Four-factor prothrombin complex concentrate side-by-side comparison

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Executive Summary

Introduction

Despite the introduction of direct-acting oral anticoagulants (DOACs) and the preference for use of DOACs for prevention and treatment of thrombosis in disease states such as venous thromboembolism and atrial fibrillation, certain clinical situations still favor the use of vitamin K antagonists (VKAs), including extremes of weight, severe renal impairment, presence of antiphospholipid syndrome, and prosthetic heart valves. Because VKAs reduce the synthesis of vitamin K-dependent clotting factors II, VII, IX, and X, patients treated with VKAs are at an elevated risk for experiencing minor and life-threatening bleeding. In cases of major bleeding or urgent/emergent procedures, rapid reversal of the anticoagulant effect is desired.

VKA reversal may be achieved by various strategies, including intravenous vitamin K, fresh frozen plasma (FFP), and prothrombin complex concentrates (PCCs). The administration of vitamin K does not result in immediate correction of coagulopathy; therefore, in situations where rapid reversal is essential, administration of vitamin K must be accompanied by a strategy that replaces vitamin K-dependent clotting factors (eg, FFP or PCCs). Historically, FFP was given for urgent VKA reversal, but most contemporary guidelines preferentially recommend PCCs for reversal of major bleeding because of operational and clinical advantages. Very few guidelines address considerations for reversal prior to emergent or urgent surgery.

With the approval of a second VKA-specific reversal agent in July 2023, two 4F-PCCs (Kcentra, CSL Behring; Balfaxar, Octapharma) are FDA approved for VKA reversal in adult patients with need for urgent surgery or other invasive procedures. Kcentra is additionally approved for urgent reversal of warfarin therapy in adult patients with acute major bleeding.

Efficacy and Safety of 4F-PCCs

The approval of Balfaxar was based on data from a head-to-head phase 3 trial. The prospective, randomized study evaluated the noninferiority of Balfaxar to Kcentra for rapid reversal of VKA-induced coagulopathy in 208 adult participants with an INR ≥2.0 who were hospitalized for urgent surgery that carried a significant risk of bleeding. Noninferiority was met at the pre-planned interim analysis with effective hemostasis achieved in 88 of 93 (94.6%) vs. 86 of 92 (93.5%) Balfaxar- and Kcentra-treated participants, respectively (proportion difference (98% CI) of 1.1% (-9.2 to 11.5%)). At end of study, the difference between Balfaxar and Kcentra in the proportion of participants who achieved hemostatic efficacy was 0.1% (95% CI, -8 to 8%). Other secondary outcomes, including achievement of INR ≤1.5 within 30 minutes of infusion's end and change in mean activities of vitamin K-dependent coagulation factors were similar in both groups.

Similar proportions of Balfaxar and Kcentra-treated patients experienced treatment-emergent and drug-related adverse events; however, a greater number of Balfaxar-treated patients experienced SAEs (13 (12.4%) vs. 6 (5.8%) for Kcentra). Only 1 serious adverse event was considered related to drug administration in the Balfaxar treatment group. Serious adverse event-associated fatal outcomes occurred in 5 patients vs. 1 patient in the Balfaxar and Kcentra treatment groups, respectively. Based on standardized MedDRA queries, numerically more thromboembolic events occurred in the Balfaxar treatment group compared with the Kcentra treatment group (3 vs.0 events, respectively). The study was not powered to determine if the differences in thromboembolic events and mortality between the 4F-PCC treatment groups are true safety differences; therefore, Octapharma is required to conduct a post-marketing observational study to assess the risk of thromboembolic events and overall mortality.

Summary

Balfaxar joins Kcentra as the second 4F-PCC indicated for reversal of VKA-induced coagulopathy. The availability of an additional PCC may help prevent future shortages and increase consumer choice. Based on results from the head-to-head trial, Balfaxar and Kcentra appear to be similarly effective in reversing coagulopathy in patients undergoing surgery. While more thromboembolic events occurred in the Balfaxar treatment group compared with the Kcentra group, the overall incidence of events was low, and the trial was underpowered to detect safety signals. Future data from real world cohorts will be necessary to determine if Balfaxar is associated with a higher occurrence of thromboembolic events. Until additional safety data is available, acquisition cost will likely be the primary consideration for formulary addition.

