Formulary Drug Reviews

Prothrombin Complex Concentrate

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Generic Name:	Prothrombin Complex Concentrate (Human)
Proprietary Name:	Kcentra (CSL Behring LLC)
Approval Rating:	Biologics License Application Approved
Therapeutic Class:	Prothrombin Complex Concentrates
Similar Drugs:	Fresh Frozen Plasma, Factor IX Complex
Sound- or Look-Alike Names:	Three-Factor Prothrombin Complex Concentrates

INDICATIONS

Prothrombin complex concentrate (human) is indicated for the urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist (eg, warfarin) therapy in adult patients with acute major bleeding.¹ It is not indicated for use in patients without acute major bleeding.¹

Strategies to reverse the effects of vitamin K antagonists include interruption of therapy, administration of vitamin K, and administration of fresh frozen plasma or prothrombin complex concentrates. Fresh frozen plasma carries a risk of infection transmission, has been associated with volume overload, requires cross-matching, and takes time to thaw and administer.² Three- and 4-factor prothrombin complex concentrates do not require cross-matching, are virally inactivated, are not associated with volume overload, and can be quickly infused. Three-factor prothrombin complex concentrates (*Bebulin VH* from Baxter and *Profilnine SD* from Grifols) contain only low levels of factor VII and are only US Food and Drug Administration (FDA)-approved for the prevention and control of bleeding in patients with factor IX deficiency (hemophilia B).³

CLINICAL PHARMACOLOGY

Prothrombin complex concentrate (human) is a purified, heat-treated, nanofiltered, preservative-free, lyophilized nonactivated 4-factor concentrate prepared from human plasma obtained from subjects in the United States. It contains vitamin K-dependent coagulation factors II, VII, IX, and X and the

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Table 1. Composition per vial of prothrombin complex concentrate 500 units¹

Ingredient	Quantity
Total protein	120 to 280 mg
Factor II	380 to 800 units
Factor VII	200 to 500 units
Factor IX	400 to 620 units
Factor X	500 to 1,020 units
Protein C	420 to 820 units
Protein S	240 to 680 units
Heparin	8 to 40 units
Antithrombin III	4 to 30 units
Human albumin	40 to 80 mg
Sodium chloride	60 to 120 mg
Sodium citrate	40 to 80 mg
Hydrochloric acid	Small amounts
Sodium hydroxide	Small amounts

antithrombotic proteins C and S. The product excipients include human antithrombin III, heparin, human albumin, sodium chloride, and sodium citrate; heparin and antithrombin are added to minimize thrombosis risk.^{1,2} Approximate quantities of each ingredient are listed in **Table 1**; precise contents of the coagulant and antithrombotic proteins are listed on the product carton.¹

In patients with an acquired coagulation factor deficiency due to vitamin K antagonist treatment, the administration of prothrombin complex concentrate can rapidly increase plasma levels of the vitamin K-dependent coagulation factors II, VII, IX, and X and the antithrombotic proteins C and S.¹ In controlled trials, the median international normalized ratio (INR) dropped from above 3 prior to treatment to 1.2 by 30 minutes after the start of a prothrombin complex concentrate infusion and 2.4 at 30 minutes after the start of a plasma infusion. Reductions were greater with the prothrombin complex concentrate than plasma through 12 hours (see **Table 2**).¹ In studies using blood samples from warfarin-treated patients, INR was restored with 3- and 4-factor prothrombin complex concentrate in samples with INR of 3, but it was more effectively corrected with the 4-factor prothrombin complex concentrate in samples with INR of 10.3. Fresh frozen plasma was less effective than prothrombin complex concentrate in shortening INR and recovering thrombin generation or factor II levels. The onset of thrombus formation

was shortened with prothrombin complex concentrate, but not with fresh frozen plasma.⁴ In a systematic review of studies conducted with 3- and 4-factor prothrombin complex concentrates for the reversal of warfarin effect, the 4-factor prothrombin complex concentrates were more effective than 3-factor prothrombin complex concentrates in decreasing the INR to 1.5 or less within 1 hour of administration.⁵

