CSL Behring

Biotherapies for Life®

Kcentra Formulary Kit

The first and only 4F-PCC for urgent warfarin reversal

Kcentra®

Prothrombin Complex Concentrate (Human)

Please see full prescribing information for Kcentra, including boxed warning, on page 42.

Important Safety Information

Kcentra 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 and its variant (vCJD), cannot be completely eliminated.

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List of Abbreviations

3F-PCC	three-factor prothrombin complex concentrate
4F-PCC	four-factor prothrombin complex concentrate
ACCP	American College of Chest Physicians
AE	adverse event
AR	adverse reaction
B19V	human parvovirus B19
BVDV	bovine viral diarrhea virus
CHF	congestive heart failure
CI	confidence interval
CJD	Creutzfeldt-Jakob disease
CMS	Centers for Medicare and Medicaid Services
CPV	canine parvovirus
DIC	disseminated intravascular coagulation
DVT	deep vein thrombosis
EAB	Endpoint Adjudication Board
FDA	Food and Drug Administration
FFP	fresh frozen plasma
GI	gastrointestinal
HAV	hepatitis A virus
HBV	hepatitis B virus
HCPCS	Healthcare Common Procedure Coding System
HCV	hepatitis C virus
HIT	heparin-induced thrombocytopenia
HIV	human immunodeficiency virus
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
ICH	intracranial hemorrhage
INR	international normalized ratio
ITT-E	intention-to-treat efficacy
ITT-S	intention-to-treat safety
IU	international unit
IV	intravenous
IVC	inferior vena cava
IVR	in vivo recovery
MI	myocardial infarction
MS-DRG	Medicare Severity-Diagnosis Related Groups
NAT	nucleic acid testing
n.d.	not determined
NTAP	new technology add-on payment
OCR	optical character recognition
PCC	prothrombin complex concentrate
PK	pharmacokinetics
PRV	pseudorabies virus
RCT	randomized controlled trial
rFVIIa	recombinant activated Factor VII
SAB	Safety Adjudication Board
SD	standard deviation
$t_{½}$	terminal half-life
TACO	transfusion-associated circulatory overload
TE	thromboembolic
TRALI	transfusion-related acute lung injury
VKA	vitamin K antagonist
WNV	West Nile virus

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1 | Executive Summary

1.1 Product Description

Kcentra, Prothrombin Complex Concentrate (Human), is a purified, heat-treated, nanofiltered, lyophilized, non-activated plasma protein concentrate made from pooled human plasma collected from US donors. It contains blood coagulation Factors II, VII, IX, and X, as well as antithrombotic Proteins C and S. Kcentra is 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 invasive procedure.

Kcentra provides several key advantages compared with plasma[1,2]:

- Effective hemostasis and earlier INR reduction
- Requires approximately 85% less volume than plasma
- Mean infusion time 7x faster
- Safety profile comparable to plasma
- No thawing or ABO typing required before administration
- Room temperature storage

Dosing of Kcentra is determined using the patient's baseline international normalized ratio (INR) and body weight. Vitamin K should be administered concurrently, through a separate infusion line, to patients receiving Kcentra to maintain factor levels once the effects of Kcentra have diminished.

1.2 Challenges Associated With Warfarin

Warfarin is commonly used for the long-term prevention and treatment of a variety of thromboembolic (TE) disorders in patients with atrial fibrillation, prosthetic heart valves, or venous thromboembolism.[3] VKAs inhibit the synthesis of functional vitamin K–dependent coagulation factors (II, VII, IX, and X), thereby reducing the risk of TE events; they also reduce vitamin K–dependent antithrombotic Proteins C and S.[3] Although warfarin is a highly effective antithrombotic agent, it has some limitations. Dose adjustment and close monitoring are necessary based on individual patients' characteristics. Despite regular monitoring, however, bleeding is the primary complication in these patients and can contribute significantly to patient mortality.[4,5]

Immediate reversal of anticoagulation is desirable for the management of VKA-treated patients experiencing acute major bleeding, particularly if the bleeding is life-threatening, or if the patient requires urgent surgery or an invasive procedure.[6,7]

1.3 Current Alternatives to Kcentra

Prior to approval of Kcentra, the only US Food and Drug Administration (FDA)–approved treatment options available in the United States for VKA reversal were plasma and vitamin K. Other coagulation factor products—3-factor PCCs, a 4-factor product with activated Factor VII, and a recombinant activated Factor VII (rFVIIa)—are sometimes used in clinical practice for VKA reversal, which is outside their approved indications.[8-13] The safety, efficacy, and appropriate dosing of these products, however, have not been established in controlled clinical trials in this setting.[14-17]

1.4 Limitations of Plasma Use

The use of plasma for warfarin reversal has a number of limitations:

- **Volume:** The low concentration of coagulation factors in plasma means that a large volume may be required to deliver enough of the factors required for effective VKA reversal. Large volumes require extended infusion time and may cause fluid overload.[18-20] Transfusion-associated circulatory overload (TACO) is the second most common cause of transfusion-related death[21-23]
- **Administration Time:** Time to initiation of VKA reversal has been shown to be the most important determinant for normalization of INR levels at 24 hours.[24] When administering plasma, the necessity of thawing and ABO typing along with lengthy infusion time can result in delayed coagulation factor replacement[1,2,25-28]
- **Safety:** Plasma can contain extraneous proteins and antibodies that cause an increased (though small) risk of allergic/transfusion reactions, transfusion-related acute lung injury (TRALI), and virus transmission[19,20,29]

1.5 Benefits of Kcentra

Kcentra, a non-activated 4F-PCC, provides a faster alternative to plasma that can be administered without thawing or ABO typing.[1] This was shown in the randomized, controlled trials (RCT) comparing the efficacy and safety of a 4F-PCC (with concurrent vitamin K) to plasma (with concurrent vitamin K) in subjects with acute major bleeding or in need of urgent surgery or invasive procedure while receiving VKA therapy. In these trials, Kcentra demonstrated non-inferior or superior hemostatic efficacy and superior early and sustained INR reduction. The relationship between INR values and clinical hemostasis in patients has not been established. Additionally, Kcentra offers a substantial reduction in volume and time required to normalize INR versus plasma (**Figure 1**).

Figure 1: Concentration Comparison Between Kcentra and Plasma[30]

1.6 Pivotal Trial Results

Efficacy

In the phase 3 RCT in acute major bleeding, Kcentra demonstrated non-inferiority (primary study objective) compared with plasma in achieving hemostatic efficacy, as well as superiority to plasma in achieving early INR reduction (**Table 1**). Kcentra maintained lower INR levels compared to plasma until 24 hours after the end of infusion.[1]

Table 1: Primary Efficacy Endpoints of Acute Major Bleeding Trial

Endpoint	No. (%) of Subjects [95% CI]		Difference Kcentra – Plasma (%) [95% CI]*
	Kcentra (N=98)	Plasma (N=104)	
Effective hemostasis	71 (72.4) [62.3 to 82.6]	68 (65.4) [54.9 to 75.8]	(7.1) [–5.8 to 19.9]
Decrease of INR to ≤1.3 at 30 minutes	61 (62.2) [52.6 to 71.8]	10 (9.6) [3.9 to 15.3]	(52.6) [39.4 to 65.9]

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

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1 | Executive Summary (cont'd)

In the phase 3 RCT of VKA-treated subjects with the need for an urgent surgery/invasive procedure, Kcentra demonstrated superiority compared with plasma in achieving hemostatic efficacy. Kcentra also demonstrated superiority to plasma in achieving early INR reduction (**Table 2**). As in the acute major bleeding trial, Kcentra maintained lower INR levels compared to plasma until 24 hours after the end of infusion.[2]

Table 2: Primary Efficacy Endpoints of Urgent Surgery/Invasive Procedure Trial

Endpoint	No. (%) of Subjects [95% CI]		Difference Kcentra – Plasma (%) [95% CI]*
	Kcentra (N=98)	Plasma (N=104)	
Effective hemostasis	78 (89.7) [83.3 to 96.1]	61 (75.3) [65.9 to 84.7]	(14.3) [2.8 to 25.8]
Decrease of INR to ≤1.3 at 30 minutes	48 (55.2) [44.7 to 65.6]	8 (9.9) [3.4 to 16.4]	(45.3) [31.9 to 56.4]

*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.

In both studies, the mean volume of infusion was approximately 85% less with Kcentra, and the mean infusion time was approximately 7 times faster (**Table 3**).[1,2]

These results are further supported by assessments of coagulation factor levels showing that mean levels of Factors II, VII, IX, and X and antithrombotic Proteins C and S increased to >50% of normal 30 minutes after the start of Kcentra infusion. In contrast, plasma infusion reached levels achieved with Kcentra several hours after the start of infusion.[1,2]

Table 3: Mean Volume and Duration of Kcentra Infusion vs Plasma

Treatment Group	Acute Major Bleeding	Urgent Surgery/Invasive Procedure
	Mean Volume of Infusion (SD)	
Kcentra	105 mL (±37)	90 mL (±32)
Plasma	865 mL (±269)	819 mL (±231)
Treatment Group	**Acute Major Bleeding**	**Urgent Surgery/Invasive Procedure**
	Mean Duration of Infusion (SD)	
Kcentra	24 min (±32)	21 min (±14)
Plasma	169 min (±143)	141 min (±113)

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Safety

Based on the combined results of the two phase 3 RCTs, Kcentra demonstrated a safety profile similar to that of plasma and consistent with the types of events observed during more than 15 years of postmarketing experience outside the United States in a population of subjects requiring urgent VKA reversal.[31]

Patients receiving VKA therapy are predisposed to TE events, and both fatal and non-fatal arterial and venous TE complications have been reported with Kcentra in clinical trials and postmarketing surveillance. However, in the RCTs in acute major bleeding and urgent surgery/invasive procedures, administration of Kcentra did not significantly increase the risk of TE events compared with plasma. A total of 13 subjects (6.8%) in the Kcentra group and 14 subjects (7.1%) in the plasma group experienced possible TE events. In the Kcentra group, the incidence of TE events was higher in subjects with a prior history of a TE event than in those without such history. Neither Kcentra nor plasma was evaluated in subjects who had a TE event, myocardial infarction (MI), disseminated intravascular coagulation (DIC), cerebral vascular accident, transient ischemic attack, unstable angina pectoris, or severe peripheral vascular disease within the 3 months before study enrollment. See the boxed warning in the full prescribing information for Kcentra in Appendix A.

The fact that Kcentra can be administered in less volume than plasma may also have important safety implications, considering that many of the patients who require VKA reversal have underlying cardiac conditions that can be worsened by volume overload.[32,33] In the two phase 3 RCTs, fluid overload events occurred in 9 subjects (4.7%, all non-related by investigator assessment) in the Kcentra group and 25 subjects (12.7%, 13 events related by investigator assessment) in the plasma group.

The 95% confidence interval (CI) for the between-group difference in fluid overload event incidence ranged from –14.1% to –2.0%. This body of evidence supports the use of Kcentra as a safe and effective alternative to plasma for subjects who have been treated with VKAs and require urgent replacement of their vitamin K–dependent coagulation factors to treat acute major bleeding or because of the need for an urgent surgery/invasive procedure.

1.7 Postmarketing Data

Since the first official approval of Kcentra (as Beriplex® P/N) in Germany in 1996, marketing authorization for the product has been granted in more than 25 countries. With an overall reporting rate of only 1 TE event for every 31,000 estimated single standard doses of Kcentra, postmarketing surveillance over 15 years supports the favorable safety profile of Kcentra.[31]

1.8 Reimbursement Information

See **Table 4** below for Medicare coding information.*

Table 4: Summary of Medicare Coding for Kcentra†

Code Type	Procedure Code	HCPCS Code	Revenue Code	Diagnosis Code(s)
Hospital Inpatient Setting	ICD-10-CM Procedure Code 30283B1‡	None	025X	Appropriate ICD-10-CM Diagnosis Code(s)
Hospital Outpatient Setting	Appropriate CPT code for Kcentra admin procedure	C9132 (Kcentra, per IU)	0636 (with C9132) + revenue code for admin CPT	Appropriate ICD-10-CM Diagnosis Code(s)

*This resource provides information from a complex and evolving medical coding system. The treating physician is solely responsible for diagnosis coding and determination of the appropriate ICD-10-CM codes that describe the patient's condition and are supported by the medical record. All codes listed are for informational purposes and are not an exhaustive list. The CPT, HCPCS, and ICD-10-CM codes provided are based on AMA or CMS guidelines. The billing party is solely responsible for coding of services (eg, CPT Coding). Because government and other third-party payor coding requirements change periodically, please verify current coding requirements directly with the payor being billed.

†Include additional billing codes as appropriate.

‡Infusion of 4F-PCC.

4F-PCC = four-factor prothrombin complex concentrate; CPT = Current Procedural Terminology; HCPCS = Healthcare Common Procedure Coding System; ICD-10-CM = International Classification of Diseases, Tenth Revision, Clinical Modification; IU = international unit.

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Kcentra®
Prothrombin Complex Concentrate (Human)

2 | Product Information and Disease Description

2.1 Product Summary

Kcentra is the first and only FDA-approved non-activated 4F-PCC indicated for urgent warfarin reversal in adult patients with acute major bleeding or the need for urgent surgery or invasive procedure.

In the treatment of patients with acute major bleeding or in need of urgent surgery or invasive procedure who require urgent VKA reversal, Kcentra provides a safe and effective alternative to plasma. Kcentra demonstrated hemostatic efficacy comparable to plasma (acute major bleeding) or superior to plasma (urgent surgery), with superior early and sustained INR reduction in both trials.[1,2] The relationship between INR values and clinical hemostasis in patients has not been established.

Kcentra replaces the deficient coagulation factors with significantly less volume than plasma, thus allowing clinicians more flexibility to control volume resuscitation and reducing patient exposure to unnecessary risk of virus transmission and other plasma-related complications. Kcentra is not associated with an increased risk of TE events compared with plasma, although patients receiving VKA therapy are predisposed to TE events, and both fatal and non-fatal arterial and venous thromboembolic complications have been reported with Kcentra in clinical trials and postmarketing surveillance. Kcentra was not evaluated in patients with TE events in the prior 3 months and may not be suitable for this group of patients.[1,2]

Overall, Kcentra provides several key advantages compared to plasma[1,2]:

- **In achieving hemostatic efficacy,** Kcentra was non-inferior to plasma in the acute major bleeding trial and superior to plasma in the urgent surgery/invasive procedure trial
- In both clinical trials Kcentra was **superior to plasma in achieving INR reduction** to ≤1.3 at 30 minutes after the end of infusion in most subjects
- **Administration of Kcentra is ~7x faster than plasma** and replaces all of the vitamin K–dependent coagulation factors depleted by warfarin: II, VII, IX, X as well as the antithrombotic Proteins C and S
- **Mean infusion volume** of Kcentra is **approximately 85% less than plasma**. Volume of Kcentra will never be >250 mL
- **Kcentra can be administered without the need for thawing** or ABO typing
- **Kcentra can be stored at room temperature** (not to exceed 25°C) for up to 36 months from the date of manufacture

2.2 Product Information

2.2.1 Indication and Usage

Kcentra®, Prothrombin Complex Concentrate (Human), is 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.

2.2.2 Dosage and Administration

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. Administer vitamin K concurrently to patients receiving Kcentra to maintain vitamin K–dependent clotting factor levels once the effects of Kcentra have diminished.

Dosing is individualized based on the patient's pre-dose INR and body weight (kg) up to 100 kg. Repeat dosing with Kcentra is not supported by clinical data and is not recommended.

Dosage

The dosing scheme for Kcentra was designed to achieve factor levels that are expected to be hemostatic, but not supraphysiologic. Makris and colleagues demonstrated that as INR increases, vitamin K–dependent coagulation factor levels, including Factor IX (reference factor for dosing calculation), decrease in a nonlinear fashion—a finding confirmed by later research.[34-36] An early study showed that the factor level responses to either a PCC or plasma depended on the pre-treatment INR, and that this information could be useful in predicting the dose needed for repletion. Subsequent work by Preston and colleagues showed reasonable responses using a graduated dosing scheme.[37]

Therefore, 3 INR subgroups (2 to <4, 4 to 6, and >6) were defined in the clinical trial program and dosing of Kcentra was determined by baseline INR values, as shown in **Table 5**. The phase 1 study reported by Ostermann et al demonstrated the in vivo recovery and pharmacokinetics (PK) of coagulation factors after Kcentra administration and provided support for the proposed dosing regimen.[38] The efficacy and safety of this regimen were demonstrated in a phase 2 study reported by Pabinger et al[39] and confirmed in 2 large phase 3 RCTs in adults with acute major bleeding (reported by Sarode et al[1]; see Section 3.3 for details) or who require an urgent surgery/invasive procedure (reported by Goldstein et al[2]; see Section 3.4 for details). For details on dosage and administration, see full prescribing information in Appendix A.

Concurrent administration of vitamin K is important to maintain the INR in the normal range beyond the immediate effects of Kcentra. Because some of the administered coagulation factors have a relatively short half-life (eg, Factor VII), normal physiologic production of vitamin K–dependent coagulation factors is important to maintain factor levels once the effects of Kcentra have diminished.

