentra (units† of Factor IX) / kg body weight	25	35	50
Maximum dose‡ (units of Factor IX)	Not to exceed 2500	Not to exceed 3500	Not to exceed 5000

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

† Units refer to International Units.

‡ Dose is based on body weight up to but not exceeding 100 kg. For patients weighing more than 100 kg, maximum dose should not be exceeded.

Example dosing calculation for 80 kg patient

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

35 units of Factor IX/kg × 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.	 Fig. 1
5. Place the diluent vial on a flat surface and hold the vial tightly. Grip the Mix2Vial transfer set together with the clear package and push the plastic spike at the blue end of the Mix2Vial transfer set firmly through the center of the stopper of the diluent vial. [*Fig. 2*]	 Fig. 2
6. Carefully remove the clear package from the Mix2Vial transfer set. Make sure that you pull up only the clear package, not the Mix2Vial transfer set. [*Fig. 3*]	 Fig. 3
7. With the Kcentra vial placed firmly on a flat surface, invert the diluent vial with the Mix2Vial transfer set attached and push the plastic spike of the transparent adapter firmly through the center of the stopper of the Kcentra vial. [*Fig. 4*] The diluent will automatically transfer into the Kcentra vial.	 Fig. 4
8. With the diluent and Kcentra vial still attached to the Mix2Vial transfer set, gently swirl the Kcentra vial to ensure that the Kcentra is fully dissolved. [*Fig. 5*] Do not shake the vial.	 Fig. 5

9. With one hand, grasp the Kcentra side of the Mix2Vial transfer set and with the other hand grasp the blue diluent-side of the Mix2Vial transfer set, and unscrew the set into two pieces. [*Fig. 6*]	 Fig. 6
10. Draw air into an empty, sterile syringe. While the Kcentra vial is upright, screw the syringe to the Mix2Vial transfer set. Inject air into the Kcentra vial. While keeping the syringe plunger pressed, invert the system upside down and draw the concentrate into the syringe by pulling the plunger back slowly. [*Fig. 7*]	 Fig. 7
11. Now that the concentrate has been transferred into the syringe, firmly grasp the barrel of the syringe (keeping the plunger facing down) and unscrew the syringe from the Mix2Vial transfer set. [*Fig. 8*] Attach the syringe to a suitable intravenous administration set.	 Fig. 8
12. After reconstitution, administration should begin promptly or within 4 hours.	
13. If the same patient is to receive more than one vial, you may pool the contents of multiple vials. Use a separate unused Mix2Vial transfer set for each product vial.	

2.3 Administration

- Do not mix Kcentra with other medicinal products; administer through a separate infusion line.
- Use aseptic technique when administering Kcentra.
- Administer at room temperature.
- Administer by intravenous infusion at a rate of 0.12 mL/kg/min (~3 units/kg/min), up to a maximum rate of 8.4 mL/min (~210 units/min).
- No blood should enter the syringe, as there is a possibility of fibrin clot formation.

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 (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

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

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

5.2 Thromboembolic Risk/Complications

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

Thromboembolic events occurred more frequently following Kcentra compared to plasma in a randomized, plasma controlled trial in subjects requiring urgent reversal of VKA anticoagulation due to acute major bleeding, and the excess in thromboembolic events was more pronounced among subjects who had a history of prior thromboembolic event, although these differences were not statistically significant *[see Adverse Reactions (6.1), and Clinical Studies (14)]*. Potential benefits of treatment with Kcentra should be weighed against the potential risks of thromboembolic events *[*see *Adverse Reactions (6)]*. Patients with a history of thrombotic events, myocardial infarction, cerebral vascular accident, transient ischemic attack, unstable angina pectoris, severe peripheral vascular disease, or disseminated intravascular coagulation, within the previous 3 months were excluded from participating in the plasma-controlled RCT. Kcentra may not be suitable in patients with thromboembolic events in the prior 3 months. Because of the risk of thromboembolism associated with reversal of VKA, closely monitor patients for signs and symptoms of thromboembolism during and after administration of Kcentra *[see 17 Patient Counseling Information]*.

5.3 Transmissible Infectious Agents

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

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

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

6 ADVERSE REACTIONS

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

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

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

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

6.1 Clinical Trials Experience

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

Randomized, Plasma-Controlled Trial in Acute Major Bleeding

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

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

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

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

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

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

	No. (%) of subjects

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

* Includes fluid overload and cardiac failure congestive

† Includes orthostatic hypotension, hypotension, and hemorrhagic shock

‡ Includes anemia, hemoglobin decreased, and hematocrit decreased

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

There were a total of 10 subjects (9.7%) who died in the Kcentra group (1 additional death occurred on day 46 just after completion of the study reporting period) and 5 (4.6%) who died in the plasma group in the plasma-controlled RCT in acute major bleeding. The 95% confidence interval for the Kcentra minus plasma between-group difference in deaths ranged from -2.7% to 13.5%. From the plasma-controlled RCT in urgent surgery/invasive procedures, there were a total of 3 subjects (3.4%) who died in the Kcentra group (1 additional death occurred on day 48 after completion of the study reporting period) and 8 (9.1%) who died in the Plasma group. The 95% confidence interval for the Kcentra minus plasma between-group difference in deaths in this trial ranged from -14.6% to 2.7%. One death in the Kcentra group in the RCT in Acute Major Bleeding and one death in the plasma group in the RCT in urgent surgery/invasive procedures were considered possibly related to study treatment according to an assessment of masked data by an independent safety adjudication board. No factors common to all deaths were identified, except for the frequent findings of a high comorbidity burden, advanced age, and death after being placed on comfort care. Although, a greater proportion of subjects in the RCT in acute