Four-factor prothrombin complex comparison side-by-side comparison

	Generic name (brand name)	
	Prothrombin complex concentrate, human-lans (Balfaxar)[1]	**Prothrombin complex concentrate, human (Kcentra)**[2]
Manufacturer	Octapharma	CSL Behring
Approval date	2023	2013
FDA-approved indications[a]	Urgent reversal of acquired coagulation factor deficiency induced by VKA (eg, warfarin) therapy in adult patients with: • Need for an urgent surgery/invasive procedure	Urgent reversal of acquired coagulation factor deficiency induced by VKA (eg, warfarin) therapy in adult patients with: • Acute major bleeding (or) • Need for an urgent surgery/invasive procedure
Off-label indications[3]	• Life-threatening bleeding associated with direct factor Xa inhibitor or direct thrombin inhibitor • Perioperative coagulopathy • Reversal of oral direct factor Xa inhibitor in patients who require urgent procedure	
Dosage, preparation, and administration		
Dose (expressed as units of Factor IX)	**Pre-treatment INR**	
	2 to <4	4 to 6 / > 6
Units/kg of body weight (up to 100 kg)	25	35 / 50
Maximum dose	NTE 2500	NTE 3500 / NTE 5000
Preparation and reconstitution	• Provided with a transfer device (Nextaro) for reconstitution of lyophilized powder in diluent (sWFI). See PI for specific instructions for reconstitution. • Product reconstitutes quickly (1-5 min) at room temperature.	• Provided with a transfer device (Mix2Vial) for reconstitution of lyophilized powder in 20 mL (nominal potency 500-unit kit) or 40 mL (nominal potency 1000-unit kit) of diluent (sWFI). See PI for specific instructions for reconstitution.
Administration	• Administer through a separate infusion line. Infusion line may be flushed with normal saline before and after administration. • Withdraw reconstituted contents into a syringe and attach syringe to a suitable administration set. • Administer by intravenous infusion at a rate of 0.12 mL/kg/min (≅ 3 units/kg/min), up to a maximum of 8.4 mL/min (≅ 210 units/min). • No blood should enter the syringe, as there is a possibility of fibrin clot formation.	• Administer through a separate infusion line. • Withdraw reconstituted contents into a syringe and attach syringe to a suitable administration set. • Administer by intravenous infusion at a rate of 0.12 mL/kg/min, up to a maximum of 8.4 mL/min (≅ 210 units/min). • No blood should enter the syringe, as there is a possibility of fibrin clot formation.
Dosage forms and strengths		
Lyophilized powder	• White to ice blue	• White or slightly colored

	Generic name (brand name)					
	Prothrombin complex concentrate, human-lans (Balfaxar)[1]			**Prothrombin complex concentrate, human (Kcentra)[2]**		
	• Potency defined by Factor IX content. Actual units of potency for each coagulation factor (Factors II, VII, IX and X), and Proteins C and S are stated on the carton. ○ 500-unit vial (range: 400-640 Factor IX units/vial) ○ 1000-unit vial (range: 800-1280 Factor IX units/vial)			• Potency defined by Factor IX content. Actual units of potency for each coagulation factor (Factors II, VII, IX, and X), and Proteins C and S are stated on the carton. ○ 500-unit vial (range: 400-620 Factor IX units/vial) ○ 1000-unit vial (range: 800-1240 Factor IX units/vial)		
Contraindications	• Known anaphylactic or severe systemic reactions to product or any components of product • Known allergy to heparin or history of HIT • IgA deficient patients with known antibodies against IgA			• Known anaphylactic or severe systemic reactions to product or any components of product. • Patients with DIC • Patients with known HIT		
Warnings/Precautions	• Discontinue infusion if allergic or anaphylactic-type reactions occur and initiate appropriate treatment. • Monitor patients for signs and symptoms of TE. Product may not be suitable in patients with thrombotic or TE in the prior 3 mos. • Made from human plasma; therefore, may carry the risk of transmitting infectious agents.					
Adverse reactions	≥ 3% of subjects: procedural pain, wound complications, asthenia, anemia, dysuria, procedural vomiting, and catheter-site related reactions.			≥ 2.8% of subjects: headache, nausea/vomiting, hypotension, and anemia.		
Special Populations						
Pregnancy, lactation	No information; use only if necessary					
Description						
Source	US Source Plasma			US Source Plasma		
Virus reduction steps	Solvent/detergent virus inactivation; nanofiltration			Ion exchange chromatography; heat treatment precipitation; adsorption; virus filtration		
Composition	**Ingredient**	**Potency range for 500 units**	**Potency range for 1000 units**	**Ingredient**	**Potency range for 500 units**	**Potency range for 1000 units**
	Total protein			Total protein	120-280 mg	240-560 mg
	Factor II	340-500 units	680-1000 units	Factor II	380-800 units	760-1600 units
	Factor VII	240-400 units	480-800 units	Factor VII	200-500 units	400-1000 units
	Factor IX	400-640 units	800-1280 units	Factor IX	400-620 units	800-1240 units
	Factor X	300-540 units	600-1080 units	Factor X	500-1020 units	1000-2040 units
	Protein C	320-560 units	640-1120 units	Protein C	420-820 units	840-1640 units
	Protein S	240-600 units	480-1200 units	Protein S	240-680 units	480-1360 units