Administration

Kcentra is available as a single-use vial of either 500 units or 1,000 units that contains non-activated coagulation Factors II, VII, IX, and X and antithrombotic Proteins C and S as a lyophilized concentrate for IV infusion. Kcentra potency (units) is defined by Factor IX content. The range of Factor IX units per vial is 400 to 620 units for the 500-unit vial and 800 to 1,240 units for the 1,000-unit vial. After reconstitution at room temperature with sterile water for injection (20 mL for the 500-unit vial and 40 mL for the 1,000-unit vial), the final concentration of drug product in Factor IX units will be in a range from 20 to 31 units/mL. The actual content of Factor IX, as measured in units of potency, is stated on the vial and carton. The actual units of potency for each coagulation factor (Factors II, VII, IX, and X) and for antithrombotic Proteins C and S are also stated on the carton.

Table 5: Dosing Guideline

Pre-treatment INR	2 to <4	4 to 6	>6
Dose* of Kcentra (units† of Factor IX)/kg body weight	25	35	50
Maximum dose‡ (units of Factor IX)	Not to exceed 2,500	Not to exceed 3,500	Not to exceed 5,000

*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.

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

Please see full prescribing information in Appendix A.

2.2.3 Manufacturing Information

Kcentra is a purified, heat-treated, nanofiltered, lyophilized, non-activated 4F-PCC prepared from human US source plasma (21 CFR 640.60). Except for the US source, Kcentra is identical to the product Beriplex® P/N, which has over 15 years of clinical experience outside the United States. The product name was changed in the United States to avoid potential confusion with another pharmaceutical product. Kcentra contains non-activated 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 and carton. The excipients are human antithrombin III, heparin, human albumin, sodium chloride, and sodium citrate. Kcentra is sterile, pyrogen free, and does not contain preservatives. **Table 6** lists the composition of Kcentra per vial.

All plasma used in the manufacture of Kcentra is obtained from US donors and tested using serologic assays for hepatitis B surface antigen and antibodies to human immunodeficiency virus (HIV)-1/2 and hepatitis C virus (HCV). The plasma is tested with nucleic acid testing (NAT) for HCV, HIV-1, hepatitis A virus (HAV), and hepatitis B virus (HBV) and found to be non-reactive (negative). The plasma is also tested by NAT for human parvovirus B19 (B19V) 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/mL. Only plasma that has passed virus screening is used for production.

Table 6: Composition per Vial of Kcentra*

Ingredient	Kcentra 500 Units	Kcentra 1,000 Units
Total protein	120 to 280 mg	240 to 560 mg
Factor II	380 to 800 units	760 to 1,600 units
Factor VII	200 to 500 units	400 to 1,000 units
Factor IX	400 to 620 units	800 to 1,240 units
Factor X	500 to 1,020 units	1,000 to 2,040 units
Protein C	420 to 820 units	840 to 1,640 units
Protein S	240 to 680 units	480 to 1,360 units
Heparin	8 to 40 units	16 to 80 units
Antithrombin III	4 to 30 units	8 to 60 units
Human albumin	40 to 80 mg	80 to 160 mg
Sodium chloride	60 to 120 mg	120 to 240 mg
Sodium citrate	40 to 80 mg	80 to 160 mg
HCl	Small amounts	Small amounts
NaOH	Small amounts	Small amounts

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

In addition, the Kcentra manufacturing process includes various steps that contribute to the reduction/inactivation of viruses (see **Figure 2**). Kcentra is manufactured from cryo-depleted plasma that is adsorbed via ion exchange chromatography, heat treated in aqueous solution for 10 hours at 60°C, precipitated, adsorbed to calcium phosphate, virus filtered, and lyophilized. These manufacturing steps were independently validated in a series of in vitro experiments for their virus inactivation/reduction capacity for both enveloped and non-enveloped viruses. **Table 7** shows the virus clearance during the manufacturing process for Kcentra expressed as the mean $\log_{10}$ reduction factor.

Figure 2: Kcentra Manufacturing Process

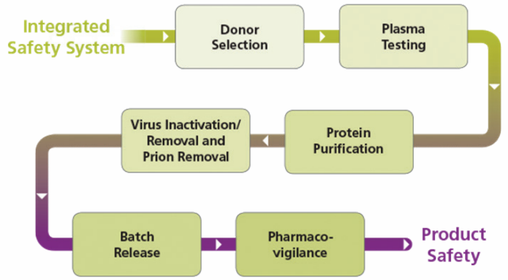

Table 7: Mean Virus Reduction Factors [$\log_{10}$] of Kcentra

Virus Studied	Manufacturing Steps			Overall Virus Reduction [$\log_{10}$]
	Heat Treatment ("Pasteurization")	Ammonium Sulphate Precipitation Followed by Ca Phosphate Adsorption	2x20 nm Virus Filtration	
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

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

HIV Human immunodeficiency virus, a model for HIV-1 and HIV-2
BVDV Bovine viral diarrhea virus, model for HCV
PRV Pseudorabies virus, a model for large enveloped DNA viruses
WNV West Nile virus
HAV Hepatitis A virus
CPV Canine parvovirus, model for B19V
n.d. Not determined

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2.3 Disease Description

2.3.1 Warfarin-related Bleeding

Warfarin is commonly used for the long-term prevention and treatment of a variety of TE disorders, including atrial fibrillation, deep vein thrombosis (DVT), and pulmonary embolism.[3,40]

Warfarin acts by inhibiting the synthesis of fully functional vitamin K–dependent coagulation Factors II, VII, IX, and X, which require carboxylation for their biologic activity. By inhibiting the vitamin K conversion cycle, warfarin induces hepatic production of partially decarboxylated proteins with reduced coagulant activity. Warfarin also results in a functional deficit of the antithrombotic Proteins C and S.[3]

The INR is a standardized means of expressing the prothrombin time ratio and provides a fair indication of hemorrhagic risk in patients taking warfarin. The risk of hemorrhage increases greatly as the INR rises above 5.0, and the risk of symptomatic thromboembolism increases when the INR is <2. The usual goal of VKA therapy is to raise the INR from the normal range (<1.3) to a range of 2 to 3. Out-of-range INR may indicate food/drug interactions or underdosing/overdosing of warfarin, which can expose patients to the risks of thrombosis or hemorrhage, respectively.[7]

Bleeding can occur at any INR (including in patients with normal INRs and not on warfarin), but evidence suggests that in warfarin-treated patients, the risk of bleeding increases as INR increases. The annual rate of warfarin-related major bleeding in clinical practice has been reported to be between 1.7% and 3.4% in the United States.[41,42]

Common sites of major bleeding related to VKAs are the gastrointestinal (GI) tract (40%–60%) and urinary tract (14%), followed by the genital tract (4%), retroperitoneum (3%), and intracranial hemorrhage (ICH, 2%–5%).[5,43] Anticoagulant-associated ICH, which is the most-feared bleeding complication of warfarin, has been reported to occur in 5% to 17% of ICH cases and is associated with a mortality rate of approximately 50%.[44,45] In addition, spontaneous ICH can occur 8 to 10 times more frequently in anticoagulated patients than in non-anticoagulated patients.[46]

The risk of bleeding has been shown to increase with the intensity and duration of anticoagulation and the presence of other risk factors, such as cancer, renal or liver insufficiency, alcohol abuse, or older age.[47] A population-based cohort study conducted over 11 years in Canada among Ontario residents ≥66 years of age showed a 4.6% per person-year risk of hemorrhage among patients >75 years of age compared with 2.9% per person-year among patients ≤75 years of age.[5]

2.3.2 Burden Associated With Warfarin-related Bleeding

Warfarin-related bleeding contributes significantly to patient mortality. In a study of 125,195 patients with atrial fibrillation who started treatment with warfarin during the study period, the risk of hemorrhage was highest during the first 30 days of therapy (11.8%, a rate that was considerably higher than those reported in RCTs of warfarin [1%–3% per person-year]). Additionally, 18.1% of patients admitted with hemorrhage died in the hospital or within 7 days of discharge.[5] In separate studies, among patients who developed warfarin-related major bleeds, the fatality rates were as high as 9.5% and 13.4%.[43,48]

Warfarin-related bleeding also results in significant morbidity related to transfusion and hospitalization.[43] The economic consequences of hemorrhagic complications in warfarin-treated patients may be very large for healthcare payers.

In addition, the aging of the general population in recent years has been accompanied by a dramatic increase in the number of patients receiving long-term warfarin therapy. Some experts expect this rise to continue, as an estimated 5.6 million individuals in the United States are predicted to have atrial fibrillation—and potentially require anticoagulation therapy—by 2050.[49]

2.4 Current US Strategies for Vitamin K Antagonist (VKA) Reversal

Emergency VKA reversal is often necessary in the critical care setting. When patients present with major bleeding due to VKA use or need an urgent surgery or invasive procedure while taking VKAs, rapid reversal of anticoagulation may be necessary, particularly if the bleeding is life-threatening.[6,7]

Therapeutic options to reverse the effects of warfarin include interruption of warfarin treatment and the administration of vitamin K and blood derivatives such as plasma, PCCs, and rFVIIa.[7] However, the FDA has not approved any 3F-PCC, 4-factor product with activated Factor VII, or rFVIIa for urgent warfarin reversal.

2.4.1 Other FDA-approved Options for Warfarin Reversal Besides Kcentra

Vitamin K

Administration of vitamin K enables synthesis of missing Factors II, VII, IX, and X and can be used in patients with non-major bleeds along with dose reduction or temporary discontinuation of warfarin. Significant correction of the INR is not seen until 6 to 8 hours after IV vitamin K use.[50] This change in INR may primarily reflect Factor VII production and may not be a true correction of coagulation defects.[9] As such, vitamin K is not recommended as monotherapy for patients with acute bleeding or the need for urgent surgery or invasive procedure. For these patients, vitamin K is used in combination with plasma or PCCs to achieve more rapid normalization of INR. In emergency situations, IV vitamin K (5–10 mg) is recommended over oral vitamin K because of its more rapid onset of action.[7,50] In one study, 66% of patients who received IV vitamin K had an INR <4.0 at 4 hours, whereas none of the patients receiving an oral vitamin K preparation had satisfactory INR reversal at 4 hours.[51]

Plasma

Plasma contains Factors II, VII, IX, and X, which are depleted by warfarin, as well as fibrinogen, plasma proteins (particularly albumin), electrolytes, physiologic anticoagulants (ie, Protein C, Protein S, antithrombin, tissue factor pathway inhibitor), and added anticoagulants such as citrate. Plasma is either prepared from single units of whole blood (a whole blood-derived unit is approximately 250 mL) or collected by apheresis (usually 500 mL).[52] Fresh frozen plasma (FFP) is widely available in the United States and is frequently used for VKA reversal. However, FFP carries the risks associated with transfusion of any blood product, which include allergy, blood-borne infection, and transfusion-related complications, such as transfusion-associated circulatory overload (TACO) and TRALI.[52] Moreover, plasma contains coagulation factors at normal physiologic levels (approximately 1 IU/mL); as a result, large volumes would be required to achieve meaningful increases in patients' coagulation factor levels.[30]

Data from clinical trials of warfarin reversal (Sarode et al[1] and Goldstein et al[2]) show that the average dose (in Factor IX units) required to replenish Factor IX levels is approximately 2,500 IU, but can be as high as 5,000 IU. To achieve this degree of factor replacement using plasma would require between 2.5 L and 5 L of plasma or 10 to 20 units of FFP. Although the average dose of plasma in the acute major bleeding trial was 865 mL, which translates to approximately 847 IU Factor IX, it is unlikely that most patients would have been able to tolerate the substantially higher fluid volumes that would be required for repletion of the coagulation factors.[30]

2.4.2 Non–FDA-approved Therapies

Other PCCs and recombinant clotting factors are sometimes used in clinical practice outside their approved indications, as an alternative to plasma or in combination with plasma and vitamin K for urgent VKA reversal in patients with acute major bleeding or the need for urgent surgery/invasive procedure.[8-13] These products are primarily approved for the treatment or prevention of bleeding in patients with hemophilia. The safety, efficacy, and most appropriate dosing regimen for these products for VKA reversal in patients with acute major bleeding or in patients needing urgent surgery/invasive procedures have not been established in controlled clinical trials.[14-17]

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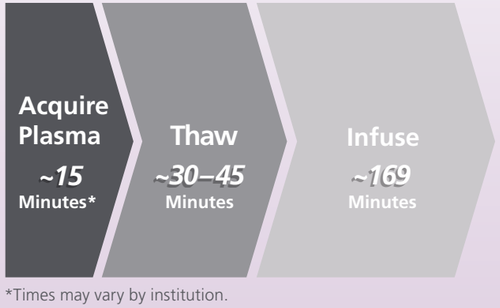
2.5 Limitations of Plasma Use

Plasma is frequently used as a coagulation factor replacement product for the urgent reversal of warfarin therapy in the United States.[47] However, in spite of its widespread use, no prospective clinical trial had been conducted to demonstrate the efficacy of plasma versus other therapeutic options until recently.[25,53] Moreover, administration of plasma has several important limitations regarding storage and administration, safety, volume, and virus transmission.

Storage and Administration

Plasma is prepared from whole blood or apheresis collection and is typically frozen at –18°C after collection for long-term storage.[26] Thawed plasma may be kept at 1°C to 6°C for up to 4 days.[26] The requirement for ABO typing, as well as thawing and bringing the plasma to between 30°C and 37°C, can delay administration of FFP (**Figure 3**).[1,2,25-27] A retrospective study by Goldstein et al[24] demonstrated that time to initiation of VKA reversal was the most important determinant for normalization of INR levels at 24 hours. Plasma must also be administered according to ABO blood group compatibility.[26] Although most US blood banks have ABO-compatible (ie, universal donor type AB) plasma on hand, the supply may be limited. To avoid these delays, some blood banks have thawed AB plasma in preparation for emergency VKA reversal, but this can put a strain on blood banks given that the AB blood type only comprises approximately 4% of the US blood supply and is available in limited quantities.[54] The amount of plasma transfused and time required to complete the transfusion are highly variable and greatly influenced by an individual patient's tolerance of volume.

Figure 3: Estimated Preparation Time for Plasma[1,2,25-27]



*Times may vary by institution.

Safety

Administration of plasma is associated with several safety challenges. Allergic reactions due to extraneous proteins are common with plasma. Although these can be managed, good transfusion practices require termination of additional blood products until a transfusion reaction evaluation can be completed by the blood bank. The most-feared complication associated with plasma is TRALI, a potentially fatal antibody-mediated reaction that was the leading cause of transfusion-related death in the United States as recently as 2011.[21] However, the risk of TRALI has been substantially decreasing in the US blood supply in recent years following the institution of mitigation strategies, some stemming from the knowledge that injury is provoked by anti-human leukocyte antigen antibodies and leukoagglutinins present in the transfused product. Combining these strategies has reduced the incidence of TRALI from approximately 1 in 5,000 to approximately 1 in 12,000.[55-57] There was one reported case of TRALI associated with FFP in 2013; however, the true incidence is not known.[21,56] An ideal reversal agent would be free of antibodies and other proteins that could cause AEs.[56]

Volume

Perhaps the most significant limitation of plasma is the volume required to increase coagulation factor levels and reduce INR. At the volumes typically used (~800 mL), plasma is often insufficient to bring factor levels up to normal.[34] Although there is no universal standard for the volume of plasma to be used for VKA reversal, a volume of 10 to 15 mL/kg is common.[58,59] Such a dose translates into >1 L of fluid (~5 units), depending on the weight of the patient (**Figure 4**).[32] This volume of plasma may cause TACO, which is the second most common cause of transfusion-related death.[21-23] Moreover, patients with compromised cardiac or renal function, which is frequently the case in the patient population receiving VKAs, are at particular risk for developing TACO.[32,33] In addition, the risk of TACO increases when plasma is administered rapidly, as is typical when acute major bleeding is present.[22,33] Despite the difficulties in tolerating high volumes of plasma, the data show that these high volumes are substantially less than those required to adequately normalize plasma factor levels or reverse INR. Studies powered to show a hematologic difference have not been performed.

Figure 4: Concentration Comparison Between Kcentra and Plasma[30]

Virus Transmission

Although improved donor screening and testing of blood products for known pathogens has greatly reduced the risk, transmission of viruses and other pathogens is still a clinically relevant risk associated with plasma transfusion.[19] The advent of NAT has significantly reduced the risk of virus transmission from plasma transfusions by allowing the identification and interception of contaminated donor units before transfusion.[60] However, other than careful donor selection and testing of blood, there are no additional virus reduction steps for plasma products. The current risk of virus transmission for blood components, including plasma, is estimated at approximately 1 in 280,000 for HBV; 1 in 1,149,000 for HCV; and 1 in 1,467,000 for HIV.[60] Together, the logistic challenges and safety concerns associated with plasma highlight the need for an alternative therapy for the urgent reversal of VKAs in patients with acute major bleeding or the need for urgent surgery or invasive procedure.

