



Advancing Transfusion and  
Cellular Therapies Worldwide

## **Information Piece**

### **Alternatives to Transfusable Single-Donor Plasma Components**

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Two products offering alternatives to plasma\* in certain circumstances have recently been licensed by the Food and Drug Administration (FDA): a solvent/detergent (SD)-treated plasma product and a four-factor prothrombin complex concentrate (PCC). This document contains information to consider in determining whether to administer these products. Considerations include potential safety, practical and logistical issues relating to the use of either product. Discussion is focused primarily on products and indications approved in the United States.

In providing this informational piece, AABB is not endorsing or recommending the use of any product. Health care practitioners must make their own determinations regarding what products and services are most appropriate to use in the treatment of patients. AABB specifically disclaims any liability resulting from the use or failure to use any product referred to in this document.

### **Solvent/Detergent-Treated Plasma (Octaplas™)**

#### **Background**

The solvent/detergent procedure for disruption of the lipid envelope and inactivation of *enveloped* viruses in plasma protein preparations was developed and licensed in the 1980s for use in the manufacture of plasma protein fractions (eg, Factor VIII preparations). In the 1990s this process was applied to units of transfusable plasma.

An SD-treated plasma product manufactured by Vitex (Melville, New York) became available in the United States in 1998. Later, after investigation of thrombotic episodes during liver transplantation, this product was found to have increased thrombotic potential attributed to low levels of the anticoagulant protein S and fibrinolytic activity. This product is no longer manufactured.

A different SD-treated plasma product – Octaplas™, Pooled Plasma (Human), Solvent/Detergent Treated Solution for Intravenous Infusion, manufactured by Octapharma (Lachen, Switzerland) – was licensed by the FDA in 2013. Compared to previous SD-treated plasma products, Octaplas™ has increased levels of protein S and alpha<sub>2</sub>-antiplasmin (also known as plasmin inhibitor, an inhibitor of clot lysis). Octaplas™ (in its current form or as a previous generation product) has been used for up to two decades in many countries in the European Union. More than seven million doses of Octaplas™ have been given to more than two million patients worldwide.<sup>1</sup>

#### **Product Characteristics**

Each lot of Octaplas™ is manufactured from pooled plasma from a single ABO group and contains plasma units collected from 630 to 1520 paid US Source Plasma donors.<sup>2</sup> The individual

*\*In this document, "transfusable plasma components" or "plasma" includes Fresh Frozen Plasma (FFP), Plasma Frozen Within 24 Hours After Phlebotomy (PF24), Plasma Frozen Within 24 Hours After Phlebotomy Held At Room Temperature Up To 24 Hours After Phlebotomy (PF24RT24), Liquid Plasma and Thawed Plasma.*

plasma units are thawed and pooled, and after filtration the plasma pool is treated with SD reagents to inactivate enveloped viruses.

Octaplas™ is tested for coagulation Factors II, V, VII, VIII, X and XI, as well as protein C, protein S, alpha<sub>2</sub>-antiplasmin, fibrinogen and ADAMTS13. The content and distribution of plasma proteins in Octaplas™ are comparable to reference ranges for healthy blood donors with two exceptions—protein S and alpha<sub>2</sub>-antiplasmin. These proteins are reduced by the SD treatment; however, levels in the final product are quality controlled to be  $\geq 0.4$  international units (IU)/mL, ie,  $\geq 40\%$  of the normal average. For a more complete description of product characteristics, please refer to the package insert available at <http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/UCM336161.pdf>.<sup>2</sup>

Units of Octaplas™ are 200 mL in volume, in contrast to Fresh Frozen Plasma (FFP) or plasma frozen within 24 hours (PF24) units, which vary from about 200-250 mL, with apheresis units containing as many as 400 to 600 mL.

## **Clinical Indications**

Octaplas™ is approved by the FDA for the following indications:

- Replacement of multiple coagulation factors in patients with acquired deficiencies
  - due to liver disease.
  - undergoing cardiac surgery and liver transplantation.
- Plasma exchange in patients with thrombotic thrombocytopenic purpura (TTP).

Octaplas™ is contraindicated in patients with:

- IgA deficiency.
- Severe deficiency of protein S.
- History of hypersensitivity to FFP or to plasma-derived products including any plasma protein.
- History of hypersensitivity reaction to Octaplas™.