Preliminary studies suggest that prothrombin complex concentrate may reverse the effects of dabigatran or rivaroxaban anticoagulation; however, consistent results have not been apparent, and more trials are necessary to establish its clinical efficacy in these situations before a formal recommendation can be made.⁶⁻¹¹

PHARMACOKINETICS

In healthy subjects, administration of a single intravenous (IV) infusion of prothrombin complex concentrate 50 units/kg yielded rapid and sustained increases in plasma concentrations of factors II, VII, IX, and X and proteins C and S.¹ At 5 minutes after infusion, concentrations were increased from baseline by a median of 122% for factor II, 62% for factor VII, 73% for factors IX, 158% for factor X, 149% for protein C, and 59% for protein S.¹² Half-lives varied from 4.2 hours for factor VII to 59.7 hours for factor II. Mean residence times varied from 6.1 hours for factor VII to 81.7 hours for factor II.¹

In patients undergoing treatment for acute major bleeding, administration of prothrombin complex concentrate (mean volume 105 mL over mean duration of 24 minutes) compared with placebo (mean volume 865 mL over mean duration of 169 minutes)

Table 2. Median INR after start of infusion of prothrombin complex concentrate or plasma in patients treated with warfarin¹

	Prothrombin complex concentrate (n = 98)	Plasma (n = 104)
Baseline	3.9	3.6
30 minutes	1.2 ^a	2.4
1 hour	1.3 ^a	2.1
2 to 3 hours	1.3 ^a	1.7
6 to 8 hours	1.3 ^a	1.5
12 hours	1.2 ^a	1.4
24 hours	1.2	1.3

Note: INR = international normalized ratio.

^aStatistically significant difference compared with plasma by 2-sided Wilcoxon test.

was associated with a greater increase in factor II and factor X and a quicker increase in factor IX, factor VI, and protein C.¹

COMPARATIVE EFFICACY

Indication: Vitamin K Antagonist-Associated Major Bleeding

Guidelines

Guideline: Evidence-Based Management of Anticoagulation Therapy, Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Reference: Holbrook A, et al, 2012¹³

Comments: Guidelines recommend the use of 4-factor prothrombin complex concentrate rather than plasma for the management of patients with vitamin K antagonist-associated major bleeding, with the additional use of vitamin K 5 to 10 mg administered by slow IV injection rather than reversal with coagulation factors alone.

Studies

Drug: Prothrombin Complex Concentrate vs Fresh Frozen Plasma

Reference: *Kcentra* prescribing information, 2013^{1,14}

Study Design: Randomized, open-label, multicenter, noninferiority study

Study Funding: CSL Behring

Patients: 212 patients who had been treated with a vitamin K antagonist and required urgent replacement of the vitamin K–dependent clotting factors to treat acute major bleeding (defined as life-threatening or potentially life-threatening, acute bleeding associated with a fall in hemoglobin of at least 2 g/dL, or bleeding requiring a blood product transfusion); 212 patients had a baseline INR of 2 or greater and recent use of a vitamin K antagonist; 202 patients were included in the modified intent-to-treat efficacy population (98 in the prothrombin complex concentrate group and 104 in the plasma group).

Intervention: Prothrombin complex concentrate 25, 35, or 50 units/kg or plasma 10, 12, or 15 mL/kg, according to the patient's baseline INR (2 to <4, 4 to 6, or >6, respectively). All patients also received IV vitamin K.

Results:

Primary Endpoint(s):

- Hemostatic efficacy with respect to adequacy of stopping an ongoing major bleed based on

assessments including vital signs, hemoglobin measurements, and computed tomography assessments: 72.4% in the prothrombin complex concentrate group and 65.4% in the plasma group (difference 7.1%; 95% confidence interval [CI], −5.8 to +19.9; met predefined non-inferiority criteria because the lower limit of the 95% CI for the difference was −5.8%, which exceeded the prespecified criterion of −10%; did not meet superiority).

- Reduction of INR to 1.3 or less at 30 minutes after the end of the infusion: 62.2% with prothrombin complex concentrate and 9.6% with plasma (difference 52.6%; 95% CI, 39.4 to 65.9; met superiority criteria).