2.6 Benefits of Kcentra

Kcentra, the first and only non-activated 4F-PCC currently available in the United States, contains the 4 vitamin K–dependent blood-clotting factors (II, VII, IX, and X) necessary to reverse the acquired coagulation factor deficiency induced by warfarin therapy. Kcentra also replenishes the antithrombotic Proteins C and S, which are also depleted by warfarin, and is approximately 25 times more concentrated than plasma (**Table 8**). In the phase 3 RCT in acute major bleeding, Kcentra demonstrated hemostatic efficacy comparable to plasma over 24 hours.[1] In the phase 3 RCT in urgent surgery/invasive procedures, Kcentra demonstrated hemostatic efficacy superior to plasma at the end of the procedure.[2] Although the relationship between INR and clinical hemostasis in patients has not been established, Kcentra provides an effective alternative to plasma transfusion that reduces INR to ≤1.3 within 30 minutes

Table 8: Factor Content by mL[26,61]

Product	Factors				Proteins	
	II	VII	IX	X	C	S
Plasma	0.97	1.05	0.82	0.94	1.07	0.97
Kcentra	31	16	29	41	27	18

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after the end of infusion. As a factor concentrate, Kcentra offers a substantial reduction in volume and time required to normalize INR versus plasma:

- **INR Reduction:** In acute major bleeding trials, 62.2% of subjects who received Kcentra had an INR ≤1.3 at 30 minutes after infusion compared to 9.6% of subjects who received plasma. In urgent surgery trials, 55.2% of subjects who received Kcentra had an INR ≤1.3 at 30 minutes after infusion compared to 9.9% of subjects who received plasma
- **Infusion Time:** In acute major bleeding trials, Kcentra averaged 24 minutes versus 169 minutes for plasma. In urgent surgery trials, Kcentra averaged 21 minutes versus 141 minutes for plasma
- **Volume:** In acute major bleeding trials, Kcentra averaged 105 mL versus 865 mL for plasma. In urgent surgery trials, Kcentra averaged 90 mL versus 819 mL for plasma

In addition, Kcentra requires no refrigeration and the lyophilized product is stable at room temperature for up to 36 months. Kcentra is stored between 2°C and 25°C (36°F–77°F), not to exceed 25°C (77°F). Kcentra also presents a low risk of exposure to blood-borne pathogens and transfusion-associated complications. As with all plasma-derived products, however, the risk of virus transmission cannot be completely eliminated. With no thawing or ABO typing required, and a low infusion volume and short infusion duration, Kcentra has the potential to reduce the time from the clinician's order to successful VKA reversal.[1,2]

Kcentra is identical to the product sold elsewhere in the world as Beriplex P/N, except that Kcentra is made solely with US-sourced plasma. Healthcare professionals outside the United States have more than 15 years of clinical experience with Beriplex P/N.

2.6.1 Clinical Benefits

2.6.1.1 Key Efficacy Findings

Acute Major Bleeding

In the prospective, phase 3b, non-inferiority RCT in subjects with major bleeding, effective hemostasis over 24 hours after the start of infusion (efficacy endpoint) was achieved in 72.4% of subjects receiving Kcentra versus 65.4% of those receiving plasma, and the 95% CI for the between-group difference ranged from –5.8% to 19.9%. Because the lower limit of the 95% CI was –5.8%, which exceeded –10%, the study demonstrated the non-inferiority of Kcentra to plasma. Based on clinical judgment, the non-inferiority margin was set at –10% (ie, if the lower limit of the 95% CI crossed –10%, Kcentra would have been considered inferior and the endpoint would not have been met). Effective hemostasis was determined by a blinded, independent Endpoint Adjudication Board (EAB) (**Table 9**).[1]

Table 9: Primary Rating of Hemostatic Efficacy Stratified by Actual Dose of Kcentra or Plasma (number and % of subjects rated "effective" in acute major bleeding RCT)

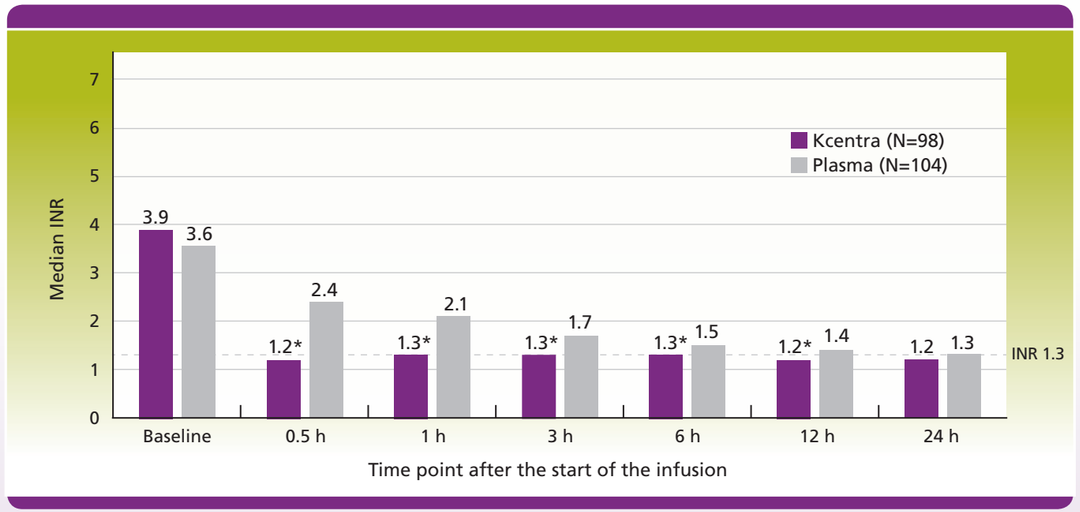
Treatment Group	Low Dose	Mid Dose	High Dose
	N=49 (K)	N=22 (K)	N=26 (K)
	N=55 (P)	N=18 (P)	N=31 (P)
Kcentra	36 (74.5%)	16 (72.7%)	18 (69.2%)
Plasma	38 (69.1%)	11 (61.1%)	19 (61.3%)
Difference*	(4.4%)	(11.6%)	(7.9%)
95% CI K–P	–13.2 to 21.9	–17.4 to 40.6	–17.0 to 32.9

*Kcentra (K) minus plasma (P).
CI = confidence interval; RCT = randomized, controlled trial.

Kcentra also decreased the INR to ≤1.3 at 30 minutes after the end of infusion in 62.2% of subjects compared with 9.6% in plasma-treated subjects, and the 95% CI for the between-group difference ranged from 39.4% to 65.9%. Because the lower limit of the CI was greater than 0, superiority compared with plasma was demonstrated. Median INR values did not reach 1.3 until 24 hours after the start of infusion in subjects administered plasma compared with 30 minutes after the start of infusion in subjects administered Kcentra (**Figure 5**). The relationship between INR and clinical hemostasis in patients has not been established.[1]

Mean levels of coagulation Factors II, VII, IX, and X all markedly increased in the Kcentra group and were >50% within 30 minutes after the start of infusion (**Figure 6**). In contrast, following administration of plasma, mean factor levels were <50% at early time points and only reached levels achieved with Kcentra many hours after the start of infusion. These data demonstrate that the administration of Kcentra results in a rapid increase in vitamin K–dependent coagulation factors without producing sustained supraphysiologic levels.[1]

Figure 5: The Difference in INR Between Kcentra and Plasma in the Acute Major Bleeding Trial Was Statistically Significant for Up to 12 Hours After Start of Infusion[1]



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

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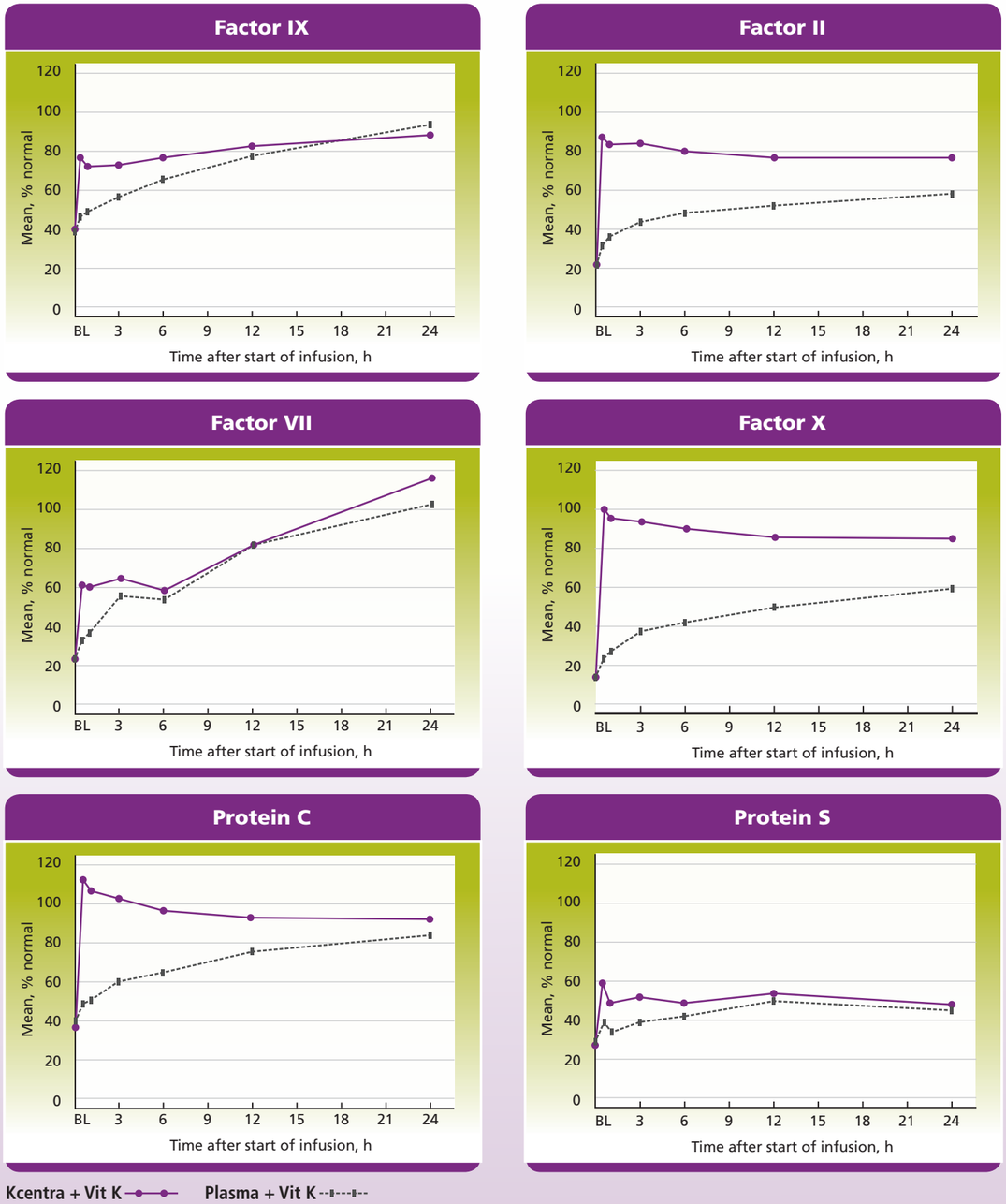
Figure 6: Mean Factor Levels (Factors II, VII, IX, and X and Proteins C and S) Over 24 Hours



The coagulation factors in Kcentra are approximately 25 times more concentrated than those in plasma. The mean volume and duration of the infusion were much less with Kcentra (**Table 10**). To put this into perspective, the mean infusion time for plasma was >2 hours longer than that for Kcentra and to achieve an equivalent level of factor replacement with plasma would require >2.6 L (10 to 12 units).[1]

The mean of 865 mL of plasma administered in the phase 3 trial was insufficient to raise factor levels to the normal range in the majority of subjects at the end of infusion, and yet the volume of plasma administered in the phase 3 trial resulted in fluid overload (**Table 10**). The rate of fluid overload in the Kcentra group was 5.8% as compared to the plasma group at 12.8%.

Urgent Surgery/Invasive Procedures

Effective hemostasis from the start of the infusion until the end of the urgent procedure (primary endpoint) was achieved in 89.7% of subjects receiving Kcentra versus 75.3% of those receiving plasma, and the 95% CI for the between-group difference ranged from 2.8% to 25.8%. Because the lower limit of the 95% CI for the between-group difference was 2.8%, which exceeded –10%, the study demonstrated the non-inferiority of Kcentra to plasma. Because the lower limit of 2.8% also exceeded 0, the study demonstrated the superiority of Kcentra to plasma for hemostatic efficacy (**Table 11**).[2]

Kcentra also decreased the INR to ≤1.3 at 30 minutes after the end of infusion in 55.2% of subjects compared with 9.9% in plasma-treated subjects, and the 95%

Table 10: Kcentra Versus Plasma for Mean Volume, Duration, and Fluid Overload Incidents

	Mean Volume of Infusion (SD)	Mean Duration of Infusion (SD)	Fluid Overload Event Incidence (%, # Related by Assessment)
Kcentra	105 mL (±37)	24 min (±32)	6 (5.8%, 0)
Plasma	865 mL (±269)	169 min (±143)	14 (12.8%, 7)

Table 11: Rating of Hemostatic Efficacy Stratified by Actual Dose of Kcentra or Plasma (number and % of subjects rated "effective" in the urgent surgery/invasive procedure RCT)[2]

	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 to 26.6	–26.5 to 43.5	–19.8 to 53.7

*Kcentra (K) minus plasma (P).
CI = confidence interval; RCT = randomized, controlled trial.

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CI for the between-group difference ranged from 31.9% to 56.4%. Because the lower limit of the CI was greater than 0, superiority compared with plasma was demonstrated. Median INR values did not reach 1.3 until 24 hours after the start of infusion in subjects administered plasma compared with 30 minutes after the start of infusion in subjects administered Kcentra (**Figure 7**).[2] The relationship between INR and clinical hemostasis in patients has not been established.

Mean levels of coagulation Factors II, VII, IX, and X, and antithrombotic Proteins C and S rapidly increased to >50% of normal at 30 minutes after the start of Kcentra infusion. In contrast, increases in mean factor levels were significantly lower at 30 minutes after the start of plasma infusion. For Kcentra, the factor levels remained elevated through 24 hours. For plasma, the levels increased gradually such that similar levels were achieved for most factors at 24 hours (data not shown; coagulation factor profiles are similar to those presented in **Figure 6** for acute major bleeding). These results demonstrate that Kcentra rapidly replaces vitamin K-dependent coagulation factors without producing sustained supraphysiologic levels.[2]

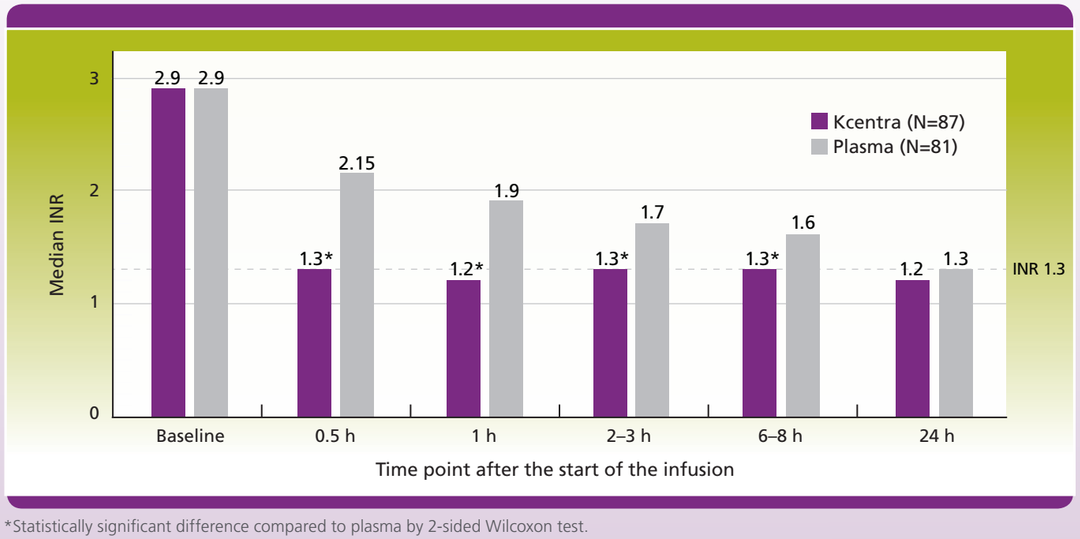
The mean duration of Kcentra infusion was approximately 7 times faster than the mean duration of plasma infusion (21 minutes vs 141 minutes, respectively). Similarly, the mean volume of Kcentra infused was 89% less than the mean volume of plasma infused (90 mL vs 819 mL, respectively).[2]

The median time from start of infusion to start of the urgent surgical procedure was shorter in the Kcentra group (3.6 hours [range, 1.9 to 10.8 hours]) than in the plasma group (8.5 hours [range, 2.8 to 18.7 hours]).[2]

Conclusion

Kcentra provides efficient VKA reversal in subjects with acute major bleeding or with a need for an urgent surgery/invasive procedure. Compared with plasma, Kcentra demonstrated non-inferior hemostatic efficacy in subjects with acute major bleeding and superior hemostatic efficacy in subjects with a need for an urgent surgery/invasive procedure. Kcentra administration resulted in superior early INR reduction and rapid factor replacement in both populations. The concentration of coagulation factors in Kcentra are approximately 25 times higher than in plasma. Kcentra is administered approximately 7 times faster and with approximately 85% less volume than plasma. In the urgent surgery/invasive procedure RCT, patients who received Kcentra had a shorter time to surgery versus those who received plasma (3.6 hours vs 8.5 hours, respectively).[2]

Figure 7: The Difference in INR Between Kcentra and Plasma Was Statistically Significant for Up to 8 Hours After Start of Infusion



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

Table 12: ARs Reported in More Than 5 Subjects (≥2.8%) Following Kcentra or Plasma Administration in RCTs

Adverse Reactions	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.
AR = adverse reaction; RCT = randomized, controlled trial.