## **Safety Considerations**

### Infectious Agents

Octaplas™ is prepared using an SD procedure that irreversibly disrupts the lipid envelope of enveloped viruses. The package insert indicates that model viruses for hepatitis B virus (HBV) and hepatitis C virus (HCV) are inactivated by  $>5 \log_{10}$  and that human immunodeficiency virus (HIV) is inactivated by  $>6 \log_{10}$ . In addition, input plasma undergoes nucleic acid testing (NAT) for these viruses prior to pooling.<sup>2</sup> Thus, compared to plasma, Octaplas™ should provide enhanced safety against HIV, HBV and HCV infection. It should also provide protection against other enveloped viruses (eg, West Nile virus and dengue virus).

Octaplas™ should not pose risks related to bacteria or parasites because it is sterile-filtered. Furthermore, the product is freeze-thawed and most bacteria and parasites do not survive that

process. However, transmission of nonenveloped viruses by SD-treated pooled plasma and/or derivatives is well recognized, and prevention of such transmission requires testing or alternative inactivation procedures. Octaplas™ contains a specified minimum level of hepatitis A virus and parvovirus B19 antibodies that may help to prevent transmission of these nonenveloped agents through immune neutralization.<sup>2</sup> The product insert contains more complete safety information.<sup>2</sup>

Octaplas™ production uses a ligand affinity column intended to bind and remove prion protein infectivity [PrP<sup>Sc</sup>, the causative agent of Creutzfeldt-Jakob disease (CJD) and variant CJD]. However, the effectiveness of this step for removal of prion infectivity has not been established and there is no product claim for prion safety.

If a new enveloped transfusion-transmitted virus were to enter the blood supply, Octaplas™ offers a theoretical safety benefit compared to other transfusable plasma components. However, concern remains that if a new transfusion-transmitted virus was nonenveloped, it could escape inactivation by the SD process and, as a result of pooling, could infect multiple recipients.

#### Transfusion-Related Acute Lung Injury (TRALI)

Various European hemovigilance systems have not reported any TRALI cases from SD-treated plasma in the 20 years these products have been used, during which time it is estimated that over 7 million units have been transfused.<sup>3</sup> In a study of a previous generation of an Octapharma SD-treated plasma product, no HLA antibody was detectable in 20 batches.<sup>4</sup> Possible explanations for the lack of detectable antibody are: 1) dilution of plasma units with HLA antibody by pooling with HLA antibody-negative plasma units; and/or 2) binding of HLA antibody to soluble HLA antigen in the pool.

#### Toxicity

There is no evidence of toxicity from residual levels of the solvent and detergent [tri(n-butyl)phosphate (TNBP) + octoxynol] in studies provided to the FDA, and no evidence of mutagenicity in vitro or in vivo in studies performed for TNBP. Other adverse effects appear qualitatively similar to those from plasma.<sup>2,5</sup>

#### Allergic Reactions

Allergic transfusion reactions can result from the transfusion of specific plasma proteins in sensitized patients. The most severe reactions occur when IgA is given to IgA-deficient transfusion recipients who have IgA antibodies. Other allergic reactions, which vary from mild urticaria to anaphylactic reactions, are due to specific non-IgA proteins in the transfused plasma. With SD-treated plasma, there may be a theoretical reduction in these non-IgA allergic reactions, because the level of the particular non-IgA protein that provokes the allergic reaction will be diluted by the pooling of plasma during manufacturing.

Hemovigilance data from Finland demonstrated a reduction in allergic reactions following a switch to exclusive use of SD-treated plasma.<sup>6</sup> Additionally, a single center in the United Kingdom reported a lower rate of allergic reactions in TTP patients receiving SD-treated plasma, including patients who had previous allergic reactions to cryosupernatant.<sup>7</sup>

## **Logistical Issues in Using the Product**

The dose of Octaplas™ is the same as for plasma; infusion of 10-15 mL/kg to raise the patient's plasma coagulation factor levels by approximately 15%-25%. When dosed by weight, Octaplas™ may require more units for an equivalent dose, because the volume in each unit may be less than in plasma units. Units should be ABO-compatible.