	Generic name (brand name)					
	Prothrombin complex concentrate, human-lans (Balfaxar)[1]			**Prothrombin complex concentrate, human (Kcentra)[2]**		
	Heparin	80-384 units	160-768 units	Heparin	8-40 units	16-80 units
	Antithrombin III	None	None	Antithrombin III	4-30 units	8-60 units
	Human albumin	None	None	Human albumin	40-80 mg	80-160 mg
	Sodium chloride	None	None	Sodium chloride	60-120 mg	120-240 mg
	Sodium citrate	16.8-23.4 mmol/L		Sodium citrate	40-80 mg	80-160 mg
	HCl, NaOH	None	None	HCl, NaOH	Small amounts	Small amounts
Mechanism of action	Provides a rapid increase in plasma levels of the vitamin K-dependent coagulation factors (FII, FVII, FIX, FX) and antithrombotic proteins C and S (collectively known as prothrombin complex). Prothrombin complex can temporarily correct the coagulation defect of patients with deficiency of ≥ 1 of these factors.					
How supplied	Package containing (no components made from natural latex): • SDV, 500 units in 20 mL or 1000 units in 40 mL • Vial of diluent (sWFI) • Transfer device			Kit containing (no components made from natural latex): • SDV, 500 or 1000 units • Vial (20 mL or 40 mL) of diluent (sWFI) • Transfer set • Alcohol swab		
Storage and Handling						
Prior to reconstitution	• Store between 2-25°C (36-77°F), this includes room temperature. Do not freeze. • Stable for 36 mos past the date of manufacture, up to the expiration date on the carton and vial labels. • Store vial in the original carton to protect from light.					
After reconstitution	• Use the solution immediately after reconstitution; however, the reconstituted solution can be stored for up to 8 h at room temperature (20-25°C). • Discard partially used vials.			• Use within 4 h following reconstitution • May be stored at 2-25° C but should be warmed to 20-25° C prior to administration. Do not freeze. • Discard partially used vials.		
Guidelines						
Major bleeding[4-10]	**American College of Cardiology Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants** • Major bleeding: Administer 4F-PCC in combination with vitamin K. If 4F-PCC is not available, administer plasma. **American College of Chest Physicians - Managing bleeding with VKAs in the context of AF treatment** • Major bleeding: Where bleeding is severe or life-threatening, immediate reversal of anticoagulant effect is required. Administration of IV vitamin K, FFP, and PCCs should be considered. PCCs are preferred over FFP due to a higher concentration of clotting factors and less volume.					