2.6.1.2 Key Safety Findings

Based on the results of the 2 phase 3 RCTs, Kcentra demonstrated a safety profile similar to that of plasma and consistent with the product's extensive postmarketing experience.[31]

Adverse reactions (ARs) were defined as AEs that began during or within 72 hours of study product infusion plus AEs considered possibly/probably related or related to study treatment according to the investigator, sponsor, or the blinded Safety Adjudication Board

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(SAB), and with at least a 1.3-fold difference between treatments. The most common ARs (frequency ≥2.8%) observed in subjects receiving Kcentra were headache, nausea/vomiting, hypotension, and anemia (**Table 12**). The most serious ARs were TE events, including stroke, pulmonary embolism, and DVT.

Fluid overload (a composite of events such as fluid overload, cardiac failure congestive, and dyspnea) occurred in 9 subjects (4.7%, all non-related by investigator assessment) in the Kcentra group compared with 25 subjects (12.7%, 13 events related by investigator assessment) in the plasma group. The 95% CI for the between-group difference ranged from –14.1% to –2.0%. Post hoc subgroup analyses were conducted according to whether subjects had a history of congestive heart failure (CHF). In the subgroup of subjects with a history of CHF, the incidence of fluid overload events was 5 (7.1%) in the Kcentra group and 17 (21.3%) in the plasma group. The incidence of fluid overload events among subjects without a history of CHF was 4 (3.3%) in the Kcentra group and 8 (6.8%) in the plasma group.

Possible TE events (composite) occurred in 13 subjects (6.8%) in the Kcentra group and 14 subjects (7.1%) in the plasma group. The incidence of TE events assessed as at least possibly related to treatment by the investigator or, in the case of serious TE events, by the blinded SAB was 9 (4.7%) in the Kcentra group and 7 (3.6%) in the plasma group. The incidence of TE events that began during or within 72 hours of infusion regardless of causality was 9 (4.7%) in the Kcentra group and 8 (4.1%) in the plasma group. Post hoc subgroup analyses were conducted according to whether subjects had a prior history of a TE event. Among subjects who received Kcentra, the incidence of TE events was 11 (8.9%) in the subgroup of subjects with a history of a prior TE event compared with 2 (3.0%) in the subgroup without such history. The incidence of TE events in the plasma group was 8 (5.7%) in the subgroup of subjects with a history of a prior TE event compared with 6 (10.7%) in the subgroup without such history. See the boxed warning in the full prescribing information in Appendix A. Finally, there were no reported cases of TRALI, hypersensitivity or allergic reactions, or confirmed virus transmission in Kcentra-treated subjects.

For both trials combined, a total of 13 subjects (6.8%) died in the Kcentra groups and 13 subjects (6.6%) died in the plasma groups. One death in the Kcentra group in the RCT in acute major bleeding and 1 death in the plasma group in the RCT in urgent surgery/invasive procedures were considered possibly related to study treatment according to the assessment of the blinded, independent SAB. 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 urgent surgery/invasive procedures received the 35 IU/kg and 50 IU/kg doses of Kcentra because more subjects in the trial in acute major bleeding had a baseline INR in the ranges of 4 to 6 and >6.0, an analysis of deaths and factor levels in subjects with major bleeding revealed that subjects who died had median factor levels similar to those in subjects who did not die. Additionally, outliers with supraphysiologic factor levels did not have a mortality rate out of proportion to the overall population.

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, and X; Proteins C and S; antithrombin III; and human albumin). Kcentra is also contraindicated in patients with DIC. Because Kcentra contains heparin, it is contraindicated in patients with heparin-induced thrombocytopenia (HIT). There were no cases of HIT in the phase 3 trials, but the trials were underpowered to detect it. There were also no cases in the pharmacovigilance report.

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

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

Safety results are presented separately for the acute major bleeding trial in Section 3.3 and for the urgent surgery/invasive procedures trial in Section 3.4.

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3 | Supporting Clinical Evidence

Kcentra has over 15 years of clinical experience as Beriplex P/N outside the United States, so the majority of scientific and medical literature regarding the product reflects Beriplex P/N not Kcentra.

In the following section, which reviews the published literature, we refer to Kcentra by the product name used in the actual publications.

3.1 Phase 1: Pharmacokinetic Study in Healthy Volunteers[38]

This phase 1 study was designed to determine the PK of coagulation Factors II, VII, IX, and X and anticoagulation Proteins C and S following a single infusion of Beriplex P/N prothrombin complex concentrate and assess safety in healthy volunteers.

Methods

The study assessed PK parameters and in vivo recovery (IVR) of coagulation factors and anticoagulant proteins for 144 hours after infusion of Beriplex P/N. The PK parameters, including terminal half-life ($t_{1/2}$), area under the concentration-time curve, clearance, mean residence time, and volume of distribution at steady state, were estimated by nonlinear regression. The IVR was calculated as the maximum percent increase in plasma concentration within 3 hours of infusion divided by dose in IU/kg. Subjects were assessed for adverse events for 7 to 10 days and had follow-up for viral markers out to 12 weeks.

Treatment

Fifteen healthy volunteers received a single 50-IU/kg infusion of Beriplex P/N.

Pharmacokinetic Results

The mean infusion rate of Beriplex P/N was 7.9 mL/min, equivalent to 196.4 IU/min. Administration of Beriplex P/N produced a rapid and sustained rise in plasma concentrations of all coagulation factors. Maximal levels were attained by the earliest postinfusion sampling point at 5 minutes. The median increase in plasma concentration at 5 minutes compared with the preinfusion level was between 59% and 159% for factors and proteins depleted by VKAs (**Table 13**). Median terminal $t_{1/2}$ was 16.7 hours for Factor IX, 59.7 hours for Factor II, 4.2 hours for Factor VII, and 30.7 hours for Factor X. Median IVR was 1.57%/IU/kg for Factor IX and >2%/IU/kg for the other coagulation factors.

Table 13: Median Increase in Plasma Concentration

Components	Median Increase 5 Minutes Postinfusion*
Factors	
II	122%
VII	62%
IX	73%
X	158%
Proteins	
C	149%
S	59%

*5 minutes postinfusion of Beriplex.

Safety Results

With the exception of 1 female subject who developed a mild common cold 7 days after infusion, which was judged to be unrelated to study product, no AEs of any kind were encountered during the study. No clinical evidence of thrombosis was observed in any subject. In contrast, no postinfusion changes were evident in plasma D-dimer concentration. During periodic postinfusion viral assessments through the 12-week follow-up period, no positive result was obtained in any subject who had a negative baseline result (at baseline, 6 subjects were positive in anti-HAV assays and 10 were positive in anti-B19V assays).

Conclusions

Infusion of Beriplex P/N produced rapid and sustained increases in coagulation factors and anticoagulant proteins with no clinical evidence of thrombosis or viral transmission.

3.2 Phase 2 (Study 3001): Registration Study in Europe[39]

This was a phase 2, prospective, single-arm, nonrandomized, open-label study designed to determine the efficacy and safety of Beriplex P/N in patients on oral anticoagulation with an INR exceeding 2 who required either emergency surgical intervention or urgent invasive diagnostic intervention or INR normalization after acute bleeding.

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Efficacy Endpoints

The primary study endpoint was normalization of INR (≤1.3) at 30 minutes after the end of Beriplex P/N infusion. Secondary endpoints were clinical hemostatic efficacy in stopping acute bleeding or preventing major bleeding during interventional procedures and IVR of Factors II, VII, IX, and X and Proteins C and S.

Treatment

A total of 43 adults were treated with Beriplex P/N for acute bleeding (17 patients) or for emergency surgical intervention (26 patients). Prior to Beriplex P/N infusion, most patients received vitamin K at the standard dosage in each center. One 25-, 35-, or 50-IU/kg body weight dose of Kcentra was administered to patients with a baseline INR of 2 to <4, 4 to 6, or >6, respectively. This study supported the dosing regimen that was subsequently confirmed in the larger phase 3 RCT (Study 3002).

Efficacy Results

The INR rapidly decreased to the target level (≤1.3) in 40 of 43 patients (93%) within 30 minutes after the end of infusion; the remaining patients achieved an INR of 1.4. Clinical hemostatic efficacy was classified as very good or satisfactory in 42 patients (98%). Plasma levels of the coagulation Factors II, VII, IX, and X and the antithrombotic Proteins C and S rose rapidly to normal or close to normal levels and remained elevated for at least 48 hours.

Safety Results

Adverse events occurred in 25 patients (58%), including 2 suspected thromboembolic complications. In 6 patients, the AEs were classified as serious, and 3 of these patients died as a result. Only 1 serious AE was considered possibly related to study product; all other serious and nonserious AEs were judged to be unrelated. The single serious AE that was possibly treatment related was a suspected pulmonary embolism resulting in the death of a 70-year-old man who entered the study with acute bleeding resulting from perforation of stomach cancer. The patient was at increased risk for thrombosis because of the presence of metastatic GI cancer. On Day 4, although bleeding was not observed, INR rebound in this patient prompted infusion of 20 IU/kg Beriplex P/N in violation of study protocol. The patient died 2 hours later.

Conclusions

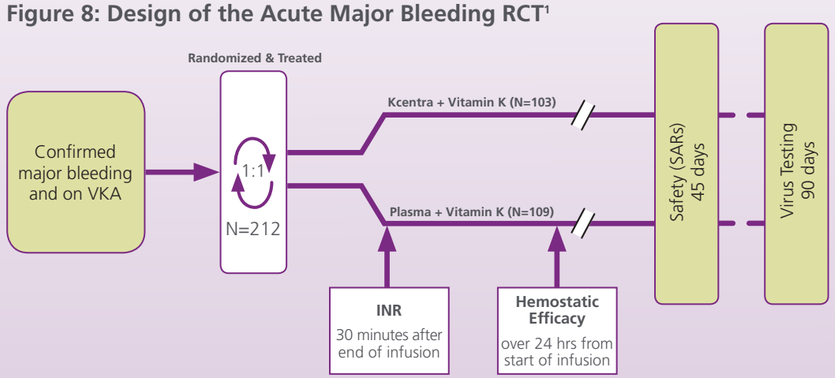
Beriplex P/N treatment normalized INR and increased coagulation factors and antithrombotic Proteins C and S following infusion. Overall, Beriplex P/N serves as an effective rapid factor restoration resource in the emergency anticoagulant reversal setting.

3.3 Phase 3 (Study 3002): Randomized, Controlled Trial of Kcentra vs Plasma in Subjects With Acute Major Bleeding[1]

Study Design

Two hundred twelve subjects who required urgent reversal of VKA therapy due to acute major bleeding were enrolled in the first prospective, phase 3b, open-label, blinded-assessor, non-inferiority RCT of Beriplex P/N (Kcentra) versus plasma at 36 sites across the United States and Europe (**Figure 8**). Subjects ranged in age from 26 years to 96 years. Site or type of bleeding included GI and other nonvisible bleeding, visible bleeding, ICH, and musculoskeletal bleeding.

Figure 8: Design of the Acute Major Bleeding RCT[1]



ITT-S (N=212) = All individuals exposed to treatment.

ITT-E (N=202) = Subset of ITT-S that presented with confirmed major bleeding and an INR >1.3.

INR = international normalized ratio; RCT = randomized, controlled trial; SARs = serious adverse reactions; VKA = vitamin K antagonist.

Inclusion Criteria

- Patients (≥18 years of age) receiving VKA therapy with an elevated INR (≥2.0 within 3 hours before study treatment) and experiencing an acute major bleeding event were eligible
- Acute major bleeding was defined as 1 of the following:
  - Life-threatening or potentially life-threatening (according to the treating physician)
  - Acute bleeding associated with a fall in hemoglobin ≥2 g/dL
  - Bleeding requiring blood product transfusion

Exclusion Criteria

Expected survival of <3 days or expected surgery* in <1 day

- Acute trauma for which reversal of VKAs alone would not be expected to control or resolve the acute bleeding event
- Use of unfractionated or low-molecular-weight heparin <24 hours before enrollment or expected need <24 hours after start of infusion†
- History of thrombotic event, MI, DIC, cerebral vascular accident, transient ischemic attack, unstable angina pectoris, or severe peripheral vascular disease at ≤3 months of enrollment
- Known history of antiphospholipid antibody syndrome
- Suspected/confirmed sepsis at enrollment
- Administration of plasma, plasma fractions, or platelets ≤2 weeks before study (administration of packed red blood cells permitted)
- Large blood vessel rupture (eg, aortic dissection or ruptured aortic aneurysm)
- Preexisting progressive fatal disease with a life expectancy of <2 months
- Known inhibitors to Factors II, VII, IX, or X, hereditary Protein C or S deficiency, or heparin-induced, type II thrombocytopenia
- Treatment with any other investigational medicinal product ≤30 days before study
- Presence or history of hypersensitivity to components of the study medication
- Patients with ICH:
  - Glasgow Coma Scale score <7‡
  - Intracerebral hematoma volume >30 cm^3 (assessed by ABC/2 formula)
  - For subdural hematomas: maximum thickness ≥10 mm, midline shift ≥5 mm
  - For subarachnoid hemorrhage: any evidence of hydrocephalus
  - Infratentorial ICH location
  - Epidural hematomas
  - Intraventricular extension of hemorrhage
  - Modified Rankin Scale score >3 before ICH

*Patients with acute major bleeding requiring minimally invasive procedures (eg, endoscopy, bronchoscopy, central lines) that were indicated for diagnostic or therapeutic reasons were not excluded per protocol, as long as plasma was intended to be given for treatment of major bleeding.

†Exclusion added at time of amendment.

‡Modified from Glasgow Coma Scale score <9 to Glasgow Coma Scale score <7 on request of FDA.

Efficacy Endpoints

The endpoints of the study were:

- Hemostatic efficacy of the intervention, assessed over a period of 24 hours from the start of the infusion
- INR reduction to ≤1.3 at 30 minutes after end of infusion

A successful study outcome required that Kcentra demonstrate non-inferiority relative to plasma for both hemostatic efficacy and decrease in INR.

Key secondary efficacy endpoints included time to INR correction and plasma levels of vitamin K–dependent Factors II, VII, IX, and X and antithrombotic Proteins C and S.

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Table 14: Dose of Study Treatment for Each Baseline INR Level[1]

Baseline INR	Kcentra (IU of Factor IX per kg)*	Plasma (mL per kg)*
2 to <4	25	10
4 to 6	35	12
>6	50	15

*Dose calculation based on 100 kg body weight for patients weighing >100 kg. Maximum dose ≤5,000 IU of Factor IX (4F-PCC) or ≤1,500 mL (plasma). Note: In this study, Kcentra was administered by "nominal dosing" (ie, assuming each vial contained 500 units).
4F-PCC = four-factor prothrombin complex concentrate; INR = international normalized ratio; IU = international unit.

Treatment

Each patient received his or her assigned study treatment dose according to baseline INR and body weight (**Table 14**). Kcentra was administered as a single IV dose at a rate not to exceed 0.12 mL/kg/minute (~3 IU/kg/minute), up to a maximum rate of 8.4 mL/minute (~210 IU/minute). Plasma was administered with a study protocol-recommended IV infusion rate of 1 U per 30-minute interval. All patients were to receive vitamin K by slow IV infusion, dosed according to 2008 American College of Chest Physicians (ACCP) guidelines (ie, 5 mg to 10 mg)[62] or local clinical practice, if different.

Efficacy Results

Two hundred two patients comprised the intention-to-treat efficacy (ITT-E) population (Kcentra, N=98; plasma, N=104), with the majority of patients older than 65 years. Demographics were similar in both groups (**Table 15**).