Once thawed, the product's shelf life is 12 hours if stored refrigerated at 2-4 C or 3 hours if stored at 20-25 C. The tighter range of required temperature control may necessitate a separate refrigerator for storage (eg, as opposed to a refrigerator used to store Red Blood Cell (RBC) units, which has an acceptable temperature range of 1-6 C). The shorter shelf life of Octaplas™ compared to other thawed plasma products should be taken into consideration with regard to inventory control. If not transfused to the originally intended recipient, Octaplas™ units need to be redistributed within 12 hours rather than within 24 hours for FFP, PF24, and PF24RT24 and within 1-5 days for Thawed Plasma. Octaplas™ cannot be refrozen if thawed, and care and attention should be taken to avoid using a product that is cloudy or has deposits.

Transfusion services electing to use Octaplas™ should consider the need to transfuse a greater number of units per patient as compared to other plasma products to achieve a therapeutic dose of coagulation factors. Transfusion services with a high percentage of current plasma wastage should be very proactive in implementing prospective auditing practices to prevent the wastage of Octaplas™. Pricing of Octaplas™ is significantly higher than that of other plasma products; determining an accurate cost-benefit analysis is difficult.<sup>8</sup>

## **Use of Octaplas™ in Special Populations**

The FDA-approved prescribing information for Octaplas™ notes that its efficacy and safety have not been evaluated in pediatric patients, women in labor and delivery, lactating women or geriatric patients.<sup>9</sup> As stated in Octaplas™ prescribing information, it is categorized as Pregnancy category C because “animal reproduction studies have not been conducted with Octaplas™ and it is not known whether Octaplas™ can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.”<sup>9</sup>

Although the product has not been approved for pediatric use, Octapharma has made a commitment to the FDA to conduct post-marketing studies in patients <16 years old who require multiple coagulation factors or therapeutic plasma exchange.<sup>10</sup> At a meeting of FDA's Blood Products Advisory Committee in September 2012, before the approval of Octaplas™ in the United States, the European experience with SD-treated plasma was described.<sup>11</sup> The pediatric experience included use in a small number of neonates (including some undergoing extracorporeal membrane oxygenation), 122 heart surgery patients ≤15 years of age, and 36 pediatric liver transplant patients. No unexpected adverse events were noted.

## **Four-Factor Prothrombin Complex Concentrate**

### **Background**

Patients taking vitamin-K-antagonist (VKA) anticoagulants such as warfarin have reduced levels of functional coagulation Factors II, VII, IX and X. Although highly efficient at reducing the risk of thrombosis, these drugs are associated with an increased risk of bleeding, which is severe enough to require hospitalization in 1% of patients per year and is fatal in 0.3% per year.<sup>12</sup> Although the warfarin-related bleeding can be catastrophic, the bleeding is stoppable. Vitamin K starts to become effective within hours, but it can take more than 24 hours to fully restore vitamin-K-dependent coagulation factors. Frozen plasma and PCCs are the two products that are widely available to replace vitamin-K-dependent clotting factors. Frozen plasma can replace the factors rapidly once infused, but it requires blood group typing, thawing and use of large volumes of fluid – all of which may place the patient at risk for TRALI, transfusion-associated circulatory overload (TACO), and other transfusion reactions. PCCs have been used for years in the treatment of hemophilia, but their use has been expanded to VKA reversal in patients who are either actively bleeding or at high risk of bleeding. Unlike individual donor plasma products, PCC products undergo pathogen reduction and are lyophilized, allowing them to be rapidly reconstituted. Thus, their use can significantly reduce the time to administration.

### **PCC Products Overview**

PCCs are prepared as either a three-factor PCC (Factor II, Factor IX and Factor X) or a four-factor PCC (Factor II, Factor VII, Factor IX and Factor X). There are many FDA-approved three-factor PCCs available in the United States. The three-factor PCCs, however, are FDA approved only for the treatment of hemophilia. The three-factor PCC concentrates are not indicated for reversal of warfarin. There is currently only one FDA-approved four-factor PCC, Kcentra™ (CSL Behring, King of Prussia, PA), but other four-factor PCCs are available outside of the United States (see appendix Tables I and II).