	American College of Gastroenterology-Canadian Association of Gastroenterology Guideline – Management of VKA in context of acute GI bleeding • Acute GI bleeding: For patients on warfarin who are hospitalized or under observation with acute GI bleeding, we suggest PCC administration compared with FFP administration (conditional recommendation, very low certainty of evidence). **American Heart Association/American Stroke Association – Guideline for the management of spontaneous ICH** • ICH: Patients with ICH whose INR is elevated because of VKA should have their VKA withheld, receive therapy to replace vitamin K-dependent factors and correct the INR, and receive IV vitamin K (Class I; Level of Evidence C). PCCs may have fewer complications and correct the INR more rapidly than FFP and might be considered over FFP (Class IIb; Level of Evidence B). **American Society for Gastrointestinal Endoscopy** • Urgent and Emergent Endoscopy: Recommend either (1) 4F-PCC and vitamin K or (2) FFP be given for life-threatening GI bleeding in patients on warfarin anticoagulant therapy (Moderate quality). **American Society of Hematology Guidelines – Managing bleeding with VKAs in the content of VTE treatment** • Major bleeding: For patients with life-threatening bleeding during VKA treatment of VTE who have an elevated INR, the ASH guideline panel suggests using 4F-PCC as an addition to cessation of VKA and IV vitamin K (conditional recommendation based on very low certainity in the evidence about effects). **Neurocritical Care Society and Society of Critical Care Medicine – Guideline for reversal of antithrombotics in ICH** • ICH: In addition to vitamin K, 3 or 4F-PCC are recommended over FFP to patients with VKA-associated ICH and INR ≥ 1.4 (strong recommendation, moderate quality evidence). The use of 4F-PCC is recommended over 3F-PCC (conditional recommendation, low quality evidence).
Perioperative management[11,12]	**American College of Surgeons Guidelines – Perioperative Management of Antithrombotic Medication (with attention to considerations in the nonelective setting)** • Perioperative management, nonelective surgery/intervention: Recommend the administration of vitamin K and 4F-PCC to patients with an elevated INR secondary to warfarin who are actively bleeding and/or require urgent surgery. **American College of Chest Physicians Clinical Practice Guideline – Perioperative Management of Antithrombotic Therapy** Perioperative management, non-urgent, elective surgery: Individualized, patient-centric recommendations that are anchored on the assessment of patients' risk for thromboembolism and risk for surgery/procedure-related bleeding. Recommended strategies include anticoagulant interruption (based on risk stratification for procedural bleed risk) and heparin bridging (based on thromboembolic risk).

Clinical Studies (head-to-head only)

Reference/study design	N	Patient Selection	Treatment Intervention	Significant Outcomes		
				Primary	**Secondary**	**Safety**
LEX-209 Study (NCT02740335)[13,14] Multicenter, randomized, double-blind, noninferiority phase 3 trial	208	**Inclusion**: • ≥ 18 y • On VKA therapy • Urgent surgery with a significant bleed risk (≥ 50 mL)	4F-PCC dose, based on body weight and baseline INR prolongation: • 2 to <4: 25 IU/kg • 4 to 6: 35 IU/kg • >6: 50 IU/kg	Prespecified NIM: -15% Hemostatic efficacy, dichotomized, assessed by IEAB	Patients with INR ≤ 1.5 • Balfaxar: 78.1% • Kcentra: 71.8% Difference (95% CI): 0.063 (-0.056, 0.181)	TEAEs • Balfaxar: 81.9% • Kcentra: 77.7% TEs Balfaxar: 3 (2.9%), 1

		• VKA withdrawal and vitamin K insufficient for reversal • INR ≥ 2.0	Infusion rate: 0.12 mL/kg/min (≅ 3 IU/kg/min) up to 8.4 mL/min (≅ 210 IU/min) **Balfaxar** (n = 105); Median dose: 25 IU/kg (range: 16-50 IU/kg) **Kcentra** (n = 103); Median dose: 25 IU/kg (range: 15-50 IU/kg)	Interim analysis: • Balfaxar: 88/93 (94.6%) • Kcentra: 86/92 (93.5%) Difference (98% CI): 1.1% (-9.2, 11.5%) Final analysis: • Balfaxar: 99/105 (94.3%) • Kcentra: 97/103 (94.2%) Difference (95% CI): 0.1% (-8, 8.2%)	RBC during surgery (volume) • Balfaxar: 3.8% (5.99 mL/kg) • Kcentra: 2.9% (5.76 mL/kg)	considered possibly related • Kcentra: 0 Deaths • Balfaxar: 5 (4.8%) • Kcentra: 1 (1%) No death was considered related to study treatment