Secondary Endpoint(s):

- Hemostatic efficacy for visible and musculoskeletal nonvisible bleeding: results not reported.
- Response of factor IX, factor II, factor VII, factor X, protein C, and protein S: results not reported.
- Time from infusion start until INR correction: results not reported.
- Time from randomization until INR correction: results not reported.
- Use of blood products and/or hemostatic agents: results not reported.
- 45-day all-cause mortality: results not reported.
- Transfusions of red blood cells: results not reported.

Comments: A similar study comparing prothrombin complex concentrate (CSL Behring) with fresh frozen plasma in 176 patients receiving oral vitamin K antagonist therapy and requiring an urgent surgical procedure with need to reverse the anticoagulant effect is described, but results have not been reported.¹⁵

Limitations: Study results are only available in the product package insert.

Drug: Prothrombin Complex Concentrate

Reference: *Kcentra* prescribing information, 2013; Pabinger I, et al, 2008^{1,16}

Study Design: Open-label, single-arm, multicenter study

Study Funding: CSL Behring

Patients: 43 patients receiving vitamin K antagonists with an INR greater than 2 and requiring emergency surgical or urgent invasive diagnostic intervention (26 patients) or experiencing an acute bleeding event (17 patients).

Intervention: Prothrombin complex concentrate (*Beriplex P/N*; CSL Behring, Germany) 25, 35, or

50 units/kg according to baseline INR (2 to <4, 4 to 6, or >6, respectively). The 25 units/kg dose was administered to 26 patients, the 35 units/kg dose to 7 patients, and the 50 units/kg dose to 10 patients. Vitamin K 5 to 20 mg was also administered to 38 patients (88%) according to individual center protocols.

Results:

Primary Endpoint(s):

- Reduction in INR to 1.3 or less within 30 minutes after the end of the infusion in 40 of 43 patients (93%); INR was 1.4 in the remaining 3 patients. Among the 17 patients who received prothrombin complex concentrate for acute bleeding, 16 patients (94%) experienced a reduction in INR to 1.3 or less. Median INR declined to 1.2 at 30 minutes from 3.2 at baseline and remained consistently between 1.2 and 1.3 throughout the 48-hour observation period.

Secondary Endpoint(s):

- Clinical hemostatic efficacy in stopping acute bleeding or preventing major bleeding during interventional procedures was judged very good in 40 patients (93%) and satisfactory in 2 patients.
- Response of factor IX, factor II, factor VII, factor X, protein C, and protein S: rapid increases were observed, with normal or near normal concentrations persisting throughout the 48-hour observation period.

Other Endpoint(s):

- Adverse events: suspected thromboembolic complications occurred in 2 patients, including a fatal pulmonary embolism.

Comments: Similar reports have described experience with the use of prothrombin complex concentrate (*Beriplex P/N*) to reverse the effects of oral vitamin K antagonists in patients with acute major bleeding or subdural hematoma or who require emergency surgery. In 42 patients treated at 1 institution, median INR was reduced from 3.98 pretreatment to less than 1.3 within 20 minutes in 33 patients; at 20 minutes after administration, the remaining 9 patients had INRs of 1.3 to 1.9.¹⁷ In 10 patients treated at another institution, INRs declined to less than 1.3 within 30 minutes of administration (from pretreatment INR values ≥ 20 in 6 patients and 8.9, 14.4, 15.8, and 18 in the other 4) and cessation of bleeding was achieved in all patients within 6 to 8 hours.¹⁸

Limitations: Noncomparative study.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

Prothrombin complex concentrate is contraindicated in patients with known anaphylactic or severe systemic reactions to the product or any components of the product including heparin, factors II, VII, IX, X, proteins C and S, antithrombin III and human albumin; patients with disseminated intravascular coagulation; or patients with known heparin-induced thrombocytopenia.¹