Table 15: Demographic and Baseline Characteristics, ITT-E Population[1]

	Kcentra (N=98)	Plasma (N=104)
Sex, n (%)		
Female	48 (49.0)	53 (51.0)
Male	50 (51.0)	51 (49.0)
Age in years		
Mean (SD)	69.8 (13.93)	69.8 (12.78)
Range	29 to 96	26 to 92
Age group in years, n (%)		
<65	33 (33.7)	31 (29.8)
≥65–<75	24 (24.5)	29 (27.9)
≥75	41 (41.8)	44 (42.3)
Baseline INR		
Median (range)	3.90* (1.8 to 20.0)	3.60* (1.9 to 38.9)
Type of bleeding, n (%)		
Gastrointestinal/other non-visible	63 (64.3)	64 (61.5)
Visible	16 (16.3)	21 (20.2)
Intracranial hemorrhage	12 (12.2)	12 (11.5)
Musculoskeletal	7 (7.1)	7 (6.7)

*Two-sided *P* value >0.05 (Wilcoxon test) for between-group difference.
INR = international normalized ratio; ITT-E = intention-to-treat efficacy; SD = standard deviation.

To minimize potential investigator bias and increase endpoint objectivity, a hemostatic efficacy scale was developed in discussion with the FDA for adjudication by a blinded EAB. Hemostatic efficacy was rated by the EAB as "Excellent," "Good," or "Poor/none." Effective hemostasis was defined as a rating of "Excellent" or "Good" over a period of 24 hours from the start of the infusion. Noneffective hemostasis was defined as a "Poor" rating or no response. Data provided to the EAB for the hemostasis assessment included hemoglobin, hematocrit, any additional hemostatic treatments, AE data, and clinical outcome over the 24-hour postinfusion period. Objective, predefined criteria for each category of bleeding were used.

The proportion of subjects who achieved effective hemostasis assessed over 24 hours was 71/98 subjects (72.4%) in the Kcentra group and 68/104 subjects (65.4%) in the plasma group. The lower limit of the 95% CI for the between-group difference was –5.8%, which exceeded –10%, thus meeting the efficacy endpoint and demonstrating the non-inferiority of Kcentra compared with plasma (**Table 16**). A post hoc analysis of the primary rating of hemostatic efficacy, stratified by actual dose of Kcentra or plasma administered, is shown in **Table 9**.

Reduction in INR to ≤1.3 at 30 minutes after the end of the infusion was achieved in 61 patients (62.2%) in the Kcentra group compared with 10 subjects (9.6%) in the plasma group. The lower limit of the 95% CI for the between-group difference was 39.4%, which demonstrated that Kcentra was superior to plasma (**Table 17**).

A significantly greater reduction in INR was observed in the Kcentra group compared with the plasma group until 12 hours after the start of infusion. Median INR was above 3.0 prior to the infusion and dropped to a median value of 1.2 at 30 minutes after start of Kcentra infusion. By contrast, median INR was 2.4 at 30 minutes after the start of plasma infusion. The relationship between INR values and clinical hemostasis in patients has not been established.

Consistent with early normalization of INR, the mean plasma levels of Factors II, VII, IX, and X markedly increased to >50% of normal 30 minutes after the start of the Kcentra infusion. In contrast, 30 minutes after the start of plasma infusion, mean coagulation factor levels were significantly lower. These data demonstrate that administration of Kcentra results in a rapid increase in vitamin K–dependent coagulation factors without producing sustained supraphysiologic levels.

The mean infusion time with Kcentra was 7 times faster than plasma (24 minutes vs 169 minutes, respectively). Similarly, the volume of Kcentra administered was 87% less than plasma (105 mL vs 865 mL, respectively).

Table 16: Rating of Hemostatic Efficacy in Subjects With Acute Major Bleeding

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

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

Table 17: Decrease of INR (≤1.3 at 30 minutes after end of infusion)

Endpoint	No. (%) of Subjects [95% CI]		Difference Kcentra – Plasma (%) [95% CI]†
	Kcentra (N=98)	Plasma (N=104)	
Decrease of INR to ≤1.3 at 30 minutes	61 (62.2) [52.6 to 71.8]	10 (9.6) [3.9 to 15.3]	(52.6) [39.4 to 65.9]

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

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Safety

This section reports safety data derived from the approved prescribing information for Kcentra. Some data differ from those reported by the blinded SAB due to additional statistical analyses performed by the FDA in finalizing the product labeling.

Patients being treated with VKA therapy have underlying disease states that predispose them to TE events. There were 9 subjects (8.7%) in the Kcentra group and 6 subjects (5.5%) in the plasma group who experienced possible TE events (**Table 18**).

Post hoc subgroup analyses of the RCT in acute major bleeding were conducted according to whether subjects had a history of a prior TE event. Among subjects who received Kcentra, the incidence of TE events was 11.6% in the subgroup of subjects with a history of a prior TE event compared to 2.9% in the subgroup without such history (**Table 19**). The incidence of TE events in the plasma group was 3.8% in the subgroup of subjects with a history of a prior TE event compared to 10.0% in the subgroup without such history.

There were 6 subjects (5.8%, all non-related by investigator assessment) in the Kcentra group who experienced fluid overload in the plasma-controlled RCT in acute major bleeding and 14 (12.8%, 7 events related by investigator assessment) who had fluid overload in the plasma group (**Table 20**).

Post hoc subgroup analyses of the RCT in acute major bleeding were conducted according to whether subjects had a prior history of CHF. The incidence of fluid overload events was 8.7% in the Kcentra group and 25% in the plasma group in the subgroup of subjects with a history of prior CHF.

Ten subjects (9.7%) died in the Kcentra group (1 additional death occurred on Day 46 just after completion of the study reporting period) and 5 (4.6%) died in the plasma group in the plasma-controlled RCT in acute major bleeding. One death in the Kcentra group in the RCT in acute major bleeding was considered possibly related to study treatment according to an assessment of masked data by an independent SAB. 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. Additionally, outliers with supraphysiologic factor levels did not have a mortality rate out of proportion to the overall population.

Conclusions

Study 3002 is the first prospective, active-controlled RCT to demonstrate that Kcentra is non-inferior to plasma for hemostatic efficacy and superior for INR reduction in subjects with acute major bleeding who require urgent VKA reversal. The relationship between INR values and clinical hemostasis in patients has not been established. Kcentra has a safety profile comparable to plasma. These results demonstrate that Kcentra is a safe and effective alternative to plasma in this patient population.

Table 18: ARs (TE events only) Following Kcentra or Plasma Administration in the Acute Major Bleeding RCT

System Organ Class	No. (%) of Subjects	
	Kcentra (N=103)	Plasma (N=109)
Any possible TE event*	**9 (8.7)**	**6 (5.5)**
TE event adverse reactions	**6 (5.5)‡**	**4 (3.7)**
Cardiac disorders		
Myocardial infarction†	0	1 (0.9)
Myocardial ischemia	0	2 (1.8)
Nervous system disorders		
Ischemic cerebrovascular accident (stroke)‡	2 (1.9)	0
Cerebrovascular disorder§	0	1 (0.9)
Vascular disorders		
Venous thrombosis calf	1 (1.0)	0
Deep vein thrombosis (DVT)‖	1 (1.0)	0
Fistula clot	1 (1.0)	0
Unknown cause of death (not confirmed TE event)		
Sudden death	1 (1.0)	0

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

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

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

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

‖One Kcentra subject had 2 DVTs, both considered related by SAB.

AR = adverse reaction; RCT = randomized, controlled trial; SAB = Safety Adjudication Board; TE = thromboembolic.

Table 19: Subjects With TE Events by Prior History of TE Event in the Acute Major Bleeding RCT

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

*History of prior thromboembolic (TE) event.

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

Table 20: Subjects With Fluid Overload Events by Prior History of CHF in the Acute Major Bleeding RCT

Subgroup	Acute Major Bleeding Study			
	Kcentra		Plasma	
	N	Fluid Overload N (%)	N	Fluid Overload N (%)
All subjects	**103**	**6 (5.8)**	**109**	**14 (12.8)**
With history of CHF	46	4 (8.7)	44	11 (25.0)
Without history of CHF	57	2 (3.5)	65	3 (4.6)

CHF = congestive heart failure; RCT = randomized, controlled trial.

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3.4 Phase 3 (Study 3003): Randomized, Controlled Trial of Kcentra vs Plasma in Subjects Requiring an Urgent Surgery/Invasive Procedure[2]

Study Design

One hundred seventy-six subjects who required urgent reversal of VKA-induced coagulopathy prior to an urgent surgery or invasive procedure were enrolled in a prospective, phase 3b, open-label, active-controlled, non-inferiority, multicenter RCT designed to compare the efficacy, safety, and tolerability of Kcentra versus plasma (**Figure 9**). Subjects were enrolled at 33 sites in the United States, Europe, and Asia; 88 were treated with Kcentra and 88 with plasma. Subjects ranged in age from 27 to 94 years. Surgical procedures included "other" (ie, cholecystectomy, amputation, hernia repair, and appendectomy), orthopedic, invasive, cardiothoracic, and cranial surgery.

Inclusion Criteria

- Subjects (≥18 years of age) who had an elevated INR (≥2 within 3 hours before start of study treatment), were currently receiving oral VKA therapy, and who required an urgent surgical or invasive procedure within 24 hours after the start of infusion were eligible
  - Withdrawal and reversal of oral VKA therapy was required because of the nature of the procedure

Exclusion Criteria

- Urgent procedures where accurate assessment of blood loss was not possible (eg, ruptured aneurysm)
- Urgent procedures where reduction of the INR to within the normal range presented an unacceptable risk for a TE complication
- History of TE events within 3 months of enrollment
- Expected survival of <2 months
- Use of heparin within 24 hours before randomization or potential need for use before completion of the procedure
- Patients in whom the study investigator thought study drug volume might be poorly tolerated

Efficacy Endpoints

- Hemostatic efficacy
  - Proportion of subjects in the Kcentra and plasma groups who achieved hemostatic efficacy from the start of infusion until the end of the urgent procedure. Effective hemostasis was defined as:
    - The difference between predicted and actual blood losses
    - Subjective hemostasis (surgeon-assessed)
    - No administration of non-study coagulation products
- INR reduction
  - Proportion of subjects in each treatment group who achieved a reduction in INR (≤1.3 at 30 minutes after the end of infusion)

This study was considered a success if Kcentra was non-inferior to plasma for hemostatic efficacy and INR reduction. If non-inferiority was demonstrated for either endpoint, Kcentra was assessed for superiority compared with plasma.

Key Secondary Endpoints

Key secondary endpoints included time to INR correction and plasma levels of vitamin K-dependent coagulation Factors II, VII, IX, and X, and antithrombotic Proteins C and S.

Exploratory Endpoints

Exploratory endpoints included the time from start of infusion to start of the urgent surgical or invasive procedure.

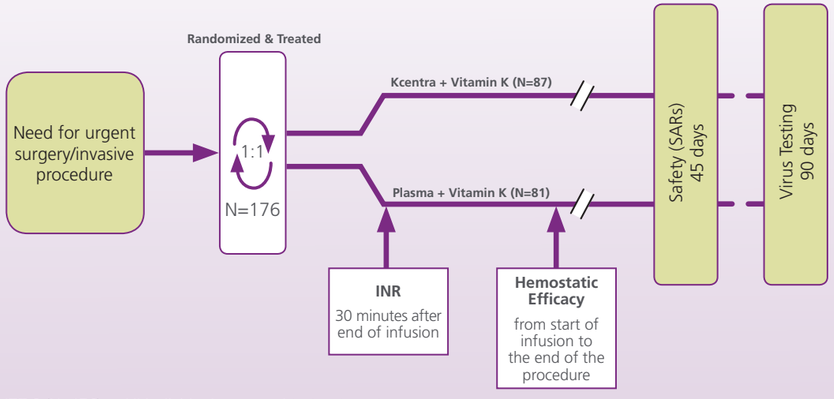
Treatment

Kcentra, plasma, and vitamin K were administered as described for the RCT in acute major bleeding. Administration of oral or IV vitamin K was allowed.

Results

A total of 168 subjects were included in the modified efficacy (ITT-E) population (Kcentra, N=87; plasma, N=81). Demographic and baseline characteristics were similar in both treatment groups (**Table 21**).

Figure 9: Design of the Urgent Surgery/Invasive Procedures RCT[2]



ITT-S (N=176) = All individuals exposed to treatment.
ITT-E (N=163) = Subset of ITT-S that presented with an INR >1.3 and underwent the intended surgical procedure.
INR = international normalized ratio; RCT = randomized, controlled trial; SARs = serious adverse reactions.

Table 21: Demographic and Baseline Characteristics in the Urgent Surgery/Invasive Procedures RCT, ITT-E Population[2]

Parameter	No. (%) of Subjects	
	Kcentra (N=87)	Plasma (N=81)
Age in years (mean)*	69.4	66
Sex, n (%)		
Male	50 (57)	50 (62)
Female	37 (43)	31 (38)
Baseline INR		
Median (range)	2.9 (2.0 to 17.0)	2.9 (2.0 to 26.7)
Reason for oral VKA therapy		
Arrhythmia	42 (48)	31 (38)
Vascular disease	17 (20)	18 (22)
Artificial heart valve or joint	13 (15)	14 (17)
TE event	12 (14)	16 (20)
Other	3 (3)	2 (2)
Type of procedure		
Major orthopedic	20 (23)	15 (19)
Invasive	13 (15)	15 (19)
Cardiothoracic	3 (3)	3 (4)
Cranial neurosurgery	1 (1)	1 (1)
Other	50 (57)	47 (58)

*>28% of subjects in both groups were ≥75 years of age.
INR = international normalized ratio; ITT-E = intention-to-treat efficacy; RCT = randomized, controlled trial; TE = thromboembolic; VKA = vitamin K antagonist.

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Subjects ranged in age from 27 to 94 years, and >28% of subjects were ≥75 years of age. There were no significant differences between groups with respect to the type or distribution of urgent surgery/invasive procedures, or the reasons for oral VKA therapy.

The proportion of subjects with effective hemostasis was 89.7% in the Kcentra group and 75.3% in the plasma group. The 95% CI for the between-group difference ranged from 2.8% to 25.8%. The lower limit of the 95% CI exceeded –10% and thereby demonstrated the non-inferiority of Kcentra versus plasma (primary objective). Because the lower limit of the 95% CI was greater than 0, the prospectively defined criterion for superiority of Kcentra for hemostatic efficacy (secondary objective) was also met (**Table 22**).

A post hoc analysis of hemostatic efficacy demonstrated that, regardless of dose, a larger proportion of subjects achieved hemostatic efficacy in the Kcentra group than in the plasma group.

Early INR reduction (≤1.3 at 30 minutes after the end of infusion) was reported in 55.2% of subjects in the Kcentra group and in 9.9% of subjects in the plasma group. The 95% CI for the between-group difference ranged from 31.9% to 56.4%. The lower limit of the 95% CI of 31.9% demonstrated superiority of Kcentra versus plasma for this endpoint (**Table 23**). The relationship between a decrease in INR to ≤1.3 and clinical hemostatic efficacy has not been established.

In the Kcentra group, median INR values declined from 2.9 at baseline to 1.3 at 30 minutes after the start of infusion. In the plasma group, median INR values declined from 2.9 at baseline to 2.15 at 30 minutes after the start of infusion. Median INR values in plasma-treated subjects did not reach 1.3 until 24 hours after the start of infusion. Reductions in INR were significantly greater in the Kcentra group than in the plasma group until 8 hours after the start of infusion. The mean duration of Kcentra infusion was approximately 7 times faster than the mean duration of plasma infusion (21 minutes vs 141 minutes, respectively). Similarly, the mean volume of Kcentra infused was 89% less than the mean volume of plasma infused (90 mL vs 819 mL, respectively), and resulted in the delivery of a much higher dose of coagulation factors (25 to 50 units/kg for Kcentra vs 10 to 15 units/kg for plasma).

The median time from start of infusion to start of the urgent surgical procedure was shorter in the Kcentra group (3.6 hours [range, 1.9 to 10.8 hours]) than in the plasma group (8.5 hours [range, 2.8 to 18.7 hours]).

Mean plasma levels of coagulation Factors II, VII, IX, and X, and antithrombotic Proteins C and S rapidly increased to >50% of normal at 30 minutes after the start of Kcentra infusion. In contrast, increases in mean factor levels were much lower at 30 minutes after the start of plasma infusion. For Kcentra, factor levels remained elevated through 24 hours. For plasma, levels increased gradually such that similar levels were achieved for most factors at 24 hours. Increases in levels of all factors were significantly greater in the Kcentra group than in the plasma group between 30 minutes and 6 hours after the start of infusion. These results demonstrate that Kcentra rapidly replaces vitamin K–dependent coagulation factors without producing sustained supraphysiologic levels.

Safety

A total of 4 subjects (4.5%) in the Kcentra group and 8 subjects (9.1%) in the plasma group experienced possible TE events (**Table 24**). In the combined safety data from both RCTs, the incidence of TE events assessed as at least possibly related to study treatment by the investigator or, in the case of serious TE events, by the blinded SAB was 9 (4.7%) in the Kcentra group and 7 (3.6%) in the plasma group.

Table 22: Rating of Hemostatic Efficacy in Subjects Who Require an Urgent Surgery/Invasive Procedure

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

*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.

Table 23: Decrease of INR (≤1.3 at 30 minutes after end of infusion)

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

†Kcentra non-inferior to plasma if lower limit of 95% CI > –10%; Kcentra superior to plasma if lower limit of 95% CI >0.
CI = confidence interval; INR = international normalized ratio; N = number of subjects.