Summary of evidence

Introduction: Despite the introduction of direct-acting oral anticoagulants and the preference for use of DOACs for prevention and treatment of thrombosis in disease states such as venous thromboembolism and atrial fibrillation, certain clinical situations still favor the use of VKAs, including extremes of weight, severe renal impairment, presence of antiphospholipid syndrome, and prosthetic heart valves.[15] Because VKAs reduce the synthesis of vitamin K-dependent clotting factors II, VII, IX, and X, patients treated with VKAs are at an elevated risk for experiencing minor and life-threatening bleeding. In orally anticoagulated patients, major bleeds occur at an annual frequency of 1 to 6% and per annum, it is estimated that approximately 10% of orally anticoagulated patients will undergo an invasive procedure, for which 1 in 10 procedures will involve an urgent or emergent intervention.[16,17] In cases of major bleeding or urgent/emergent procedures, rapid reversal of the anticoagulant effect is desired.

VKA reversal may be achieved by various treatment approaches, including IV vitamin K, FFP, and PCCs. The administration of vitamin K does not result in immediate correction of coagulopathy; therefore, in situations where rapid reversal is essential, administration of vitamin K must be accompanied by a strategy that replaces vitamin K-dependent clotting factors (eg, FFP or PCCs).[4] Historically, FFP was given for urgent VKA reversal, but most contemporary guidelines preferentially recommend PCCs for reversal of major bleeding because of operational and clinical advantages.[4-10] Some of the advantages of PCCs are shorter pre-administration time, faster administration, lower infusion volume, lower risk of pathogen transmission, and more rapid INR correction.[4] While most guidelines provide recommendations for VKA reversal for major bleeding or for elective interventions,[4-10,12] very few address considerations for reversal in the non-elective perioperative setting. The American College of Surgeons[11] recommends that 4F-PCC and vitamin K be given to patients with an elevated INR secondary to warfarin who require urgent surgery based on the results of a head-to-head trial that demonstrated more rapid correction of INR with 4F-PCC compared with FPP in patients needing urgent surgical or invasive interventions.[18] A recent systematic review and network meta-analysis conducted by members of the Clinical Transfusion Medicine Committee from the Association for the Advancement of Blood and Biotherapies, concluded that PCCs may have an efficacy advantage over FFP in time to reversal of INR and achievement of hemostasis, but the certainity of evidence is low.[19]

4F-PCCs: In 2013, the FDA approved the first VKA-specific reversal agent, 4F-PCC (Kcentra, CSL Behring) for urgent reversal of warfarin therapy in adult patients with acute major bleeding. This indication was later expanded to include urgent reversal of VKA therapy in adult patients needing an urgent surgery or other invasive procedure.[2] In July 2023, a second 4F-PCC (Balfaxar, Octapharma) was FDA approved for VKA reversal in adult patients with need for urgent surgery/invasive procedure.[1] Although not FDA approved for treatment of acute major bleeding, Balfaxar has been available in Germany since 2003 and subsequently licensed in 87

additional countries; therefore, multiple studies, including a head-to-head comparison against FFP, demonstrate safety and efficacy for reversal of VKA-induced coagulopathy in adults with an acute major bleed.[14,20]

Balfaxar is a lyophilized, nonactivated 4-factor concentrate produced from human plasma obtained from US donors. Satisfactory viral reduction is achieved through the dedicated steps of solvent/detergent treatment and nanofiltration. It contains vitamin K-dependent coagulation factors II, VII, IX, and X and the anticoagulation proteins C and S. Product excipients include heparin and sodium citrate.[1] Unlike Kcentra, it does not contain human albumin and antithrombin III.[1,2]

