Kcentra™ (Prothrombin Complex Concentrate: 4-factor PCC)

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Kcentra™ was added to the NorthShore formulary September 2013. It is the only 4-factor PCC currently available in the US. With the addition of Kcentra™, FEIBA® has been taken off the NorthShore formulary.

Indication: Urgent reversal of warfarin therapy in patients with acute major bleeding. Kcentra™ is not approved for use in patients without acute major bleed.

Mechanism of Action: Kcentra™ is made from pooled human plasma and contains all four coagulation factors (II, VII, IX, and X) inhibited by warfarin as well as antithrombotic proteins C and S. In comparison, 3-factor PCC products (Profilnine ® and Bebulin ®) do not have appreciable levels of factor VII. FEIBA® contains activated factor VII in addition to factors II, IX, and X.

Contraindications: Hypersensitivity to PCC or any of its components, DIC, known HIT (product contains heparin).

Black Box Warning: Patients receiving warfarin therapy may have underlying risk for thromboembolic (TE) events. Administration of Kcentra™ may predispose patients to TE complications; however, the Phase III study[10] did not report increased incidence in serious TE events as compared to FFP. Patients with a history of TE event including MI, DIC, CVA, TIA, unstable angina pectoris, or severe PVD within the prior three months, or patients with a known history of antiphospholipid antibody syndrome were excluded from the Phase III study.[10] Kcentra™ may not be suitable for use in these patients. Monitor closely for signs and symptoms of TE complications.

Adverse reactions:
- Common (≥ 2.8%): headache, nausea/vomiting, arthralgia, and hypotension.
- Serious: arterial and venous thromboembolic events including stroke, PE, and DVT.

Table 1: Management of Supra-Therapeutic INR Values due to Warfarin[1]

INR	Bleeding?	Withhold Warfarin?	Routine Vitamin K?	Other Reversal Agents?
4.5-10	No	Yes	No	No
> 10	No	Yes	Yes - 2.5 mg PO x 1	No
Any	Yes	Yes	Yes - 5-10 mg IV	Give FFP 2-4 units OR Kcentra™ (see Table 2 for dosing)

Advantages of Kcentra™ as compared to FFP:
- Shorter time to administration; products can be reconstituted instead of thawed.
- Decreased volume associated with use; reduces risk for fluid overload.
- Does not require blood type compatibility.
- No risk for transfusion-related lung-injury (TRALI).

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[10]:
- 216 adults on warfarin therapy with INR ≥ 2 (within 3 hours of study treatment) and acute major bleed requiring reversal were randomized to treatment with Kcentra™ or FFP.
- 202 patients were included in the intent-to-treat efficacy (ITT-E, received any portion of study drug) population (4F-PCC, n= 98; FFP, n= 104).
- Acute major bleed was defined as one of the following: life-threatening or potentially life-threatening bleed; acute bleeding associated with a fall in hemoglobin ≥ 2 g/dL; or bleeding requiring blood product transfusion.
- Baseline patient demographics and characteristics were similar.
    - Baseline INR in patients receiving 4F-PCC versus FFP was a median of 3.90 (1.8-20.0) and 3.60 (1.9-38.9), respectively.
- See table 2 for Kcentra™ doses; all patients were given concurrent slow intravenous vitamin K. Need to administer through a dedicated IV infusion line.

- Co-primary outcomes:
    1. Hemostatic efficacy assessed over the 24 hours after the start of the infusion
    2. INR reduction to ≤ 1.3 within 30 minutes of the end of infusion
- Results:
    - Hemostasis: 71 patients in the 4F-PCC treatment group versus 68 patients in the FFP treatment group achieved hemostasis efficacy rating of excellent or good ("effective hemostasis") as determined by a blinded, independent endpoint adjudication board. Kcentra™ was found to be non-inferior to FFP for hemostatic efficacy. No difference was found between groups with excellent hemostatic efficacy rating at 24 hours (p= 0.50). A post hoc analysis demonstrated that significantly more patients with visible and musculoskeletal bleeding who received 4F-PCC received a rating of excellent hemostasis.
    - INR Reduction: 61 patients treated with 4F-PCC versus 10 patients on FFP achieved rapid INR reduction to ≤ 1.3 thirty minutes after infusion. This finding supports the superiority of 4F-PCC over FFP in rapid INR reduction. The clinical significance of faster INR reversal is not clear.

Table 2: Kcentra™ Dose (based on baseline INR)	
INR < 4	25 units/kg Max 2500 units
INR 4-6	35 units/kg Max 3500 units
INR > 6	50 units/kg Max 5000 units
- Round dose to nearest 500 units - For pts ≥ 100 kg, use 100 kg to calculate dose	
Monitoring	
- Repeat INR 3 hours after administration - Additional doses of Kcentra™ are not recommended (may increase risk for thrombosis) - Co-administer IV vitamin K to maintain vitamin K dependent clotting factors and achieve goal INR - Target INR ≤ 1.3	
Preparation of Dose	
- Multiple vials often required per dose, pharmacy to prepare and pool doses into IVPB - Estimated preparation time: 30-45 minutes - Page pharmacy as soon as order is placed	

- Mean factor levels were significantly higher in the 4F-PCC treatment group at through 6 hours (other than Factor VII at 6 hours); however, at 24 hours, the factor levels in the FFP group trended toward those in the 4F-PCC group.
- No difference between groups for: mean number of PRBCs transfused, length of stay, and 30-day mortality.
- Safety profiles: similar between groups.
    - Total adverse events: 66 patients in the 4F-PCC group and 71 patients in the FFP group reported ≥ 1 adverse event with only 10 and 23, respectively, of the events considered treatment related.
        - Fluid overload occurred 2-3X as often in the FFP group.
    - TE: 2 patients receiving 4F-PCC and 2 patients receiving FFP were determined by a blinded, independent safety adjudication board to have serious TE events that were treatment related. Based on this, incidence of TE is ~4% with 4F-PCC and ~3% with FFP.
- Conclusion: Kcentra™ is non-inferior to FFP for hemostatic efficiency and is superior to FFP for rapid decrease in INR.

Use with Novel Oral Anticoagulants[3]:

- Limited data available. A study on 12 healthy male volunteers showed that administration of a single bolus of Kcentra™ (50 units/kg) immediately and completely reversed the effects of rivaroxaban but had no effect on dabigatran.

References:

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7. Kcentra Prescribing Information. 2013. CSL Behring LLC, Kankakee, IL.
8. Peng, Ze and CSL Behring LLC. 2013. Summary Basis for Regulatory Action. Submitted to the FDA for approval on 26 April 2013. STN 125421/0.
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