In a Phase IIIb open-label, noninferiority, randomized controlled trial of 216 patients by Sarode and colleagues,<sup>13</sup> Kcentra™ (dosed as per package insert) was compared to FFP dosed at 10-15 mL/kg in patients experiencing major bleeding associated with the use of VKA. All patients in the trial received intravenous vitamin K, and the doses of PCC and the number of units of plasma infused were calculated based on the individual body weight of the patients and international normalized ratio (INR) values. The median administration duration and product volume of PCC were 17 minutes and 99.4 mL vs 148 minutes and 813.5 mL for plasma. Statistically more patients treated with PCC achieved an INR  $\leq$ 1.30 within 30 minutes than did patients in the plasma cohort. Effective hemostasis was achieved in 72.4% of patients receiving four-factor PCC vs 65.4% receiving plasma. Among the patients with visible or musculoskeletal bleeding, 82.6% of those given PCC achieved effective hemostasis at 4 hours compared with 50% in the plasma group. The rates of thromboembolic events (7.8% for PCC and 6.4% for plasma) were comparable, as were the mean number of RBC units transfused and the median hospital length of stay. Five deaths occurred in the plasma group and 10 deaths occurred in the PCC group, one of which was deemed to be treatment-related.<sup>13,14</sup>

### **FDA-Approved Kcentra™ Indications**

Kcentra™ is indicated for the urgent reversal of acquired coagulation factor deficiency induced by VKA therapy in adult patients with 1) acute major bleeding or 2) need for an urgent surgery or other invasive procedure.<sup>15</sup>

## **Kcentra™ Dosing**

The FDA-approved Kcentra™ dose is calculated based on the patient's pretreatment INR, which determines the number of IUs of Factor IX that are multiplied by the patient's body weight in kilograms. The Kcentra™ package insert

(<http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=eee1afb8-324c-42e4-8bf0-f0c9da5e6d42>)<sup>15</sup> contains additional information regarding dose including maximum doses.

Although not approved by the FDA, other dosing strategies for four-factor PCCs have been used.<sup>16-25</sup>

## **Complications, Contraindications and Limitations of Kcentra™<sup>15,25</sup>**

### Complications: Thromboembolic Events and Other Adverse Reactions

A boxed warning regarding fatal and nonfatal arterial and venous thromboembolic events (eg, stroke, pulmonary embolism and deep vein thrombosis) is included in the package insert. This is due at least in part to the fact that patients receiving VKA are already at risk of thromboembolic events, and Kcentra™ reverses their therapeutic effect. The boxed warning also indicates that Kcentra™ has not been studied in – and, therefore, may not be suitable for – patients who have had the following conditions within the previous 3 months: a thromboembolic event, myocardial infarction, disseminated intravascular coagulation (DIC), cerebrovascular incident, transient ischemic attack, unstable angina pectoris or severe peripheral vascular disease. The most common adverse reactions reported within 72 hours of administration in a randomized controlled trial were headache (7.8% of patients), hypotension (4.9%), nausea and vomiting (3.9%) and arthralgia (3.9%). Among various other adverse reactions, intracranial hemorrhage was reported in 2.9% of patients.<sup>15,25</sup>

### Contraindications: Heparin-Induced Thrombocytopenia/DIC/IgA Deficiency/Anaphylactic or Severe Allergic Reactions

Kcentra™ is contraindicated in patients with known heparin-induced thrombocytopenia (since it contains heparin), DIC, or a history of anaphylactic or severe allergic reactions to any of its contents (eg, heparin, Factors II, VII, IX and X; proteins C and S; antithrombin; and human albumin). Kcentra™ is not devoid of IgA and, thus, caution must be used in treating patients with IgA deficiency.<sup>24</sup>

### Limitations

Because Kcentra™ is prepared from human pooled plasma, it poses the theoretical risk of transmitting infectious agents that might survive the extraction and viral attenuation steps of the manufacturing process (eg, prions and some viruses). The safety and efficacy of Kcentra™ in the pediatric population have not been reported as of the time this information piece was prepared.

## **Alternatives to Kcentra™**

Plasma preparations, including FFP, PF24, Thawed Plasma and Octaplas™, are the alternatives to Kcentra™ for the urgent reversal of warfarin therapy in adult patients with acute major bleeding (appendix Table II).<sup>25</sup> Although vitamin K<sub>1</sub> is also FDA-approved for reversing the effects of VKA, its effects have a delayed onset. Therefore, it is more appropriately used as an adjunct to Kcentra™ or plasma in the setting of acute major bleeding, not as a substitute. Other PCC preparations are not indicated; they have insufficient or unknown content of Factor VII

and/or are not FDA approved for urgent warfarin reversal in the United States. Recombinant Factor VIIa lacks Factors II, IX and X and is also not FDA approved for VKA reversal. The combined use of three-factor PCC or recombinant Factor VIIa with plasma, or each other, has been reported, but the safety and efficacy of those factor preparations in such combinations have not been adequately assessed and do not have FDA approval. It should be noted that only plasma and vitamin K<sub>1</sub> are currently FDA approved for the reversal of VKA in other, less urgent, clinical settings.