major bleeding than in the RCT in surgery/invasive procedure received the highest two recommended doses of Kcentra because more subjects in the trial in acute major bleeding had a baseline INR in the ranges of 4–6 and > 6.0, an analysis of deaths and factor levels in subjects with major bleeding revealed that subjects who died had similar median factor levels to subjects that did not die. Additionally, outliers with supraphysiologic factor levels did not have a mortality rate out of proportion to the overall population.

Fluid Overload

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

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

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

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

Thromboembolic Events

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

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

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

System Organ Class	No. (%) of subjects	
	Acute Major Bleeding Study	Urgent Surgery/Invasive Procedures Study

	Kcentra (N = 103)	Plasma (N = 109)	Kcentra (N = 88)	Plasma (N = 88)
Any possible TEE*	**9 (8.7%)**	**6 (5.5%)**	**4 (4.5)**	**8 (9.1)**
TEE Adverse reactions	**6 (5.5%)**	**4 (3.7%)**	**4 (4.5)**	**4 (4.5)**
Cardiac disorders				
Myocardial infarction	0	1 (0.9%)	0	2 (2.3)
Myocardial ischemia	0	2 (1.8%)	0	0
Nervous system disorders				
Ischemic cerebrovascular accident (stroke)	2 (1.9%)	0	1 (1.1)	0
Embolic cerebral infarction	0	0	0	1 (1.1)
Cerebrovascular disorder	0	1 (0.9%)	0	0
Vascular disorders				
Venous thrombosis calf	1 (1.0%)	0	0	0
Venous thrombosis radial vein	0	0	1 (1.1)	0
Thrombosis (microthrombosis of toes)	0	0	1 (1.1)	0
Deep vein thrombosis (DVT)	1 (1.0%)	0	1 (1.1)	1 (1.1)
Fistula Clot	1 (1.0%)	0	0	0
Unknown Cause of Death (not confirmed TEE)				
Sudden death	1 (1.0%)	0	0	0

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

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

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

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

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

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

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

6.2 Postmarketing Experience

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Congenital Factor Deficiencies

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

11 DESCRIPTION

Kcentra is a purified, heat-treated, nanofiltered and lyophilized non-activated four-factor Prothrombin Complex Concentrate (Human) prepared from human U.S. Source Plasma (21 CFR 640.60). It contains the Vitamin K dependent Coagulation Factors II, VII, IX and X, and the antithrombotic Proteins C and S. Factor IX is the lead factor for the potency of the preparation as stated on the vial label. The excipients

are human antithrombin III, heparin, human albumin, sodium chloride, and sodium citrate. Kcentra is sterile, pyrogen-free, and does not contain preservatives.

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

Table 7: Composition per Vial of Kcentra*

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

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

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

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

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

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

Virus Studied	Manufacturing Steps			
	Heat treatment ("Pasteurization")	Ammonium sulphate precipitation followed by Ca Phosphate adsorption	2 × 20nm Virus Filtration	Overall Virus Reduction [$\log_{10}$]
Enveloped Viruses				
HIV	≥ 5.9	≥ 5.9	≥ 6.6	≥ 18.4
BVDV	≥ 8.5	2.2	≥ 6.0	≥ 16.7

PRV	3.8	7.2	≥ 6.6	≥ 17.6
WNV	≥ 7.4	n.d.	≥ 8.1	≥ 15.5
Non-Enveloped Viruses				
HAV	4.0	1.8	≥ 6.1	≥ 11.9
CPV	[0.5]*	1.5	6.5	8.0

HIV Human immunodeficiency virus, a model for HIV-1 and HIV-2

BVDV Bovine viral diarrhea virus, model for HCV

PRV Pseudorabies virus, a model for large enveloped DNA viruses

WNV West Nile virus

HAV Hepatitis A virus

CPV Canine parvovirus, model for B19V

n.d. not determined

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

A dose-dependent acquired deficiency of the Vitamin K-dependent coagulation factors occurs during Vitamin K antagonist treatment. Vitamin K antagonists exert anticoagulant effects by blocking carboxylation of glutamic acid residues of the Vitamin K-dependent coagulation factors during hepatic synthesis, lowering both factor synthesis and function. The administration of Kcentra rapidly increases plasma levels of the Vitamin K-dependent coagulation Factors II, VII, IX, and X as well as the antithrombotic Proteins C and S.

Coagulation Factor II

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

Coagulation Factor VII

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

Coagulation Factor IX

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

Coagulation Factor X

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

Protein C

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

Protein S

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

12.2 Pharmacodynamics

International Normalized Ratio (INR)

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

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

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

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

INR = international normalized ratio; NC = not collected.