Table 24: ARs (TE Events Only) Following Kcentra or Plasma Administration in the Urgent Surgery/Invasive Procedures RCT

System Organ Class	No. (%) of Subjects	
	Kcentra (N=88)	Plasma (N=88)
Any possible TE event*	**4 (4.5)**	**8 (9.1)**
TE event adverse reactions	**4 (4.5)**	**4 (4.5)**
Cardiac disorders		
Myocardial infarction	0	2 (2.3)
Myocardial ischemia	0	0
Nervous system disorders		
Ischemic cerebrovascular accident (stroke)	1 (1.1)	0
Embolic cerebral infarction	0	1 (1.1)
Cerebrovascular disorder	0	0
Vascular disorders		
Venous thrombosis calf	0	0
Venous thrombosis radial vein	1 (1.1)	0
Thrombosis (microthrombosis of toes)	1 (1.1)	0
Deep vein thrombosis (DVT)	1 (1.1)	1 (1.1)
Fistula clot	0	0
Unknown cause of death (not confirmed TE event)		
Sudden death	0	0

*Tabulation of possible TE events includes subjects with confirmed TE events as well as 1 subject in the plasma group who died of unknown causes on Day 18.
AR = adverse reaction; RCT = randomized, controlled trial; TE = thromboembolic.

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Post hoc subgroup analyses were conducted according to whether subjects had a history of a prior TE event. Five subjects (8.1%) in the plasma group and 3 subjects (5.5%) in the Kcentra group with a prior history of a TE event developed TE events (**Table 25**). Three subjects (11.5%) in the plasma group and 1 subject (3.0%) in the Kcentra group without a prior history of a TE event developed TE events.

Eleven subjects (12.5%) in the plasma group and 3 subjects (3.4%) in the Kcentra group developed fluid overload events.

Post hoc subgroup analyses were conducted according to whether subjects had a prior history of CHF. Six subjects (16.7%) in the plasma group and 1 subject (4.2%) in the Kcentra group with a prior history of CHF developed fluid overload events. Five subjects (9.6%) in the plasma group and 2 subjects (3.1%) in the Kcentra group without a prior history of CHF developed fluid overload events (**Table 26**).

Three subjects (3.4%) died in the Kcentra group (1 additional death occurred on Day 48 after completion of the study reporting period) and 8 (9.1%) subjects died in the plasma group. The 95% CI for the between-group difference in deaths ranged from –14.6% to 2.7%. One death in the plasma group was considered possibly related to treatment according to the SAB. 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.

Conclusions

Study 3003 is the first prospective, active-controlled RCT to demonstrate that Kcentra is superior to plasma for hemostatic efficacy and superior for INR reduction in subjects who require urgent VKA reversal prior to an urgent surgical or invasive procedure. The relationship between INR values and clinical hemostasis in patients has not been established. Kcentra has a safety profile comparable to plasma. These results demonstrate that Kcentra is a safe and effective alternative to plasma in this patient population.

Table 25: Subjects With TE Events by Prior History of TE Events in the Urgent Surgery/Invasive Procedures RCT[2]

Subgroup	Kcentra		Plasma	
	N	TE Events,* N (%)	N	TE Events, N (%)
All subjects	**88**	**4 (4.5)**	**88**	**8 (9.1)**
With history of TE event†	55	3 (5.5)	62	5 (8.1)
Without history of TE event	33	1 (3.0)	26	3 (11.5)

*2 additional subjects who had received Kcentra (not listed in the table) developed non-intravascular events (catheter-related/IVC filter insertion).
†History of prior TE event >3 months from study entry (TE event within 3 months not studied).
IVC = inferior vena cava; RCT = randomized, controlled trial; TE = thromboembolic.

Table 26: Subjects With Fluid Overload Events by Prior History of CHF in the Urgent Surgery/Invasive Procedure RCT

Subgroup	Kcentra		Plasma	
	N	Fluid Overload, N (%)	N	Fluid Overload, N (%)
All subjects	**88**	**3 (3.4)**	**88**	**11 (12.5)**
With history of CHF	24	1 (4.2)	36	6 (16.7)
Without history of CHF	64	2 (3.1)	52	5 (9.6)

CHF = congestive heart failure; RCT = randomized, controlled trial.

3.5 Conclusion

Available evidence from phase 2 and phase 3 clinical trials demonstrates that Kcentra rapidly replaces deficient coagulation factors and provides effective VKA reversal in subjects with acute major bleeding or who require an urgent surgery/invasive procedure. In the acute major bleeding RCT, Kcentra was non-inferior to plasma in achieving effective hemostasis and superior to plasma in normalizing INR values and restoring levels of coagulation factors and antithrombotic Proteins C and S. In the urgent surgery/invasive procedures RCT, Kcentra was superior to plasma in achieving effective hemostasis, normalizing INR values, and restoring levels of coagulation factors and antithrombotic Proteins C and S. The relationship between clinical hemostasis and INR values in patients has not been established.[1,2,39]

Notably, analysis of INR and coagulation factor levels from the start of infusion demonstrated a dramatic difference in favor of Kcentra. Most Kcentra-treated subjects experienced normalization of INR and coagulation factor levels within 30 minutes after the end of infusion. In contrast, subjects who received plasma required several hours. Additionally, a significantly larger volume and longer infusion duration were required for plasma plus vitamin K to replace deficient coagulation factors compared with Kcentra plus vitamin K.[1,2]

The safety and tolerability of Kcentra and plasma were similar and consistent with their known safety profiles in a population requiring urgent VKA reversal because of acute major bleeding or the need for an urgent surgery/invasive procedure. Notably, TE event rates were similar in subjects who received Kcentra or plasma, and most TE events and deaths were related to patients' underlying disease rather than Kcentra or plasma administration.

Overall, the results of the first 2 prospective, randomized comparisons of a 4F-PCC versus plasma confirm that Kcentra is a safe and effective alternative to plasma for urgent VKA reversal in subjects with acute major bleeding or requiring an urgent surgery/invasive procedure. This conclusion is supported by data from several other studies reported in the literature.[37,39,63]

Please see Important Safety Information on page 40.

Please see full prescribing information for Kcentra, including boxed warning, on page 42.

4 | Postmarketing Data

The first official approval of Kcentra (as Beriplex P/N) was granted in Germany on February 16, 1996. To date, marketing authorization for the product has been granted in more than 25 countries.

Between February 1996 and March 2012, nearly 1.3 billion IU of Kcentra were administered worldwide.[31] During this period, 21 suspected cases of TE events were reported, including 13 events that occurred in patients receiving Kcentra for anticoagulant reversal. This reflects an overall reporting rate of approximately 1 TE event for every 31,000 estimated single standard doses of Kcentra, which suggests significant underreporting. Because postmarketing reporting of ARs is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure. Further analysis determined that all patients reporting these events had preexisting or concomitant conditions that were likely to result in thromboembolism. There were no cases of confirmed virus transmission or suspected HIT type II related to Kcentra administration.[31]

In summary, postmarketing surveillance of Kcentra over 15 years resulted in 21 reports of TE events. Postmarketing surveillance supports the favorable safety profile of Kcentra.[31]

5 | Reimbursement Information

A CMS ICD-10-CM procedure code has been created to report the administration of Kcentra (**Table 27**).*

Table 27: Summary of Medicare Coding for Kcentra†

Code Type	Procedure Code	HCPCS Code	Revenue Code	Diagnosis Code(s)
Hospital Inpatient Setting	ICD-10-CM Procedure Code 30283B1‡	None	025X (for Kcentra)	Appropriate ICD-10-CM Diagnosis Code(s)
Hospital Outpatient Setting	Appropriate CPT code for Kcentra admin procedure	C9132 (Kcentra, per IU)	0636 (with C9132) + revenue code for admin CPT	Appropriate ICD-10-CM Diagnosis Code(s)

*This resource provides information from a complex and evolving medical coding system. The treating physician is solely responsible for diagnosis coding and determination of the appropriate ICD-10-CM codes that describe the patient's condition and are supported by the medical record. All codes listed are for informational purposes and are not an exhaustive list. The CPT, HCPCS, and ICD-10-CM codes provided are based on AMA or CMS guidelines. The billing party is solely responsible for coding of services (eg, CPT Coding). Because government and other third-party payor coding requirements change periodically, please verify current coding requirements directly with the payor being billed.

†Include additional billing codes as appropriate.

‡Infusion of 4F-PCC.

4F-PCC = four-factor prothrombin complex concentrate; CPT = Current Procedural Terminology; HCPCS = Healthcare Common Procedure Coding System; ICD-10-CM = International Classification of Diseases, Tenth Revision, Clinical Modification; IU = international unit.

6 | Sample Forms—Medicare Claim Forms

A sample 1500 Health Insurance Claim Form is provided on the following page. This claim form currently is the only accepted form for submitting paper claims to government and commercial health insurance carriers.

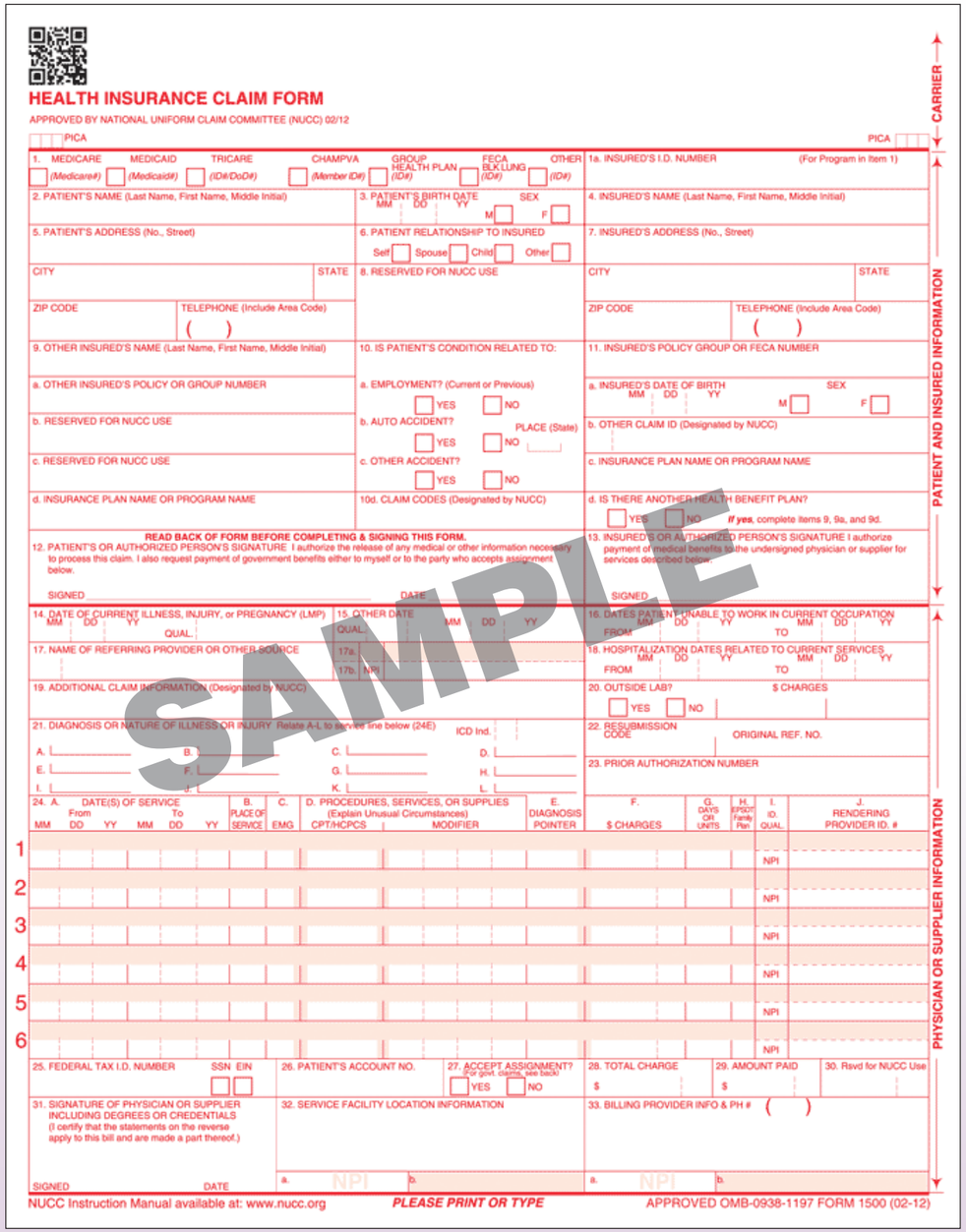
Because most paper claims submitted to Medicare and other insurance carriers are electronically read using optical character recognition (OCR) equipment, the only acceptable claim forms are those printed in OCR Red, J6983 (or exact match) ink. Claims submitted on forms that cannot be read by the OCR equipment will be returned. Claims must be submitted as originals.

Photocopied claims are not accepted. Completion instructions for Form CMS-1500 and print specifications may be found in Chapter 26 of the "Medicare Claims Processing Manual" available at http://www.cms.gov/manuals/downloads/clm104c26.pdf on the CMS website.

Visit the National Uniform Claim Committee "1500 Claim Form Reference Instruction Manual" at http://www.nucc.org for additional information. At the top of the website, select 1500 Claim Form, then 1500 Instructions.[64]

Please see Important Safety Information on page 40.

6 | Sample Forms—Medicare Claim Forms (cont'd)



HEALTH INSURANCE CLAIM FORM

APPROVED BY NATIONAL UNIFORM CLAIM COMMITTEE (NUCC) 02/12

PICA

1. MEDICARE (Medicare#) MEDICAID (Medicaid#) TRICARE (ID#/DoD#) CHAMPVA (Member ID#) GROUP HEALTH PLAN (ID#) FECA BLK LUNG (ID#) OTHER (ID#)

1a. INSURED'S I.D. NUMBER (For Program in Item 1)

2. PATIENT'S NAME (Last Name, First Name, Middle Initial)

3. PATIENT'S BIRTH DATE MM DD YY SEX M F

4. INSURED'S NAME (Last Name, First Name, Middle Initial)

5. PATIENT'S ADDRESS (No., Street)

6. PATIENT RELATIONSHIP TO INSURED Self Spouse Child Other

7. INSURED'S ADDRESS (No., Street)

CITY STATE

8. RESERVED FOR NUCC USE

CITY STATE

ZIP CODE TELEPHONE (Include Area Code) ( )

ZIP CODE TELEPHONE (Include Area Code) ( )

9. OTHER INSURED'S NAME (Last Name, First Name, Middle Initial)

10. IS PATIENT'S CONDITION RELATED TO:

11. INSURED'S POLICY GROUP OR FECA NUMBER

a. OTHER INSURED'S POLICY OR GROUP NUMBER

a. EMPLOYMENT? (Current or Previous) YES NO

a. INSURED'S DATE OF BIRTH MM DD YY SEX M F

b. RESERVED FOR NUCC USE

b. AUTO ACCIDENT? PLACE (State) YES NO

b. OTHER CLAIM ID (Designated by NUCC)

c. RESERVED FOR NUCC USE

c. OTHER ACCIDENT? YES NO

c. INSURANCE PLAN NAME OR PROGRAM NAME

d. INSURANCE PLAN NAME OR PROGRAM NAME

10d. CLAIM CODES (Designated by NUCC)

d. IS THERE ANOTHER HEALTH BENEFIT PLAN? YES NO If yes, complete items 9, 9a, and 9d.

READ BACK OF FORM BEFORE COMPLETING & SIGNING THIS FORM.

12. PATIENT'S OR AUTHORIZED PERSON'S SIGNATURE I authorize the release of any medical or other information necessary to process this claim. I also request payment of government benefits either to myself or to the party who accepts assignment below.

SIGNED DATE

13. INSURED'S OR AUTHORIZED PERSON'S SIGNATURE I authorize payment of medical benefits to the undersigned physician or supplier for services described below.

SIGNED

14. DATE OF CURRENT ILLNESS, INJURY, or PREGNANCY (LMP) MM DD YY QUAL.

15. OTHER DATE QUAL. MM DD YY

16. DATES PATIENT UNABLE TO WORK IN CURRENT OCCUPATION MM DD YY FROM TO MM DD YY

17. NAME OF REFERRING PROVIDER OR OTHER SOURCE

17a.