Octapharma submitted data from a head-to-head phase 3 trial (LEX-209; NCT02740335) to support Balfaxar licensure. Results from the study are available in abstract form only.[13] Briefly, the prospective, randomized study evaluated the noninferiority of Balfaxar to Kcentra for rapid reversal of VKA-induced coagulopathy in 208 adult participants with an INR ≥2.0 who were hospitalized for urgent surgery that carried a significant risk of bleeding (≥ 50 mL expected blood loss in normal coagulation state). In both groups, patients received a single IV 4F-PCC dose of 25, 35, or 50 IU/kg body weight based on 3 standardized tiers of baseline INR prolongation. Balfaxar was deemed noninferior if the proportion of subjects who achieved effective hemostasis at the end of the surgery, assessed on a 4-point hemostatic efficacy scale, was not lower than 15% of that achieved within the Kcentra group. Noninferiority was met at the pre-planned interim analysis with effective hemostasis achieved in 88 of 93 (94.6%) vs. 86 of 92 (93.5%) Balfaxar- and Kcentra-treated participants, respectively (proportion difference (98% CI) of 1.1% (-9.2 to 11.5%)). At end of study, the difference between Balfaxar and Kcentra in the proportion of participants who achieved hemostatic efficacy was 0.1% (95% CI, -8 to 8%). Other secondary outcomes, including achievement of INR ≤1.5 within 30 minutes of infusion's end and change in mean activities of vitamin K-dependent coagulation factors were similar in both groups.[13,14]

Similar proportions of Balfaxar and Kcentra-treated patients experienced treatment-emergent (81.9% vs. 77.7%, respectively) and drug-related adverse events (both 1.0%); however, a greater number of patients experienced a SAE in the Balfaxar treatment group (13 (12.4%) vs. 6 (5.8%) for Kcentra). Only 1 SAE was considered related to drug administration in the Balfaxar treatment group. SAE-associated fatal outcomes occurred in 5 patients vs. 1 patient in the Balfaxar and Kcentra treatment groups, respectively. Investigators did not attribute any of the deaths to factor administration. Based on standardized MedDRA queries, numerically more thromboembolic events occurred in the Balfaxar treatment group compared with the Kcentra treatment group (3 (2.9%) vs. 0, respectively) of which 1 event in 1 subject was deemed possibly causally related to Balfaxar. The study was not powered to determine if the differences in thromboembolic events and mortality between the 4F-PCC treatment groups are true safety signals; therefore, Octapharma is required to conduct a post-marketing observational study to assess the risk of thromboembolic events and overall mortality.[13,14]

In addition to the commitment to conduct a post-marketing observational study, Octapharma is currently recruiting participants for LEX-210 (NCT04867837), a study that evaluates the use of low or high-dose Balfaxar in patients experiencing acute major bleeding while on anti-factor Xa therapy and LEX-211 (NCT05523297), a study that compares Balfaxar with FFP in adult cardiac surgery patients. For health systems that use 4F-PCC for anti-factor Xa reversal, the ongoing LEX-210 study may help to clarify the optimal 4F-PCC dose but will not resolve uncertainties about choice of reversal agent for anti-factor Xa-induced coagulopathy.

Summary: Balfaxar joins Kcentra as the second 4F-PCC indicated for reversal of VKA-induced coagulopathy. The availability of an additional PCC may help prevent future shortages and increase consumer choice. Based on results from the head-to-head trial, Balfaxar and Kcentra appear to be similarly effective in reversing coagulopathy in patients undergoing surgery. While more thromboembolic events occurred in the Balfaxar treatment group compared with the Kcentra group, the overall incidence of events was low, and the trial was underpowered to detect safety signals. Future data from real world cohorts will be necessary to determine if Balfaxar is associated with a higher occurrence of thrombotic events. Until additional safety data is available, acquisition cost will be the primary consideration for formulary addition.

Footnote: [a]Data from the Vizient Clinical Data Base for July 2021 through June 2023 suggests that 1% of encounters with a surgical diagnosis-related group and a diagnosis (eg, VTE, AF, etc) with an indication for an oral anticoagulant, received vitamin K and 4F-PCC.

Abbreviations: AF: atrial fibrillation; CI: confidence interval; DIC: disseminated intravascular coagulation; FFP: fresh frozen plasma; 4F-PCC: Four factor prothrombin complex concentrate; GI: gastrointestinal; HIT: heparin induced thrombocytopenia; ICH: intracranial hemorrhage; IEAB: independent efficacy assessment board; INR: international normalized ratio; IU: international units; IV: intravenous; NIM: noninferiority margin; NTE: not to exceed; PCC: prothrombin complex concentrate; PI: package insert; RBC: red blood cell; sWFI: sterile water for injection; SDV: single-dose vial; TE: thromboembolic events; TEAEs: treatment emergent adverse events; VKA: vitamin K antagonists; VTE: venous thromboembolism

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