* Statistically significant difference compared to plasma by 2-sided Wilcoxon test

12.3 Pharmacokinetics

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

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

Parameter	Factor IX	Factor II	Factor VII	Factor X	Protein C	Protein S
Terminal half-life (h)	42.4 (41.6)	60.4 (25.5)	5.0 (1.9)	31.8 (8.7)	49.6 (32.7)	50.4 (13.4)
IVR (%/units/kg bw)*	1.6 (0.4)	2.2 (0.3)	2.5 (0.4)	2.2 (0.4)	2.9 (0.3)	2.0 (0.3)

AUC (IU/dL × h)	1850.8 (1001.4)	7282.2 (2324.9)	512.9 (250.1)	6921.5 (1730.5)	5397.5 (2613.9)	3651.6 (916.3)
Clearance (mL/ kg × h)	3.7 (1.6)	1.0 (0.3)	7.4 (4.1)	1.3 (0.3)	1.5 (0.9)	1.2 (0.3)
MRT (h)†	47.3 (49.5)	82.0 (34.2)	7.1 (2.7)	45.9 (12.6)	62.4 (42.1)	70.3 (18.3)
Vd_{ss} (mL/kg)‡	114.3 (54.6)	71.4 (13.7)	45.0 (10.7)	55.5 (6.7)	62.2 (17.4)	78.8 (11.6)

* IVR: In Vivo Recovery

† MRT: Mean Residence Time

‡ Vd_{ss}: Volume of Distribution at steady state

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

Table 11: In vivo Recovery in RCTs*

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

* ITT-E: Intention to Treat – Efficacy Population

† CI: Confidence Interval

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

14 CLINICAL STUDIES

Acute Major Bleeding RCT: The efficacy of Kcentra has been evaluated in a prospective, open-label, (blinded assessor), active-controlled, non-inferiority, multicenter RCT in subjects who had been treated with VKA therapy and who required urgent replacement of their Vitamin K-dependent clotting factors to treat acute major bleeding. A total of 216 subjects with acquired coagulation factor deficiency due to oral Vitamin K antagonist therapy were randomized to a single dose of Kcentra or plasma. Two hundred twelve (212) subjects received Kcentra or plasma for acute major bleeding in the setting of a baseline INR ≥ 2.0 and recent use of a VKA anticoagulant. The doses of Kcentra (25 units/kg, 35 units/kg, or 50

units/kg) based on nominal Factor IX content and plasma (10 mL/kg, 12 mL/kg, or 15 mL/kg) were calculated according to the subject's baseline INR (2–< 4, 4–6, > 6, respectively). The observation period lasted for 90 days after the infusion of Kcentra or plasma. The modified efficacy (ITT-E) population for Kcentra included 98 subjects and for plasma included 104 subjects. Additionally, intravenous Vitamin K was administered.

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

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

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

CI = confidence interval; N = number of subjects

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

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

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

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

* Kcentra minus Plasma

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

limit of the 95% CI of 39.4% demonstrated superiority of Kcentra versus plasma for this endpoint *[see Table 14]*.

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

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

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

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

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

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

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

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

CI = confidence interval; N = number of subjects

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

Results of a post-hoc analysis of hemostatic efficacy stratified by actual dose of Kcentra or plasma administered in the urgent surgery/invasive procedure RCT are presented in Table 16.

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

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

* Kcentra minus Plasma

An additional endpoint was the reduction of INR to ≤ 1.3 at 30 minutes after the end of infusion of Kcentra or plasma for all subjects that received study product. The proportion of subjects with this decrease in INR was 55.2% in the Kcentra group and 9.9% in the plasma group. The 95% confidence interval for the difference in proportions of Kcentra minus plasma was 31.9% to 56.4%. The lower limit of the 95% CI of 31.9% demonstrated superiority of Kcentra versus plasma for this endpoint *[see Table 17]*. The relationship between a decrease in INR to less than or equal to 1.3 and clinical hemostatic efficacy has not been established.