### **Summary**

Octaplas™ and Kcentra™ are FDA-approved plasma alternatives. Both products have specific indications and contraindications and, as with all blood products, carry risks. The treatment risks must be balanced against the risks of not being treated.

Octaplas™ is a pathogen-reduced, sterile, pyrogen-free, frozen solution of SD-treated pooled human plasma. Its most notable safety advantages are reduction of the risk of transfusion-transmission of enveloped viruses (including HIV and HCV and HBV, which are currently rare) and the reduction in the incidence of TRALI reactions (when compared to programs that still transfuse plasma from multiparous women who have not undergone HLA antibody screening). However, it would not offer protection against new nonenveloped viruses that enter the blood supply and potentially increases the risk of transmitting such viruses due to pooling and the resulting exposure of multiple recipients to the plasma from an infected donor.

As an alternative to plasma, the content and distribution of plasma proteins is comparable to reference ranges for healthy blood donors with two exceptions—protein S and alpha<sub>2</sub>-antiplasmin. These proteins are affected by the SD treatment, so levels in the final product are quality controlled to be  $\geq 0.4$  IU/mL, ie,  $\geq 40\%$  of the normal average. Octaplas™ is FDA approved for replacement of multiple coagulation factors in patients with acquired deficiencies due to liver disease or patients undergoing cardiac surgery and liver transplantation, as well as plasma exchange in patients with TTP. However, there are significant differences in storage time and storage temperature, as well as possible variations in unit volume, of Octaplas™ compared to other plasma products, which may result in operational differences for transfusion services. There are also cost differences between Octaplas™ and other plasma products.

The four-factor PCC, Kcentra™, is an acceptable alternative to plasma for VKA reversal in adult patients with acute major bleeding or in need of urgent surgery or other invasive procedure. Kcentra™ reduces INR and increases vitamin-K-dependent factor levels more rapidly than plasma, does so in a smaller volume, and its hemostatic efficacy is at least comparable to that of plasma. However, contraindications and exclusion criteria should be carefully considered prior to selecting Kcentra™ for VKA reversal; cost may also be a relevant issue. Practitioners should stay informed regarding the results of post-marketing surveillance of Kcentra™, in case unexpected adverse events emerge following its more widespread use.

## References

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## Appendix

**Table I: Most Common Indications for PCC Products Available Internationally  
(Information Derived from Package Inserts)**

<b>Product</b>	<b>Most Common Indication</b>
Beriplex (same formulation as Kcentra™, Confidex)	Treatment and perioperative prophylaxis of bleeding in acquired deficiency of the prothrombin complex coagulation factors, such as deficiency caused by treatment with vitamin K antagonists, or in case of overdose of vitamin K antagonists, when rapid correction of the deficiency is required. Treatment and perioperative prophylaxis of bleeding in congenital deficiency of any of the vitamin-K-dependent coagulation factors when purified specific coagulation factor products are not available.
Cofact	Treatment of bleeding and perioperative prophylaxis of bleeding in acquired deficiency of the prothrombin complex coagulation factors, such as deficiency caused by treatment with vitamin K antagonists, or in case of overdose of vitamin K antagonists, when rapid correction of the deficiency is required. Treatment of bleeding and perioperative prophylaxis in congenital deficiency of any of the vitamin-K-dependent coagulation factors when purified specific coagulation product is not available.
Kaskadil	Treatment of bleeding and perioperative prophylaxis of bleeding in acquired deficiency of the prothrombin complex coagulation factors, such as deficiency caused by treatment with vitamin K antagonists, or in case of overdose of vitamin K antagonists, when rapid correction of the deficiency is required.
Kcentra™	Urgent reversal of acquired coagulation factor deficiency induced by vitamin-K-antagonist therapy in adult patients with 1) acute major bleeding or 2) need for an urgent surgery or other invasive procedure.
Octaplex	Treatment of bleeding and perioperative prophylaxis of bleeding in acquired deficiency of the prothrombin complex coagulation factors, such as deficiency caused by treatment with vitamin K antagonists, or in case of overdose of vitamin K antagonists, when rapid correction of the deficiency is required. Treatment of bleeding and perioperative prophylaxis in congenital deficiency of the vitamin-K-dependent coagulation Factors II and X when purified specific coagulation factor product is not available.
PPSB / Human Prothrombin Complex	Treatment of deficiencies of coagulation Factors II, VII, IX and X, including hemophilia B; anticoagulant overdose, vitamin K deficiency; coagulopathy caused by liver diseases; prolonged prothrombin time prior to surgery; bleeding of hemophilia A with anti-VIII; reversal of hemorrhage caused by warfarin anticoagulant.