Warnings and Precautions

Prothrombin complex concentrate labeling contains a black box warning of the risk of arterial and venous thromboembolic complications. Both fatal and nonfatal arterial and venous thromboembolic complications have been reported with the use of prothrombin complex concentrate. Such events occurred more frequently with the use of prothrombin complex concentrate than the use of plasma in a randomized study in patients requiring urgent reversal of vitamin K antagonist anticoagulation due to acute major bleeding. Patients treated with vitamin K antagonists have underlying conditions that predispose them to thromboembolic events. The potential impact of reversing vitamin K antagonist therapy should be considered in relation to the potential risk of thromboembolic events. Resumption of anticoagulant therapy should be considered as soon as the risk of thromboembolic events outweighs the risk of acute bleeding. Following administration of prothrombin complex concentrate, patients should be monitored for signs and symptoms of thromboembolic events. Prothrombin complex concentrate was not studied in patients 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.¹

Hypersensitivity reactions including flushing, urticaria, tachycardia, anxiety, angioedema, wheezing, nausea, vomiting, hypotension, tachypnea, dyspnea, pulmonary edema, and bronchospasm have been observed with prothrombin complex concentrate. If severe reactions occur, administration should be immediately discontinued and appropriate treatment initiated.¹

Because this product is derived from human blood, it may carry a risk of transmitting infectious agents.¹ With 15 years of use of this blood-derived product in Europe (*Beriplex P/N*; CSL Behring), no incidences of viral transmission have been documented.¹⁹

Table 3. Adverse reactions reported in (3 or more subjects) following administration of *Kcentra* or plasma in the randomized controlled trial for the treatment of acute major bleeding¹

	Prothrombin complex concentrate (n = 103)	Plasma (n = 109)
Headache	7.8%	1.8%
Hypotension	4.9%	2.8%
Nausea/vomiting	3.9%	0.9%
Arthralgia	3.9%	0%
Skin laceration/contusion/subcutaneous hematoma	2.9%	0.9%
Tachycardia	2.9%	0.9%
Blood pressure increased/hypertension	2.9%	0%
INR increased	2.9%	0%
Intracranial hemorrhage	2.9%	0%
Mental status changes	2.9%	0%
Constipation	1.9%	5.5%
Hypokalemia	1.9%	4.6%
Respiratory distress/dyspnea/hypoxia	1.9%	3.7%
Fluid overload	1%	5.5%
Breath sounds abnormal/rates	1%	2.8%
Chest pain	1%	2.8%
Insomnia	1%	2.8%
Anemia	0%	3.7%
Pulmonary edema	0%	3.7%
Transfusion reaction	0%	3.7%
Diarrhea	0%	2.8%
Hypomagnesemia	0%	2.8%

Note: INR = international normalized ratio.

Prothrombin complex concentrate was extensively studied in elderly patients; 71% of patients in the 2 primary studies were 65 years and older and 43% were 75 years and older. There were no differences in the safety profile in any age group.¹ The safety and effectiveness of prothrombin complex concentrate have not been assessed in pediatric patients.¹

Prothrombin complex concentrate is classified as Pregnancy Category C. It should only be prescribed for a pregnant woman if clearly needed.¹ It is not known whether prothrombin complex concentrate is excreted in human milk; therefore, it should only be used in a breast-feeding woman if clearly needed.¹

ADVERSE REACTIONS

The most common adverse reactions, observed in at least 2.8% of patients receiving prothrombin

complex concentrate, were headache, nausea/vomiting, arthralgia, and hypotension.¹ Adverse events that occurred in at least 1% of patients treated with prothrombin complex concentrate or plasma comparator are summarized in **Table 3**.

Serious adverse reactions associated with the use of prothrombin complex concentrate have included stroke, pulmonary embolism, and deep vein thrombosis.¹ Thromboembolic events occurred in 9 patients in the prothrombin complex concentrate group (8 patients with a history of thromboembolic events) and 6 patients in the plasma group (3 with a history of thromboembolic events) among patients treated with prothrombin complex concentrate and plasma in the randomized controlled trial.¹

DRUG INTERACTIONS

Drug interactions have not been reported.

Table 4. Dosing recommendations for *Kcentra*¹

Dose	Pretreatment INR		
	2 to < 4	4 to 6	> 6
Dose in units of factor IX/kg body weight ^a	25	35	50
Maximum dose in units of factor IX	2,500	3,500	5,000

Note: INR = international normalized ratio.