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

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

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

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

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

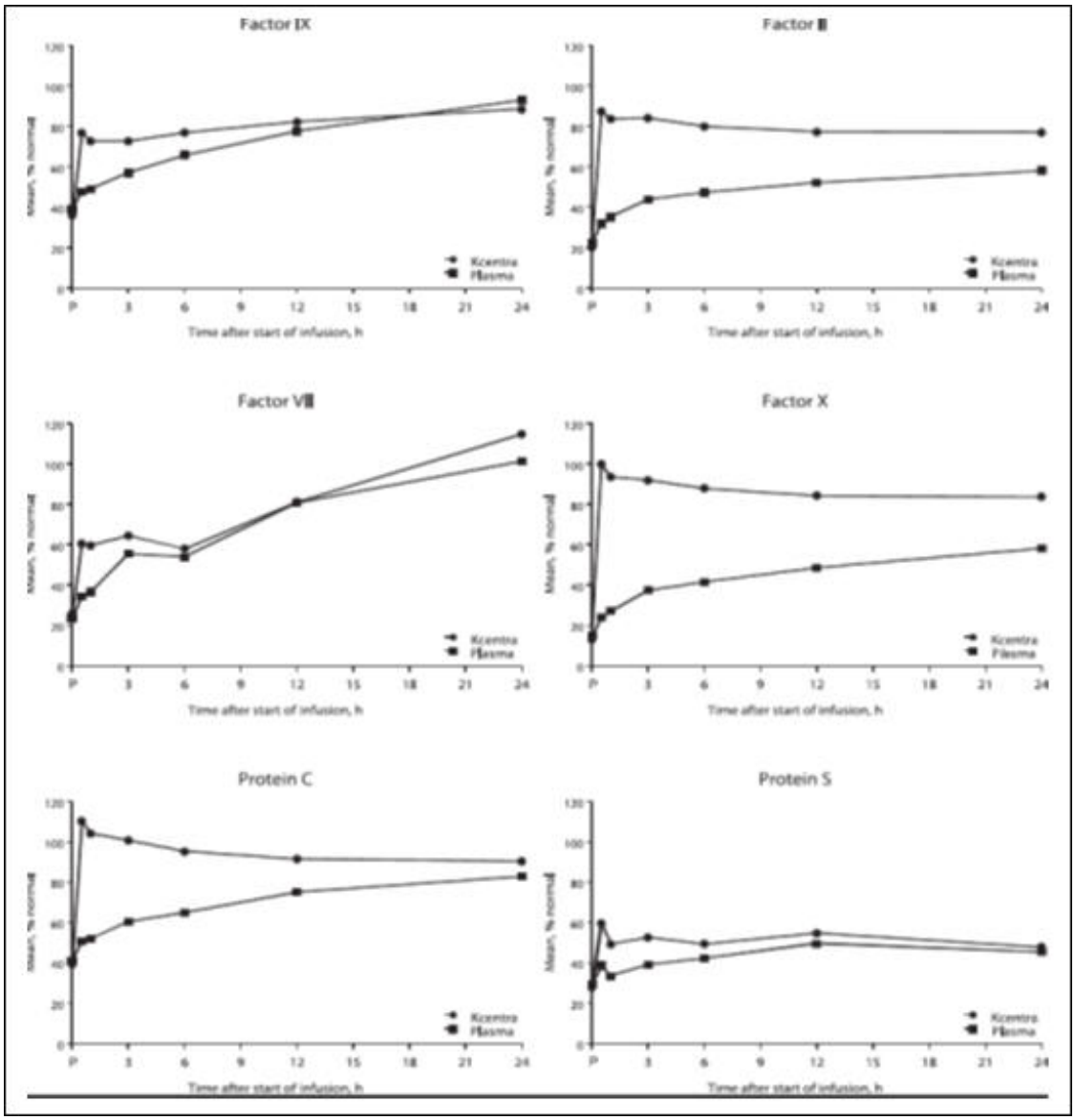
Of the 17 evaluable subjects receiving Kcentra for acute bleeding, 16 subjects (94%) experienced a decrease in INR to ≤ 1.3 within 30 minutes after the end of the Kcentra infusion.

In RCTs, levels of Coagulation Factors II, VII, IX, X, and Antithrombotic Proteins C and S were measured after the infusion of Kcentra or plasma and the results were similar for subjects with acute major bleeding or subjects requiring an urgent surgery or invasive procedure. In the plasma-controlled

RCT in acute major bleeding, the mean duration of Kcentra infusion was 24 minutes (± 32 minutes) and the mean duration of infusion for plasma was 169 minutes (± 143 minutes). The mean infusion volume of Kcentra was 105 mL ± 37 mL and the mean infusion volume of plasma was 865 mL ± 269 mL. In the plasma-controlled RCT for patients needing urgent surgery/invasive procedures, the mean duration of Kcentra infusion was 21 minutes (± 14 minutes) and the mean duration of infusion for plasma was 141 minutes (± 113 minutes). The mean infusion volume of Kcentra was 90 mL ± 32 mL and the mean infusion volume of plasma was 819 mL ± 231 mL.

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

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



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

15 REFERENCES

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

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

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

Each kit consists of the following:

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

Storage and Handling

Prior to Reconstitution

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

After Reconstitution

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)]*.