**Table II: Four-Factor Prothrombin Complex Concentrate Products Available in Select Countries Worldwide**

<b>Country</b>	<b>Products Available</b>
Algeria, Tunisia	Prothromplex Total, Baxter
Australia	Beriplex, CSL Behring
Austria and Germany	Beriplex P/N, CSL Behring Octaplex, Octapharma Prothromplex Total, Baxter
Brazil	Beriplex, CSL Behring Octaplex, Octapharma Prothromplex-T, Baxter
Canada	Beriplex P/N, CSL Behring Octaplex, Octapharma
China	Human Prothrombin Complex, HUALAN BIO  PPSB, Shanghai RAAS Blood Products Co Ltd
France	Beriplex, CSL Behring Kaskadil, LFB Octaplex, Octapharma
Netherlands	Beriplex, CSL Behring Cofact, Sanquin Octaplex, Octapharma
Switzerland	Beriplex P/N, CSL Behring Octaplex, Octapharma Prothromplex NF, Baxter
United Kingdom	Beriplex, CSL Behring Octaplex, Octapharma
United States	Kcentra™ (aka Beriplex, Confidex), CSL Behring

**Table III: Comparison of Vitamin-K-Antagonist (VKA) Reversal Options**

<b>Characteristic</b>	<b>Four-Factor PCC</b>	<b>Plasma</b>	<b>Vitamin K<sub>1</sub></b>
Standardized Factor Content	Yes	No; factor content is variable and unquantified	N/A; vitamin K <sub>1</sub> acts indirectly by serving as a co-factor in the $\gamma$ -carboxylation of Factors II, VII, IX and X, which is required for their function
Preparation Time	Minimal; for reconstitution in diluent	Delays possible due to thaw time of plasma, if frozen product is used, and for ABO typing of patient, if type-specific plasma is administered	Minimal; for dilution in intravenous (IV) solution
Typical Volume per Treatment*	About 100 mL, depending on dose	About 700-1200 mL (10-15 mL/kg)	Typically 50 mL (for a 1-10 mg/kg IV dose)
Infusion Duration	About 15-20 minutes (not to exceed 8.4 mL/minute or $\approx$ 210 units/minute, per package insert)	Variable; typically $\geq$ 1-2 hours; depends on volume of plasma infused and rate of infusion; infusion rate may be limited by patient's ability to tolerate the added volume	About 20-30 minutes for IV infusion (not to exceed 1 mg/minute, per package insert)
Onset of Action	Upon completion of infusion, ie, about 15-20 minutes	Upon completion of infusion, which depends on volume of plasma and rate of infusion	Detectable shortening of international normalized ratio by 2-4 hours after IV administration; full effect not seen until $\geq$ 24 hours

Contraindicated in Patients with Recent Thrombotic or Thromboembolic Events	Yes	No	No
Cost	High	Intermediate	Minimal
Repeat Infusion	Not recommended; co-administration of vitamin K <sub>1</sub> prolongs duration of VKA reversal	Possible, as needed; co-administration of vitamin K <sub>1</sub> may avoid need for additional transfusion	Possible, as needed
Risk of Thromboembolic Events Due to VKA Reversal	Yes	Yes	Theoretical
Other Adverse Effects <sup>+</sup>	Allergic reactions to product constituents; theoretical infectious risk; theoretical risk of heparin-induced thrombocytopenia	Allergic and other transfusion reactions, such as transfusion-related acute lung injury and transfusion-associated circulatory overload; infectious risk	Rare anaphylactoid reactions during IV infusion; possible refractoriness to resumption of VKA with use of high doses

\* Volume of four-factor PCC represents the median of 98 patients treated for acute major bleeding, as described in reference 4; the median (range) of plasma transfused per patient in reference 4 was 814 mL (400-1525 mL).

<sup>+</sup> Only selected adverse effects are listed. See the relevant package insert for a description of additional adverse effects of Kcentra™ and vitamin K<sub>1</sub>, and see reference 25 for other untoward effects of plasma.