^aUp to, but not exceeding, 100 kg body weight.

RECOMMENDED MONITORING

INR and clinical response should be monitored during and after treatment.¹

DOSING

The actual potency per vial of factors II, VII, IX, and X and proteins C and S are stated on the carton; dosing is stated in terms of factor IX potency. Prothrombin complex concentrate dosing should be individualized based on the patient's current predose INR value and body weight (Table 4). Prothrombin complex concentrate should be diluted with 20 mL of the provided diluent (sterile water for injection) to provide a product with a final concentration in factor IX units of 20 to 31 units/mL, depending on the potency stated on the product labeling. Vitamin K should be administered concurrently with prothrombin complex concentrate. Repeat dosing of the prothrombin complex concentrate has not been studied and is not recommended.¹

Diluted prothrombin complex concentrate should be administered by IV infusion at a rate of 0.12 mL/kg/min (about 3 units/kg/min) up to a maximum rate of 8.4 mL/min (about 210 units/min).¹

PRODUCT AVAILABILITY

Prothrombin complex concentrate received FDA approval on April 29, 2013 and was approved in Europe in 1996.^{1,19} It is available in a single-use vial, packaged as a kit with a 20 mL vial of sterile water for injection, a Mix2Vial filter transfer set, and an alcohol swab. It should be stored between 2°C and 25°C (36°F to 77°F) and protected from light, temperatures exceeding 25°C (77°F), and freezing temperatures. Following reconstitution, it must be used within 4 hours; reconstituted product can be stored at 2°C to 25°C (36°F to 77°F), but if cooled, it should be warmed to 20°C to 25°C (68°F to 77°F) prior to administration.¹

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS)

No REMS is required for prothrombin complex concentrate.

CONCLUSION

The 4-factor prothrombin complex concentrate (human) offers advantages over 3-factor prothrombin complex concentrate and fresh frozen plasma in patients requiring urgent reversal of warfarin anticoagulation due to acute major bleeding. Compared with fresh frozen plasma, prothrombin complex concentrate does not require cross-matching, is virally inactivated, does not cause volume overload, and can be quickly infused. In clinical trials, prothrombin complex concentrate was able to produce a rapid reduction in INR and hemostatic efficacy.

The Institute for Safe Medication Practices (ISMP) has expressed concern that heightened awareness is necessary for prothrombin complex concentrate orders within an institution.²⁰ If formulary approved, this agent must be ordered by its proprietary name.

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Continuing Education Case Study Quiz

Goal—The goal of this program is to educate pharmacists about the use of prothrombin complex concentrate (human) for the treatment of patients with bleeding induced by vitamin K antagonist.

Objectives—At the completion of this program, the reader will be able to:

1. Describe the pharmacology and pharmacokinetics of prothrombin complex concentrate (human).
 2. Discuss the risks associated with the use of prothrombin complex concentrate (human).
 3. Discuss the dosage, reconstitution, and administration of prothrombin complex concentrate (human).
 4. Apply the information on the use of prothrombin complex concentrate (human) to a case study.
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1. The US Food and Drug Administration (FDA)-approved indication for prothrombin complex concentrate (human) is:
 - a. Reversal of vitamin K antagonists in adults without acute major bleeding.
 - b. Reversal of vitamin K antagonists in adults with acute major bleeding.
 - c. Reversal of factor IX deficiency in children and adults with acute major bleeding.
 - d. Reversal of factor IX deficiency in adults without acute major bleeding.
2. Prothrombin complex concentrate (human) contains which of the following clotting factors?
 - a. Factors II, VII, IX, X
 - b. Factors IIa, VII, XII, XIII
 - c. Factors II, IX, X
 - d. Factors VII, IX, X, XII
3. Fresh frozen plasma and prothrombin complex concentrate (human) differ in what way?
 - a. Prothrombin complex concentrate contains more clotting factors than fresh frozen plasma.
 - b. Fresh frozen plasma is less likely to transmit infection.
 - c. Prothrombin complex concentrate does not require cross-matching.
 - d. Fresh frozen plasma causes a greater decrease in international normalized ratio (INR) through 12 hours.
4. What are the respective half-lives of factors II and VII?
 - a. 30 minutes and 1 hour
 - b. 6 hours and 8 hours
 - c. 59.7 hours and 4.2 hours
 - d. 81.7 hours and 6.1 hours
5. In the study comparing prothrombin complex concentrate with fresh frozen plasma in 212 patients with acute major bleeding, what was the difference in hemostatic efficacy between prothrombin complex concentrate and fresh frozen plasma?
 - a. -5.8%
 - b. 19.9%
 - c. 7.1%
 - d. 9.6%
6. Prothrombin complex concentrate (human) is contraindicated in patients with known hypersensitivity to which of the following?
 - a. Heparin
 - b. Neomycin
 - c. Fondaparinux
 - d. Fibronectin
7. Prothrombin complex concentrate (human) is in Pregnancy Category:
 - a. B.
 - b. C.
 - c. D.
 - d. X.
8. Because prothrombin complex concentrate (human) is derived from human plasma, it may carry a risk of transmitting infectious agents. How many incidences of viral transmission have been documented during its use in Europe?
 - a. 0
 - b. 15
 - c. 43
 - d. 65