Manufactured by:
CSL Behring GmbH
35041 Marburg Germany
US License No. 1765

Distributed by:
CSL Behring LLC
Kankakee, IL 60901 USA

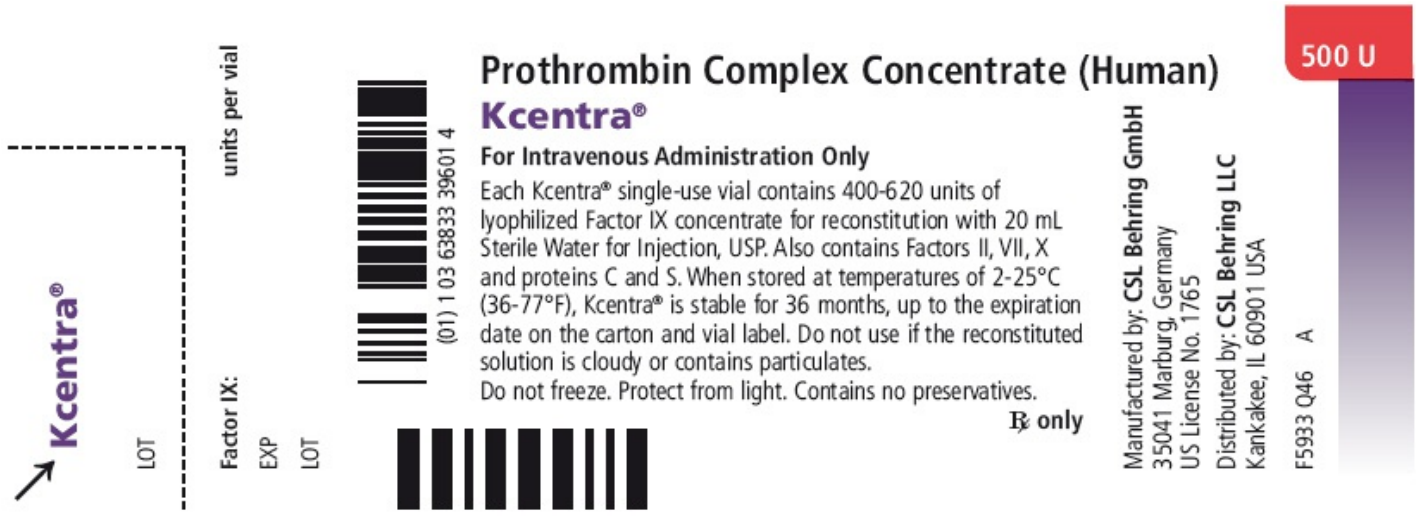
PRINCIPAL DISPLAY PANEL - 500 U Vial Label

500 U

Prothrombin Complex Concentrate (Human)
Kcentra®
For Intravenous Administration Only

Each Kcentra® single-use vial contains 400-620 units of lyophilized Factor IX concentrate for reconstitution with 20 mL Sterile Water for Injection, USP. Also contains Factors II, VII, X and proteins C and S. When stored at temperatures of 2-25°C (36-77°F), Kcentra® is stable for 36 months, up to the expiration date on the carton and vial label. Do not use if the reconstituted solution is cloudy or contains particulates.
Do not freeze. Protect from light. Contains no preservatives.

Rx only



PRINCIPAL DISPLAY PANEL - 500 U Kit Carton

NDC 63833-386-02

500 U Range

Prothrombin Complex Concentrate (Human)
Kcentra®

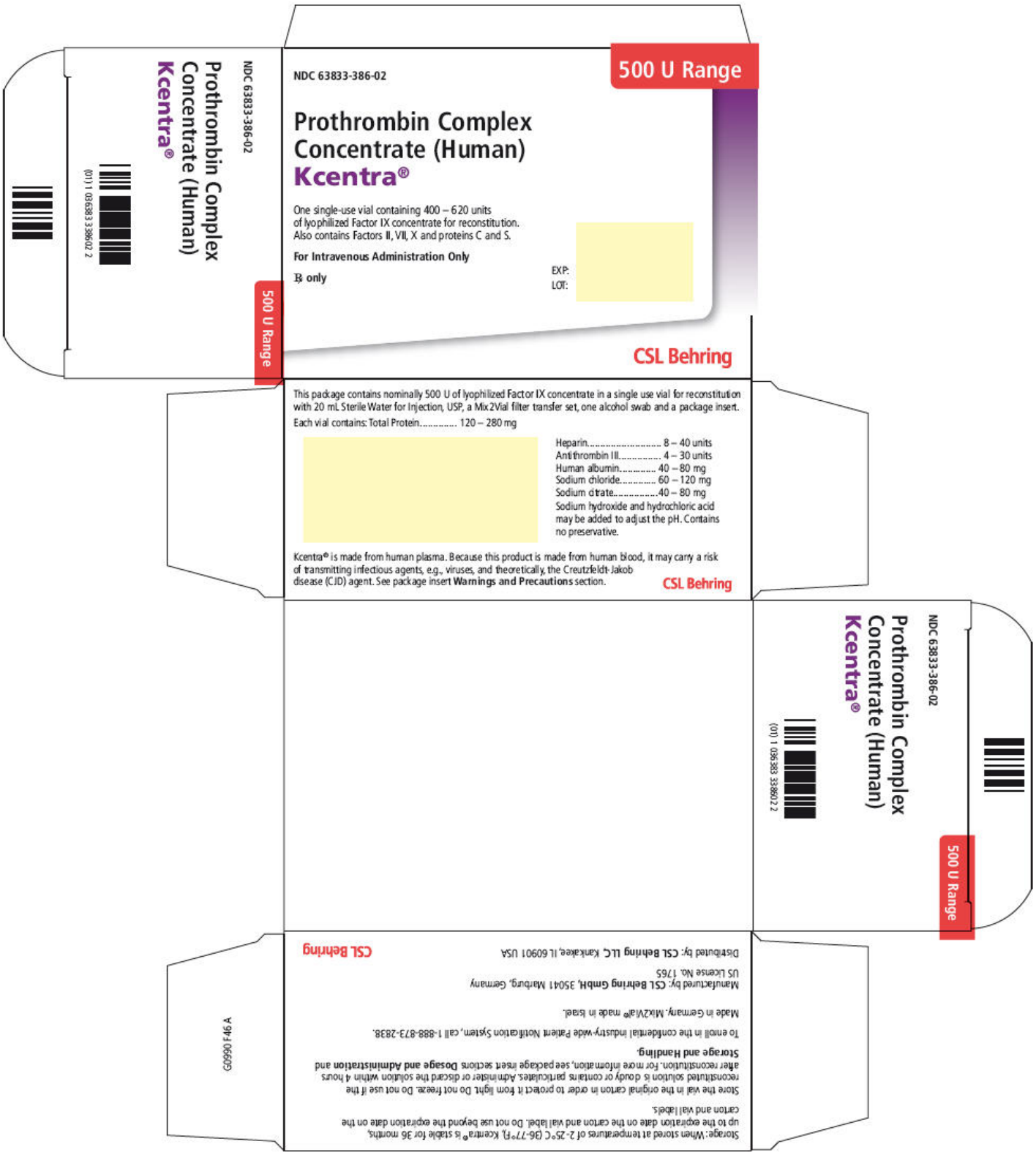
One single-use vial containing 400 – 620 units
of lyophilized Factor IX concentrate for reconstitution.
Also contains Factors II, VII, X and proteins C and S.