17b. NPI

18. HOSPITALIZATION DATES RELATED TO CURRENT SERVICES MM DD YY FROM TO MM DD YY

19. ADDITIONAL CLAIM INFORMATION (Designated by NUCC)

20. OUTSIDE LAB? YES NO $ CHARGES

21. DIAGNOSIS OR NATURE OF ILLNESS OR INJURY Relate A-L to service line below (24E) ICD Ind.

A. B. C. D. E. F. G. H. I. J. K. L.

22. RESUBMISSION CODE ORIGINAL REF. NO.

23. PRIOR AUTHORIZATION NUMBER

24. A. DATE(S) OF SERVICE From MM DD YY	To MM DD YY	B. PLACE OF SERVICE	C. EMG	D. PROCEDURES, SERVICES, OR SUPPLIES (Explain Unusual Circumstances) CPT/HCPCS	MODIFIER	E. DIAGNOSIS POINTER	F. $ CHARGES	G. DAYS OR UNITS	H. EPSDT Family Plan	I. ID. QUAL.	J. RENDERING PROVIDER ID. #
1										NPI	
2										NPI	
3										NPI	
4										NPI	
5										NPI	
6										NPI	

25. FEDERAL TAX I.D. NUMBER SSN EIN

26. PATIENT'S ACCOUNT NO.

27. ACCEPT ASSIGNMENT? (For govt. claims, see back) YES NO

28. TOTAL CHARGE $

29. AMOUNT PAID $

30. Rsvd for NUCC Use

31. SIGNATURE OF PHYSICIAN OR SUPPLIER INCLUDING DEGREES OR CREDENTIALS (I certify that the statements on the reverse apply to this bill and are made a part thereof.)

SIGNED DATE

32. SERVICE FACILITY LOCATION INFORMATION

a. NPI b.

33. BILLING PROVIDER INFO & PH # ( )

a. NPI b.

NUCC Instruction Manual available at: www.nucc.org

PLEASE PRINT OR TYPE

APPROVED OMB-0938-1197 FORM 1500 (02-12)

CARRIER

PATIENT AND INSURED INFORMATION

PHYSICIAN OR SUPPLIER INFORMATION

SAMPLE

Please see full prescribing information for Kcentra, including boxed warning, on page 42.

Kcentra® Prothrombin Complex Concentrate (Human)

7 | Contact Information

Kcentra Hotline

TOLL-FREE: 1-855-4KCENTRA
(1-855-452-3687)

The Kcentra Hotline is available 24 hours a day, 7 days a week. Speak with a Kcentra Hotline representative for:

- Additional product information
- Medical inquiries
- Reimbursement support
- Resources

For more information about Kcentra, visit **www.Kcentra.com**.

8 | Important Safety Information

Important Safety Information

Kcentra 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 and its variant (vCJD), cannot be completely eliminated.

Please see full prescribing information for Kcentra, including boxed warning, on page 42.

Please see full prescribing information for Kcentra, including boxed warning, on page 42.

Appendix A: Prescribing Information

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 (2.2) 10/2018
----------INDICATIONS AND USAGE----------
Kcentra, Prothrombin Complex Concentrate (Human), is a blood coagulation factor replacement product indicated for the urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients with:
- acute major bleeding or
- need for an urgent surgery/invasive procedure. (1)

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

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

* Dosing is based on body weight. Dose based on actual potency is stated on the vial, which will vary from 20-31 Factor IX units/mL after reconstitution. The actual potency for 500 unit vial ranges from 400-620 units/vial. The actual potency for 1000 unit vial ranges from 800-1240 units/vial.
† Units refer to International Units.
‡ Dose is based on body weight up to but not exceeding 100 kg. For patients weighing more than 100 kg, maximum dose should not be exceeded.

----------DOSAGE FORMS AND STRENGTHS----------
- Kcentra is available as a white or slightly colored lyophilized concentrate in a single-use vial containing coagulation Factors II, VII, IX and X, and antithrombotic Proteins C and S. (3)

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

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

----------ADVERSE REACTIONS----------
- The most common adverse reactions (ARs) (frequency ≥ 2.8%) observed in subjects receiving Kcentra were headache, nausea/vomiting, hypotension, and anemia. (6)
- The most serious ARs were thromboembolic events including stroke, pulmonary embolism, and deep vein thrombosis. (6)

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

See 17 for PATIENT COUNSELING INFORMATION

Revised: October 2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

CSL Behring

FULL PRESCRIBING INFORMATION

Kcentra®
Prothrombin Complex Concentrate (Human)

WARNING: ARTERIAL AND VENOUS THROMBOEMBOLIC COMPLICATIONS
Patients being treated with Vitamin K antagonists (VKA) therapy have underlying disease states that predispose them to thromboembolic events. Potential benefits of reversing VKA should be weighed against the potential risks of thromboembolic events (TE), especially in patients with the history of a thromboembolic event. Resumption of anticoagulation should be carefully considered as soon as the risk of thromboembolic events outweighs the risk of acute bleeding.
- **Both fatal and non-fatal arterial and venous thromboembolic complications have been reported with Kcentra in clinical trials and post marketing surveillance. Monitor patients receiving Kcentra for signs and symptoms of thromboembolic events. (5.2)**
- **Kcentra was not studied in subjects who had a thromboembolic event, myocardial infarction, disseminated intravascular coagulation, cerebral vascular accident, transient ischemic attack, unstable angina pectoris, or severe peripheral vascular disease within the prior 3 months. Kcentra may not be suitable in patients with thromboembolic events in the prior 3 months. (5.2)**

1 INDICATIONS AND USAGE
Kcentra®, (Prothrombin Complex Concentrate (Human)), is a blood coagulation factor replacement product indicated for the urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients with:
- acute major bleeding or
- need for an urgent surgery/invasive procedure.

2 DOSAGE AND ADMINISTRATION
For intravenous use only.

2.1 Dosage
- Measurement of INR prior to treatment and close to the time of dosing is important because coagulation factors may be unstable in patients with acute major bleeding or an urgent need for surgery and other invasive procedures.
- Individualize Kcentra dosing based on the patient's current 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 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 Kcentra using aseptic technique with 20 mL (nominal potency 500 U kit) or 40 mL (nominal potency 1000 U kit) of Sterile Water for Injection (diluent) provided in the kit.
- Do not use Kcentra beyond the expiration date on the vial label and carton.
- Kcentra is for single use only. Contains no preservatives. Discard partially used vials.

Table 2: Kcentra Reconstitution Instructions

1. Ensure that the Kcentra vial and diluent vial are at room temperature.	
2. Remove flip caps from the Kcentra and diluent vials.	
3. Wipe the stoppers with the alcohol swab provided and allow to dry prior to opening the Mix2Vial package.	
4. Open the Mix2Vial package by peeling off the lid. [*Fig. 1*] Do **not** remove the Mix2Vial from the blister package.	 Fig. 1
5. Place the diluent vial on an even, clean surface and hold the vial tight. Take the Mix2Vial together with the blister package and push the spike of the **blue** adapter end **straight down** through the diluent vial stopper. [*Fig. 2*]	 Fig. 2
6. Carefully remove the blister package from the Mix2Vial set by holding at the rim, and pulling **vertically** upwards. Make sure that you only pull away the blister package and not the Mix2Vial set. [*Fig. 3*]	 Fig. 3
7. Place the **Kcentra vial** on an even and firm surface. Invert the diluent vial with the Mix2Vial set attached and push the spike of the **transparent** adapter end **straight down** through the Kcentra vial stopper. [*Fig. 4*] The diluent will automatically flow into the Kcentra vial. **Note:** If the vacuum in the Kcentra vial is accidentally lost during reconstitution with the Mix2Vial device, the transfer with the Mix2Vial will not work. In this case, separate the set into two pieces as illustrated in Fig. 6 below; do not discard the diluent vial. Place the Kcentra vial aside on a flat surface. Remove the blue adapter end from the diluent vial of the Mix2Vial set (Fig. 5) by lifting and bending the blue adapter to the side until it disconnects from the diluent vial. For reconstitution: • Using a separate sterile needle and syringe, withdraw the remaining diluent. Remove the needle from the syringe. • Attach the syringe to the transparent adapter of the Kcentra vial as illustrated in Fig. 8 below, and transfer the entire diluent volume into the Kcentra vial. Remove syringe. • Gently swirl the Kcentra vial to ensure the product is fully dissolved. Do not shake. • Proceed to step 10.	 Fig. 4  Fig. 5
8. With one hand, grasp the Kcentra-side of the Mix2Vial set and with the other hand grasp the diluent-side and unscrew the set carefully counterclockwise into two pieces (Fig. 6). Discard the diluent vial with the blue Mix2Vial adapter attached.	 Fig. 6

9. Gently swirl the Kcentra vial with the transparent adapter attached until the substance is fully dissolved (Fig. 7). Do not shake.	 Fig. 7
10. Draw air into an empty, sterile syringe. While the Kcentra vial is upright, connect the syringe to the Mix2Vial's Luer Lock fitting by screwing clockwise. Inject air into the Kcentra vial (Fig. 8).	 Fig. 8
11. While keeping the syringe plunger pressed, turn the system upside down and draw the solution into the syringe by pulling the plunger back slowly (Fig. 9).	 Fig. 9
12. Now that the solution has been transferred into the syringe, firmly hold on to the barrel of the syringe (keeping the syringe plunger facing down) and disconnect the transparent Mix2Vial adapter from the syringe by unscrewing counterclockwise (Fig. 10). Attach the syringe to a suitable intravenous administration set.	 Fig. 10
13. After reconstitution, administration should begin promptly or within 4 hours.	
14. If the same patient is to receive more than one vial, you may pool the contents of multiple vials. Use a separate unused Mix2Vial transfer set for each product vial.	

2.3 Administration

- Do not mix Kcentra with other medicinal products; administer through a separate infusion line.
- Visually inspect the reconstituted solution for particulate matter and discoloration prior to administration whenever solution and container permit. Reconstituted Kcentra solution should be colorless, clear to slightly opalescent, and free from visible particles. Do not use if the solution is cloudy, discolored, or contains particulates.
- Use aseptic technique when adminstering Kcentra.
- Administer at room temperature.
- Administer by intravenous infusion at a rate of 0.12 mL/kg/min (~3 units/kg/min), up to a maximum rate of 8.4 mL/min (~210 units/min).
- No blood should enter the syringe, as there is a possibility of fibrin clot formation.

3 DOSAGE FORMS AND STRENGTHS

- Kcentra is available as a white or slightly colored lyophilized concentrate in a single use vial containing coagulation Factors II, VII, IX and X, and antithrombotic Proteins C and S.
- Kcentra potency (units) is defined by Factor IX content. The actual potency for 500 unit vial ranges from 400-620 Factor IX units/vial. The actual potency for 1000 unit vial ranges from 800-1240 Factor IX units/vial. The actual content of Factor IX as measured in units of potency for the vial before reconstitution is stated by the expiration date. When reconstituted, the final concentration of drug product in Factor IX units will be in a range from 20-31 units/mL.
- The actual units of potency for each coagulation factor (Factors II, VII, IX and X), and Proteins C and S are stated on the carton.

4 CONTRAINDICATIONS

Kcentra is contraindicated in:

- Patients with known anaphylactic or severe systemic reactions to Kcentra or any components in Kcentra including heparin, Factors II, VII, IX, X, Proteins C and S, Antithrombin III and human albumin.
- Patients with disseminated intravascular coagulation (DIC).
- Patients with known heparin-induced thrombocytopenia (HIT). Kcentra contains heparin *[see Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

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

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

5.2 Thromboembolic Risk/Complications

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

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

5.3 Transmissible Infectious Agents

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

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

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

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.

Please see Important Safety Information on page 40.

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.

Appendix A: Prescribing Information (cont'd)

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			Overall Virus Reduction [$\log_{10}$]
	Heat treatment ("Pasteurization")	Ammonium sulphate precipitation followed by Ca Phosphate adsorption	2 x 20 nm Virus Filtration	
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

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

HIV Human immunodeficiency virus, a model for HIV-1 and HIV-2
BVDV Bovine viral diarrhea virus, model for HCV
PRV Pseudorabies virus, a model for large enveloped DNA viruses
WNV West Nile virus
HAV Hepatitis A virus
CPV Canine parvovirus, model for B19V
n.d. not determined

12 CLINICAL PHARMACOLOGY

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)

* Statistically significant difference compared to plasma by 2-sided Wilcoxon test
INR = international normalized ratio; NC = not collected.

12.3 Pharmacokinetics

Fifteen healthy subjects received 50 units/kg of Kcentra. No subjects were receiving VKA therapy or were experiencing acute bleeding. A single intravenous Kcentra infusion produced a rapid and sustained increase in plasma concentration of Factors II, VII, IX and X as well as Proteins C and S. The PK analysis *[see Table 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 x h)	1850.8 (1001.4)	7282.2 (2324.9)	512.9 (250.1)	6921.5 (1730.5)	5397.5 (2613.9)	3651.6 (916.3)
Clearance (mL/ kg x h)	3.7 (1.6)	1.0 (0.3)	7.4 (4.1)	1.3 (0.3)	1.5 (0.9)	1.2 (0.3)
MRT (h)†	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]*.

Please see Important Safety Information on page 40.

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]

* 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

	Low Dose	Mid Dose	High Dose
	N = 49 (K) N = 55 (P)	N = 22 (K) N = 18 (P)	N = 26 (K) 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]

* Kcentra non-inferior to plasma if lower limit of 95% CI > –10%; Kcentra superior to plasma if lower limit of 95% CI > 0.
CI = confidence interval; INR = international normalized ratio; N = total subjects

Urgent Surgery/Invasive Procedure RCT

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

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

* Kcentra non-inferior to plasma if lower limit of 95% CI > –10%; Kcentra superior to plasma if lower limit of 95% CI > 0.
CI = confidence interval; N = number of subjects
Results of a post-hoc analysis of hemostatic efficacy stratified by actual dose of Kcentra or plasma administered in the urgent surgery/invasive procedure RCT are presented in Table 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 = 62 (P)	N = 10 (K) N = 10 (P)	N = 8 (K) 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]		Difference Kcentra – Plasma (%) [95% CI]*
	Kcentra (N = 87)	Plasma (N = 81)	
Decrease of INR to ≤ 1.3 at 30 min	48 (55.2%) [44.7; 65.6]	8 (9.9%) [3.4; 16.4]	(45.3%) [31.9; 56.4]

* Kcentra non-inferior to plasma if lower limit of 95% CI > -10%; Kcentra superior to plasma if lower limit of 95% CI > 0.
CI = confidence interval; INR = international normalized ratio; N = total subjects

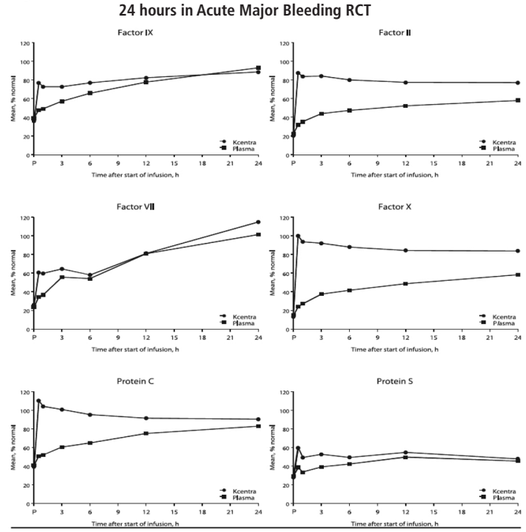
The European Bleeding and Surgical Study was an open-label, single-arm, multicenter study.[1] Forty-three (43) subjects who were receiving VKA were treated with Kcentra, because they either (1) required a surgical or an invasive diagnostic intervention (26 subjects), or (2) experienced an acute bleeding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

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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

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

17 PATIENT COUNSELING INFORMATION

- Inform patients of the signs and symptoms of allergic hypersensitivity reactions, such as urticaria, rash, tightness of the chest, wheezing, hypotension and/or anaphylaxis experienced during or after injection of Kcentra *[see Warnings and Precautions (5.1)]*.
- Inform patients of signs and symptoms of thrombosis, such as limb or abdomen swelling and/or pain, chest pain or pressure, shortness of breath, loss of sensation or motor power, altered consciousness, vision, or speech *[see Warnings and Precautions (5.2)]*.
- Inform patients that, because Kcentra is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent *[see Warnings and Precautions (5.3) and Description (11)]*.