9. Prior to administration, prothrombin complex concentrate (human) should be reconstituted with:
 - a. 20 mL sterile water for injection.
 - b. 31 mL sterile water for injection.
 - c. 8.4 mL 0.9% sodium chloride for injection.
 - d. 20 mL 0.9% sodium chloride for injection.
10. Which of the following impacts of reversing warfarin must be considered before administration of prothrombin complex concentrate (human)?
 - a. Increased bleeding risk
 - b. Decreased vitamin K requirements
 - c. Thrombocytopenia
 - d. Increased risk of thromboembolic events
13. Thirty minutes after administration of prothrombin complex concentrate (human) and vitamin K, N.H.'s INR is 2.3. Which of the following is the preferred course of action?
 - a. Administer another dose of prothrombin complex concentrate (human) at the maximum dose and maximum rate.
 - b. Administer another dose of prothrombin complex concentrate (human) and vitamin K at the minimum and maximum doses respectively.
 - c. Administer an alternative therapy for warfarin reversal.
 - d. Assess for clinical response.

Case History

N.H. is a 59-year-old male, weighing 90 kg, with a history of hypertension, untreated hyperuricemia, and atrial fibrillation. He is currently taking lisinopril/hydrochlorothiazide 20 mg/12.5 mg once daily and warfarin 5 mg once daily. After a second gout flare-up, his doctor prescribed allopurinol 100 mg once daily. Two weeks following the initiation of allopurinol, N.H. presents to the emergency room with an acute major gastrointestinal bleed and an INR of 5.2.

11. What is the recommended dose of prothrombin complex concentrate (human) for N.H. in units of factor IX?
 - a. 2,250 units given as a single dose
 - b. 2,250 units given as 2 divided doses
 - c. 3,150 units given as a single dose
 - d. 3,150 units given as 2 divided doses
12. What is the maximum infusion rate of prothrombin complex concentrate (human) for N.H.?
 - a. 40 mL/min
 - b. 210 units/min
 - c. 400 units/min
 - d. 135 mL/min
14. When should N.H.'s warfarin therapy be resumed?
 - a. It should not be resumed due to the risk of bleeding.
 - b. When risk of thromboembolic events outweighs the risk of bleeding.
 - c. After at least 3 months, but not more than 6 months.
 - d. When the INR is at least 1.3 due to the risk of thromboembolic events.
15. An extra vial of prothrombin complex concentrate (human) was inadvertently reconstituted but not used in the treatment of N.H. What would be an appropriate storage and use of the reconstituted product?
 - a. Store protected from light, between 2°C and 25°C (36°F to 77°F); discard after 24 hours.
 - b. Store protected from light, between 2°C and 25°C (36°F to 77°F); discard after 4 hours.
 - c. Store protected from light, between 2°C and 25°C (36°F to 77°F); discard after expiration date indicated on carton.
 - d. Store protected from light, below 0°C (32°F); discard after 4 hours.

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