For Intravenous Administration Only

Rx only

EXP:
LOT:

CSL Behring



PRINCIPAL DISPLAY PANEL - 1000 U Vial Label

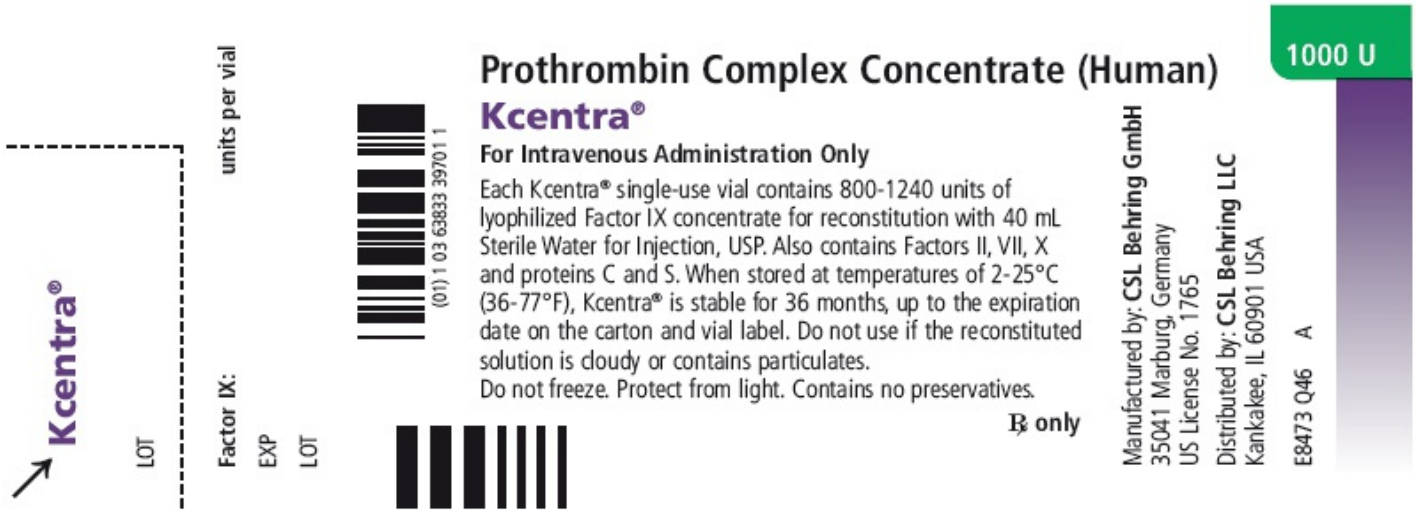
1000 U

Prothrombin Complex Concentrate (Human)
Kcentra®
For Intravenous Administration Only

Each Kcentra® single-use vial contains 800-1240 units of lyophilized Factor IX concentrate for reconstitution with 40 mL

Sterile Water for Injection, USP. Also contains Factors II, VII, X and proteins C and S. When stored at temperatures of 2-25°C (36-77°F), Kcentra® is stable for 36 months, up to the expiration date on the carton and vial label. Do not use if the reconstituted solution is cloudy or contains particulates.
Do not freeze. Protect from light. Contains no preservatives.