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Appendix B: Listing of Kcentra Clinical Trials

Author	Study Title	Publication	Study Type/N	Start Date/ End Date	Location(s)
Prospective interventional studies					
Sarode R et al	Efficacy and Safety of a 4-Factor Prothrombin Complex Concentrate in Patients on Vitamin K Antagonists Presenting With Major Bleeding: A Randomized, Plasma-Controlled Phase IIIb Study (Study 3002)	*Circulation.* 2013;128(11): 1234-1243.	Randomized, controlled, open label, phase 3b, non-inferiority (N=212)	June 2008/ November 2010 (completed)	United States, Armenia, Belarus, Bulgaria, Romania, Russia, Ukraine
Goldstein J et al	Four-Factor Prothrombin Complex Concentrate Versus Plasma for Rapid Vitamin K Antagonist Reversal in Patients Needing Urgent Surgical or Invasive Interventions: a Phase 3b, Open-Label, Non-Inferiority, Randomised Trial (Study 3003)	*Lancet.* 2015; 385(9982): 2077-2087.	Randomized, controlled, open label, phase 3b, non-inferiority (N=176)	February 2009/ March 2013 (completed)	United States, Armenia, Belarus, Bulgaria, Romania, Russia, Ukraine
Pabinger I et al	Prothrombin Complex Concentrate (Beriplex® P/N) for Emergency Anticoagulation Reversal: A Prospective Multinational Clinical Trial	*Journal of Thrombosis and Haemostasis.* 2008;6(4): 622-631.	Non-randomized, open label, multinational, phase 2 (N=43)	October 2005/ November 2006	Austria, Germany, Hungary, Israel, Lithuania, Netherlands, Poland, Switzerland
Preston FE et al	Rapid Reversal of Oral Anticoagulation With Warfarin by a Prothrombin Complex Concentrate (Beriplex): Efficacy and Safety in 42 Patients	*British Journal of Haematology.* 2002;116(3): 619-624.	Non-randomized, open label, cohort (N=42)	1998/2001	Royal Hallamshire Hospital, Sheffield, UK

Author	Study Title	Publication	Study Type/N	Start Date/ End Date	Location(s)
Prospective interventional studies (cont'd)					
Lorenz R et al	Successful Emergency Reversal of Phenprocoumon Anticoagulation With Prothrombin Complex Concentrate: A Prospective Clinical Study	*Blood Coagulation and Fibrinolysis.* 2007;18(6): 565-570.	Non-randomized, open label, cohort (N=8)	June 1996/ June 1997	Munich, Münster, Leipzig, Marburg, and Hannover, Germany
Lorenz R et al	Efficacy and Safety of a Prothrombin Complex Concentrate With Two Virus-Inactivation Steps in Patients With Severe Liver Damage	*European Journal of Gastroenterology and Hepatology.* 2003;15:15-20.	Non-randomized, open label, cohort (N=22)		Munich, Münster, Leipzig, Marburg, and Hannover, Germany
Evans G et al	Beriplex P/N Reverses Severe Warfarin-Induced Overanticoagulation Immediately and Completely in Patients Presenting With Major Bleeding	*British Journal of Haematology.* 2001;115(4): 998-1001.	Non-randomized, open label, cohort (N=10)		Addenbrooke's Hospital, Cambridge University Hospitals NHS Trust, Cambridge, UK
Makris M et al	Emergency Oral Anticoagulant Reversal: The Relative Efficacy of Infusions of Fresh Frozen Plasma and Clotting Factor Concentrate on Correction of the Coagulopathy	*Thrombosis & Haemostasis.* 1997;77:477-480.	Non-randomized, open label, cohort (N=41) (29 received PCC)	1991/1994	Royal Hallamshire Hospital, Sheffield, UK

Please see Important Safety Information on page 40.

Please see full prescribing information for Kcentra, including boxed warning, on page 42.

Appendix B: Listing of Kcentra Clinical Trials (cont'd)

Author	Study Title	Publication	Study Type/N	Start Date/ End Date	Location(s)
Retrospective observational studies					
Bruce D, Nokes T	Prothrombin Complex Concentrate (Beriplex P/N) in Severe Bleeding: Experience in a Large Tertiary Hospital	*Critical Care.* 2008;12:R105.	Single-center cohort (N=30)	April 2002/ July 2004	Derriford Hospital, Plymouth, UK
Hanke A et al	Long-Term Safety and Efficacy of a Pasteurized Nanofiltrated Prothrombin Complex Concentrate (Beriplex P/N): A Pharmacovigilance Study	*British Journal of Anaesthesia.* 2013;110(5): 764-772.	Pharmacovigilance	February 1996/ March 2012	NA
Ostermann H et al	Pharmacokinetics of Beriplex P/N Prothrombin Complex Concentrate in Healthy Volunteers	*Thrombosis & Haemostasis.* 2007;98:790-797.	PK and IVR (N=15)	June 2005/ September 2005	Clinical Pharmacology Research Unit of Parexel International GmbH, Berlin, Germany
Schick KS et al	Prothrombin Complex Concentrate in Surgical Patients: Retrospective Evaluation of Vitamin K Antagonist Reversal and Treatment of Severe Bleeding	*Critical Care.* 2009;13:R191.	Single-center case series (N=50)	January 2004/ December 2004	University of Munich Hospital, Munich, Germany
NCT 01053169 www.clinicaltrials.gov	Observational Study of Prophylaxis and Treatment of Acute Perioperative Bleeding With Beriplex® P/N (Probe Study)	Unpublished	Multicenter cohort (N=445)	May 2010/ January 2012 (completed)	United Kingdom

Please see Important Safety Information on page 40.

Please see full prescribing information for Kcentra, including boxed warning, on page 42.

Appendix C: References

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Appendix C: References (cont'd)

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Notes

Please see Important Safety Information on page 40.

Please see full prescribing information for Kcentra, including boxed warning, on page 42.

Speak with a Kcentra Hotline representative for:

- Additional product information
- Medical inquiries
- Reimbursement support
- Resources

Kcentra Hotline

TOLL-FREE: 1-855-4KCENTRA
(1-855-452-3687)

Kcentra Quick Guide

Get fast access to Kcentra tools and content without the need for an internet connection. With an easy-to-use interface created just for Kcentra, save time when:

- Determining the recommended dose
- Accessing information on reconstitution and administration

For more information about Kcentra, visit **www.Kcentra.com**.

Please see Important Safety Information on page 40.
Please see full prescribing information for Kcentra, including boxed warning, on page 42.

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

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 (2.2) 10/2018

----------INDICATIONS AND USAGE----------

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

- acute major bleeding or
- need for an urgent surgery/invasive procedure. (1)

----------DOSAGE AND ADMINISTRATION----------

For intravenous use after reconstitution only..

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

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

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

† Units refer to International Units.

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

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

- Kcentra is available as a white or slightly colored lyophilized concentrate in a single-use vial containing coagulation Factors II, VII, IX and X, and antithrombotic Proteins C and S. (3)

----------CONTRAINDICATIONS ----------

Kcentra is contraindicated in patients with:

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

----------WARNINGS AND PRECAUTIONS----------

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

----------ADVERSE REACTIONS----------

- The most common adverse reactions (ARs) (frequency ≥ 2.8%) observed in subjects receiving Kcentra were headache, nausea/vomiting, hypotension, and anemia. (6)
- The most serious ARs were thromboembolic events including stroke, pulmonary embolism, and deep vein thrombosis. (6)

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

See 17 for PATIENT COUNSELING INFORMATION

Revised: October 2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

CSL Behring

FULL PRESCRIBING INFORMATION

Kcentra® Prothrombin Complex Concentrate (Human)

WARNING: ARTERIAL AND VENOUS THROMBOEMBOLIC COMPLICATIONS

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

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

1 INDICATIONS AND USAGE

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

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

2 DOSAGE AND ADMINISTRATION

For intravenous use only.

2.1 Dosage

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

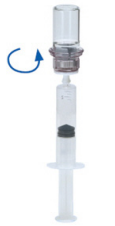
Monitor INR and clinical response during and after treatment. In clinical trials, Kcentra decreased the INR to ≤ 1.3 within 30 minutes in most subjects. The relationship between this or other INR values and clinical hemostasis in patients has not been established *[see Clinical Studies (14)]*.

2.2 Preparation and Reconstitution

- Reconstitute Kcentra using aseptic technique with 20 mL (nominal potency 500 U kit) or 40 mL (nominal potency 1000 U kit) of Sterile Water for Injection (diluent) provided in the kit.
- Do not use Kcentra beyond the expiration date on the vial label and carton.
- Kcentra is for single use only. Contains no preservatives. Discard partially used vials.

Table 2: Kcentra Reconstitution Instructions

1. Ensure that the Kcentra vial and diluent vial are at room temperature.	
2. Remove flip caps from the Kcentra and diluent vials.	
3. Wipe the stoppers with the alcohol swab provided and allow to dry prior to opening the Mix2Vial package.	
4. Open the Mix2Vial package by peeling off the lid. [*Fig. 1*] Do **not** remove the Mix2Vial from the blister package.	 Fig. 1
5. Place the diluent vial on an even, clean surface and hold the vial tight. Take the Mix2Vial together with the blister package and push the spike of the **blue** adapter end **straight down** through the diluent vial stopper. [*Fig. 2*]	 Fig. 2
6. Carefully remove the blister package from the Mix2Vial set by holding at the rim, and pulling **vertically** upwards. Make sure that you only pull away the blister package and not the Mix2Vial set. [*Fig. 3*]	 Fig. 3
7. Place the **Kcentra vial** on an even and firm surface. Invert the diluent vial with the Mix2Vial set attached and push the spike of the **transparent** adapter end **straight down** through the Kcentra vial stopper. [*Fig. 4*] The diluent will automatically flow into the Kcentra vial. **Note:** If the vacuum in the Kcentra vial is accidentally lost during reconstitution with the Mix2Vial device, the transfer with the Mix2Vial will not work. In this case, separate the set into two pieces as illustrated in Fig. 6 below; do not discard the diluent vial. Place the Kcentra vial aside on a flat surface. Remove the blue adapter end from the diluent vial of the Mix2Vial set (Fig. 5) by lifting and bending the blue adapter to the side until it disconnects from the diluent vial. For reconstitution: • Using a separate sterile needle and syringe, withdraw the remaining diluent. Remove the needle from the syringe. • Attach the syringe to the transparent adapter of the Kcentra vial as illustrated in Fig. 8 below, and transfer the entire diluent volume into the Kcentra vial. Remove syringe. • Gently swirl the Kcentra vial to ensure the product is fully dissolved. Do not shake. • Proceed to step 10.	 Fig. 4  Fig. 5
8. With one hand, grasp the Kcentra-side of the Mix2Vial set and with the other hand grasp the diluent-side and unscrew the set carefully counterclockwise into two pieces (Fig. 6). Discard the diluent vial with the blue Mix2Vial adapter attached.	 Fig. 6

9. Gently swirl the Kcentra vial with the transparent adapter attached until the substance is fully dissolved (Fig. 7). Do not shake.	 Fig. 7
10. Draw air into an empty, sterile syringe. While the Kcentra vial is upright, connect the syringe to the Mix2Vial's Luer Lock fitting by screwing clockwise. Inject air into the Kcentra vial (Fig. 8).	 Fig. 8
11. While keeping the syringe plunger pressed, turn the system upside down and draw the solution into the syringe by pulling the plunger back slowly (Fig. 9).	 Fig. 9
12. Now that the solution has been transferred into the syringe, firmly hold on to the barrel of the syringe (keeping the syringe plunger facing down) and disconnect the transparent Mix2Vial adapter from the syringe by unscrewing counterclockwise (Fig. 10). Attach the syringe to a suitable intravenous administration set.	 Fig. 10
13. After reconstitution, administration should begin promptly or within 4 hours.	
14. If the same patient is to receive more than one vial, you may pool the contents of multiple vials. Use a separate unused Mix2Vial transfer set for each product vial.	

2.3 Administration

- Do not mix Kcentra with other medicinal products; administer through a separate infusion line.
- Visually inspect the reconstituted solution for particulate matter and discoloration prior to administration whenever solution and container permit. Reconstituted Kcentra solution should be colorless, clear to slightly opalescent, and free from visible particles. Do not use if the solution is cloudy, discolored, or contains particulates.
- Use aseptic technique when adminstering Kcentra.
- Administer at room temperature.
- Administer by intravenous infusion at a rate of 0.12 mL/kg/min (~3 units/kg/min), up to a maximum rate of 8.4 mL/min (~210 units/min).
- No blood should enter the syringe, as there is a possibility of fibrin clot formation.

3 DOSAGE FORMS AND STRENGTHS

- Kcentra is available as a white or slightly colored lyophilized concentrate in a single use vial containing coagulation Factors II, VII, IX and X, and antithrombotic Proteins C and S.
- Kcentra potency (units) is defined by Factor IX content. The actual potency for 500 unit vial ranges from 400-620 Factor IX units/vial. The actual potency for 1000 unit vial ranges from 800-1240 Factor IX units/vial. The actual content of Factor IX as measured in units of potency for the vial before reconstitution is stated by the expiration date. When reconstituted, the final concentration of drug product in Factor IX units will be in a range from 20-31 units/mL.
- The actual units of potency for each coagulation factor (Factors II, VII, IX and X), and Proteins C and S are stated on the carton.

4 CONTRAINDICATIONS

Kcentra is contraindicated in:

- Patients with known anaphylactic or severe systemic reactions to Kcentra or any components in Kcentra including heparin, Factors II, VII, IX, X, Proteins C and S, Antithrombin III and human albumin.
- Patients with disseminated intravascular coagulation (DIC).
- Patients with known heparin-induced thrombocytopenia (HIT). Kcentra contains heparin *[see Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

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

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

5.2 Thromboembolic Risk/Complications

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

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

5.3 Transmissible Infectious Agents

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

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

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

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			Overall Virus Reduction [$\log_{10}$]
	Heat treatment ("Pasteurization")	Ammonium sulphate precipitation followed by Ca Phosphate adsorption	2 x 20 nm Virus Filtration	
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

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

HIV Human immunodeficiency virus, a model for HIV-1 and HIV-2
BVDV Bovine viral diarrhea virus, model for HCV
PRV Pseudorabies virus, a model for large enveloped DNA viruses
WNV West Nile virus
HAV Hepatitis A virus
CPV Canine parvovirus, model for B19V
n.d. not determined

12 CLINICAL PHARMACOLOGY

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)

* Statistically significant difference compared to plasma by 2-sided Wilcoxon test
INR = international normalized ratio; NC = not collected.

12.3 Pharmacokinetics

Fifteen healthy subjects received 50 units/kg of Kcentra. No subjects were receiving VKA therapy or were experiencing acute bleeding. A single intravenous Kcentra infusion produced a rapid and sustained increase in plasma concentration of Factors II, VII, IX and X as well as Proteins C and S. The PK analysis *[see Table 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 x h)	1850.8 (1001.4)	7282.2 (2324.9)	512.9 (250.1)	6921.5 (1730.5)	5397.5 (2613.9)	3651.6 (916.3)
Clearance (mL/ kg x h)	3.7 (1.6)	1.0 (0.3)	7.4 (4.1)	1.3 (0.3)	1.5 (0.9)	1.2 (0.3)
MRT (h)†	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]

* 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

	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]

* Kcentra non-inferior to plasma if lower limit of 95% CI > –10%; Kcentra superior to plasma if lower limit of 95% CI > 0.
CI = confidence interval; INR = international normalized ratio; N = total subjects

Urgent Surgery/Invasive Procedure RCT

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

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

* Kcentra non-inferior to plasma if lower limit of 95% CI > –10%; Kcentra superior to plasma if lower limit of 95% CI > 0.
CI = confidence interval; N = number of subjects
Results of a post-hoc analysis of hemostatic efficacy stratified by actual dose of Kcentra or plasma administered in the urgent surgery/invasive procedure RCT are presented in Table 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]		Difference
	Kcentra (N = 87)	Plasma (N = 81)	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]

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

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

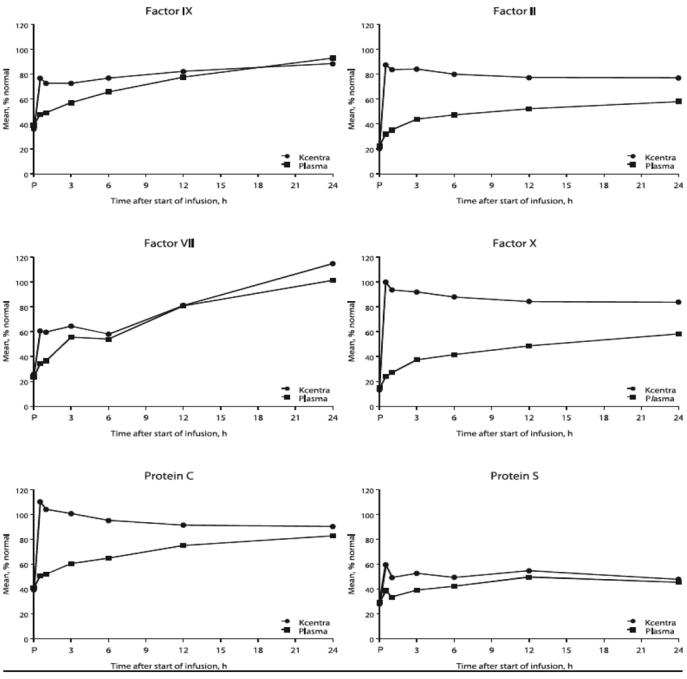
The European Bleeding and Surgical Study was an open-label, single-arm, multicenter study.[1] Forty-three (43) subjects who were receiving VKA were treated with Kcentra, because they either (1) required a surgical or an invasive diagnostic intervention (26 subjects), or (2) experienced an acute bleeding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

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

17 PATIENT COUNSELING INFORMATION

- Inform patients of the signs and symptoms of allergic hypersensitivity reactions, such as urticaria, rash, tightness of the chest, wheezing, hypotension and/or anaphylaxis experienced during or after injection of Kcentra *[see Warnings and Precautions (5.1)]*.
- Inform patients of signs and symptoms of thrombosis, such as limb or abdomen swelling and/or pain, chest pain or pressure, shortness of breath, loss of sensation or motor power, altered consciousness, vision, or speech *[see Warnings and Precautions (5.2)]*.
- Inform patients that, because Kcentra is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent *[see Warnings and Precautions (5.3) and Description (11)]*.

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