Rx only



PRINCIPAL DISPLAY PANEL - 1000 U Kit Carton

NDC 63833-387-02

1000 U Range

Prothrombin Complex Concentrate (Human) Kcentra®

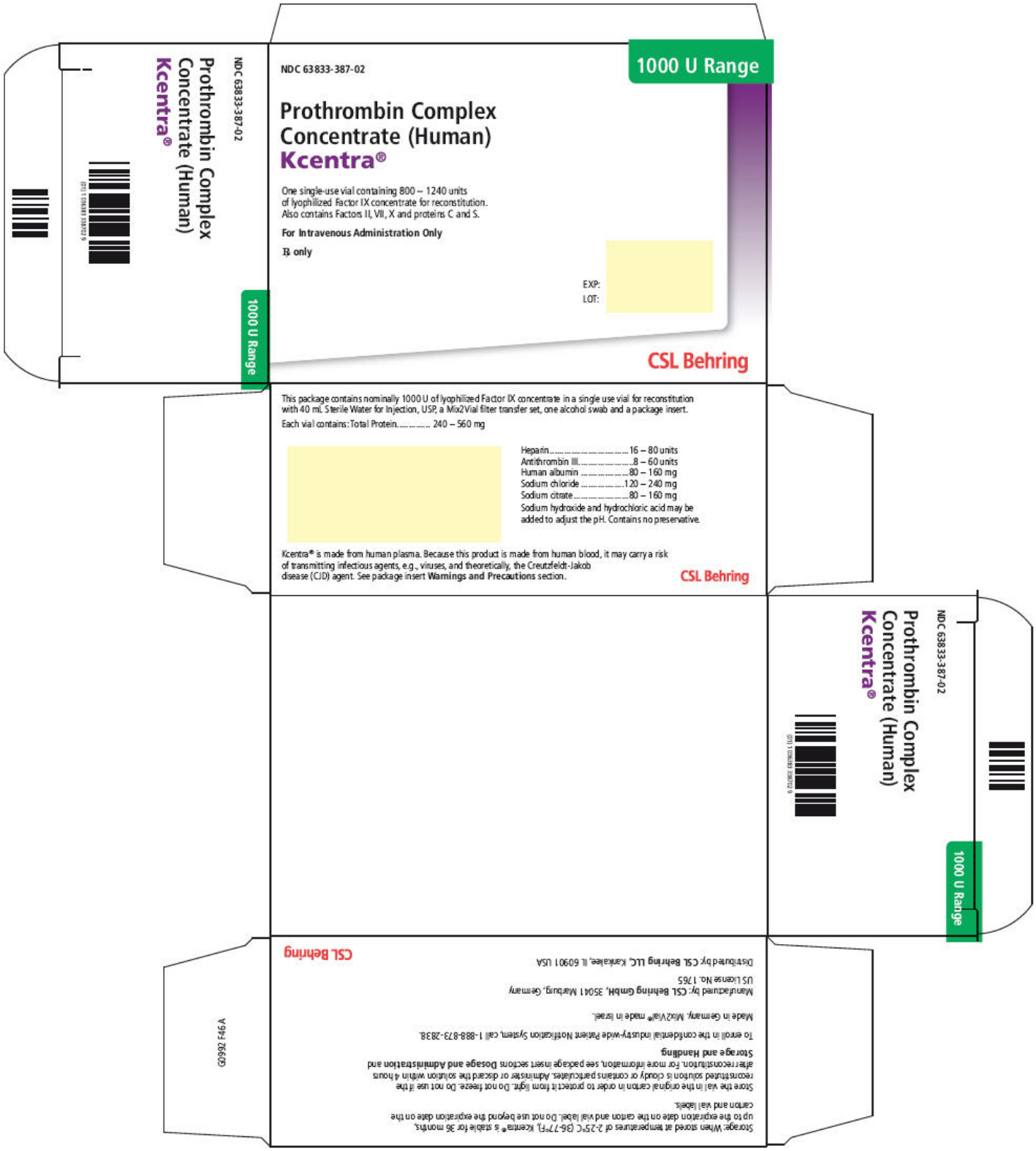
One single-use vial containing 800 – 1240 units of lyophilized Factor IX concentrate for reconstitution. Also contains Factors II, VII, X and proteins C and S.

For Intravenous Administration Only

Rx only

EXP:
LOT:

CSL Behring



KCENTRA

prothrombin, coagulation factor vii human, coagulation factor ix human, coagulation factor x human, protein c, protein s human, and water kit

Product Information			
Product Type	PLASMA DERIVATIVE	**Item Code (Source)**	NDC:63833-386

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63833-386-02	1 in 1 CARTON		

Quantity of Parts		
Part #	Package Quantity	Total Product Quantity
Part 1	1 VIAL, SINGLE-USE	20 mL
Part 2	1 VIAL, SINGLE-USE	20 mL

Part 1 of 2

KCENTRA

prothrombin, coagulation factor vii human, coagulation factor ix human, coagulation factor x human, protein c, and protein s human injection, powder, lyophilized, for solution

Product Information	
Item Code (Source)	NDC:63833-396
Route of Administration	INTRAVENOUS

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
PROTHROMBIN (UNII: 8FB1K07F16) (PROTHROMBIN - UNII:8FB1K07F16)	PROTHROMBIN	590 U in 20 mL
COAGULATION FACTOR VII HUMAN (UNII: 4156XVB4QD) (COAGULATION FACTOR VII HUMAN - UNII:4156XVB4QD)	COAGULATION FACTOR VII HUMAN	350 U in 20 mL
COAGULATION FACTOR IX HUMAN (UNII: 6U90Y1795T) (COAGULATION FACTOR IX HUMAN - UNII:6U90Y1795T)	COAGULATION FACTOR IX HUMAN	510 U in 20 mL
COAGULATION FACTOR X HUMAN (UNII: 0P94UQE6SY) (COAGULATION FACTOR X HUMAN - UNII:0P94UQE6SY)	COAGULATION FACTOR X HUMAN	760 U in 20 mL
Protein C (UNII: 3Z6S89TXPW) (Protein C - UNII:3Z6S89TXPW)	Protein C	620 U in 20 mL
Protein S Human (UNII: 90J3F6N5FN) (Protein S Human - UNII:90J3F6N5FN)	Protein S Human	460 U in 20 mL

Inactive Ingredients	
Ingredient Name	Strength
Heparin (UNII: T2410KM04A)	24 U in 20 mL
Antithrombin III Human (UNII: T0LTO7L82X)	17 U in 20 mL
Albumin Human (UNII: ZIF514RVZR)	60 U in 20 mL
Sodium chloride (UNII: 451W47IQ8X)	90 U in 20 mL
Sodium citrate, unspecified form (UNII: 1Q73Q2JULR)	60 U in 20 mL
Hydrochloric acid (UNII: QTT17582CB)	
Sodium hydroxide (UNII: 55X04QC32I)	

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63833-396-01	20 mL in 1 VIAL, SINGLE-USE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125421	04/29/2013	

Part 2 of 2

STERILE WATER

water injection, solution

Product Information	
Item Code (Source)	NDC:63833-761
Route of Administration	INTRAVENOUS

Inactive Ingredients	
Ingredient Name	Strength
Water (UNII: 059QF0KO0R)	

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63833-761-20	20 mL in 1 VIAL, SINGLE-USE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125421	04/29/2013	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125421	04/29/2013	

KCENTRA

prothrombin, coagulation factor vii human, coagulation factor ix human, coagulation factor x human, protein c, protein s human, and water kit

Product Information			
Product Type	PLASMA DERIVATIVE	**Item Code (Source)**	NDC:63833-387

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:63833-387-02	1 in 1 CARTON		

Quantity of Parts		
Part #	**Package Quantity**	**Total Product Quantity**
Part 1	1 VIAL, SINGLE-USE	40 mL
Part 2	1 VIAL, SINGLE-USE	40 mL

Part 1 of 2

KCENTRA

prothrombin, coagulation factor vii human, coagulation factor ix human, coagulation factor x human, protein c, and protein s human injection, powder, lyophilized, for solution

Product Information	
Item Code (Source)	NDC:63833-397
Route of Administration	INTRAVENOUS

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
PROTHROMBIN (UNII: 8FB1K07F16) (PROTHROMBIN - UNII:8FB1K07F16)	PROTHROMBIN	1180 U in 40 mL
COAGULATION FACTOR VII HUMAN (UNII: 4156XVB4QD) (COAGULATION FACTOR VII HUMAN - UNII:4156XVB4QD)	COAGULATION FACTOR VII HUMAN	700 U in 40 mL
COAGULATION FACTOR IX HUMAN (UNII: 6U90Y1795T) (COAGULATION FACTOR IX HUMAN - UNII:6U90Y1795T)	COAGULATION FACTOR IX HUMAN	1020 U in 40 mL
COAGULATION FACTOR X HUMAN (UNII: 0P94UQE6SY) (COAGULATION FACTOR X HUMAN - UNII:0P94UQE6SY)	COAGULATION FACTOR X HUMAN	1520 U in 40 mL
Protein C (UNII: 3Z6S89TXPW) (Protein C - UNII:3Z6S89TXPW)	Protein C	1240 U in 40 mL
Protein S Human (UNII: 90J3F6N5FN) (Protein S Human - UNII:90J3F6N5FN)	Protein S Human	920 U in 40 mL

Inactive Ingredients

Ingredient Name	Strength
Heparin (UNII: T2410KM04A)	48 U in 40 mL
Antithrombin III Human (UNII: T0LTO7L82X)	34 U in 40 mL
ALBUMIN HUMAN (UNII: ZIF514RVZR)	120 mg in 40 mL
Sodium chloride (UNII: 451W47IQ8X)	180 mg in 40 mL
Sodium citrate, unspecified form (UNII: 1Q73Q2JULR)	120 mg in 40 mL
Hydrochloric acid (UNII: QTT17582CB)	
Sodium hydroxide (UNII: 55X04QC32I)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63833-397-01	40 mL in 1 VIAL, SINGLE-USE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125421	12/13/2013	

Part 2 of 2

STERILE WATER

water injection, solution

Product Information

Item Code (Source)	NDC:63833-761
Route of Administration	INTRAVENOUS

Inactive Ingredients

Ingredient Name	Strength
Water (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63833-761-40	40 mL in 1 VIAL, SINGLE-USE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125421	04/29/2013	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125421	12/13/2013	

Labeler - CSL Behring GmbH (326530474)

Registrant - CSL Behring LLC (058268293)

Establishment

Name	Address	ID/FEI	Business Operations
CSL Behring GmbH		326530474	MANUFACTURE

Revised: 2/2017 CSL Behring GmbH