

# Use of Prothrombin Complex Concentrates (PCC)

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# Use of Prothrombin Complex Concentrates (PCC)

## Exclusion Criteria

1. Acidosis with a pH of less than 7.10
2. Temperature below 96° F
3. Platelet count less than 50,000/mm<sup>3</sup>
4. Patient is deemed to have non-survivable acute injuries or illness per neurosurgery and/or trauma fellow/attending.

## Approved Indications for Use at UC Health

**All other considerations for using PCC must be done under the direction or consultation of a hematologist/oncologist.**

1. Prevention & treatment of hemorrhagic episodes in Factor IX deficiency -Hemophilia B patients (FDA-Approved)
  - Treatment of bleeding episodes in hemophilia B.
2. Trauma (Off-Label)
  - TBI patients needing emergent placement of devices like external ventricular drains (goal INR is ≤ 1.4)
  - Order must be given by trauma/neurosurgery/ED/neurocritical care attending or fellow physician.
  - Do NOT administer PCC if thromboelastography (TEG) is obtained and R time is normal.
3. Life-Threatening, Non-Anticoagulant Coagulopathy with Acute Bleeding (Off-Label)
  - Treatment of patients in a life-threatening coagulopathic state with acute bleeding, who are unresponsive to significant clotting factor replacement defined in TABLE A.
  - Do NOT administer PCC if thromboelastography (TEG) is obtained and R time is normal.
4. Warfarin-Associated Acute, Life-Threatening Bleeding (Off-Label)
  - Reversal of warfarin in patients with coagulopathy (i.e., elevated INR) and acute, life-threatening bleeding supplemented with vitamin K 5-10 mg by slow intravenous infusion in NS (over 60 mins) that time and/or volume status precludes the use of FFP 10 mL/kg
  - Patients with warfarin-associated intracranial hemorrhage that time and/or volume status precludes the use of FFP 10 mL/kg
  - Order must be given by trauma / neurosurgery / ED / neurocritical care attending or fellow physician in the case of ICH.
5. Non-Warfarin Oral Anticoagulant Reversal with Acute Bleeding (Off-Label)
  - PCC's can be considered per Table B in patients with acute, life-threatening bleeding due to rivaroxaban, apixaban, or dabigatran that:
    - a. Time and/or volume status precludes the use of FFP 5-10 mL/kg or clinical and laboratory response to FFP 5-10 mL/kg is suboptimal
    - b. History and lab criteria are met (TABLE B)

**TABLE A**

Laboratory parameter	Required clotting factor replacement
Platelets < 50,000/mm <sup>3</sup>	Administration of > 12 units of platelets
INR ≥ 1.5	Administration of 10 – 15 ml/kg FFP and Vitamin K 10 mg IV
PTT > 50 sec	Administration of Protamine 50 mg IV only if due to heparin use
Fibrinogen < 100mg/dL	Administration of > 10 units of cryoprecipitate

**TABLE B**

Drug	Criteria
Dabigatran	<ul style="list-style-type: none"> <li>– Last dose administered within 12 hours or 24 hours in patients with CrCl below 60 mL/min</li> <li>– aPTT GREATER than 40 seconds or thrombin time (TT) GREATER than 65 seconds</li> </ul>
Rivaroxaban	<ul style="list-style-type: none"> <li>– Last dose administered within 12 hours or 24 hours in patients with CrCl below 50 mL/min</li> <li>– PT GREATER than 16 sec</li> </ul>
Apixaban	<ul style="list-style-type: none"> <li>– Last dose administered within 12 hours or 24 hours in patients with serum creatinine above 1.5 mg/dL</li> <li>– PT GREATER than 16 sec</li> </ul>

### Dosing / Administration / Storage

- All doses will be rounded to the nearest vial size to decrease medication waste.
- For intravenous (IV) bolus use only.
- Vials of PCC must be refrigerated and are stable up to the listed expiration date.
- Vials can be stored at room temperature for up to 3 months
- **After reconstitution the product must be used within 3 hours**

### Recommended Dosing for UC Health-Approved Indications of PCC

1. Prevention & treatment of hemorrhagic episodes in Factor IX deficiency -Hemophilia B patients (FDA-Approved)

*Indications:*

Prevention of bleeding in surgical interventions or treatment of bleeding episodes

*Recommended Dose:*

- Minor: 25 IU /kg IV bolus over 2-5 minutes
- Moderate: 50 IU/kg
- Major: 100 IU/kg

2. Trauma (Off-Label)

- 3F PCC 25 IU/Kg IV bolus over 2-5 minutes as a single dose.
- May repeat x1 dose in cases of inadequate response based on reassessment per guideline criteria: see pg. 1 - Trauma (*Off-Label*)
- As 3F PCCs contain low amounts of factor VII, adding a low dose of FFP should be considered (e.g., FFP 3 – 10 mL/kg).

3. Life-Threatening Coagulopathy with Acute Bleeding (Off-Label)

- 3F PCC 25 IU/Kg IV bolus over 2-5 minutes as a single dose.
- May repeat x1 dose in cases of inadequate response based on reassessment per guideline criteria: see pg. 1 - Trauma (*Off-Label*)
- As 3F PCCs contain low amounts of factor VII, adding a low dose of FFP should be considered (e.g., FFP 3 – 10 mL/kg).

4. Warfarin-Associated Acute, Life-Threatening Bleeding (Off-Label) (see subsections a. and b.)

a. Acute, Life-Threatening, Non-Intracranial Bleeding

- 3F PCC 25 IU/Kg IV bolus over 2-5 minutes as a single dose.
- May repeat x1 dose in cases of inadequate response based on reassessment per guideline criteria: see pg. 1 - Trauma (*Off-Label*)
- As 3F PCCs contain low amounts of factor VII, adding a low dose of FFP should be considered (e.g., FFP 3 – 10 mL/kg).

b. Warfarin-Associated Intracranial Hemorrhage (TABLE C, pg. 3)

5. Non-Warfarin Anticoagulant Reversal with Acute Bleeding (Off-Label)

- PCC's can be considered in patients with acute life-threatening bleeding due to rivaroxaban, apixaban, or dabigatran that time and/ or volume status precludes the use of FFP.

<u>Drug</u>	<u>Potential Reversal Agents/Therapy</u>
- Dabigatran	<ol style="list-style-type: none"> <li>1. Activated charcoal if &lt; 2 hours from last dose</li> <li>2. Extended hemodialysis of 2 to 3+ hours, as appropriate</li> <li>3. aPCC (Feiba) 8 Units/kg IV (consider administering prior to dialysis line or insertion of drain, as appropriate)</li> </ol> <p>- May use up to 25 IU/kg IV for severe life-threatening bleeding</p>
-Rivaroxaban	<ol style="list-style-type: none"> <li>1. Activated charcoal if &lt; 2 hours from last dose</li> <li>2. 3F-PCC 25-50 Units/Kg IV +/- rFVIIa 30 mcg/kg IV</li> </ol>
-Apixaban	<ol style="list-style-type: none"> <li>1. Activated charcoal if &lt; 2 hours from last dose</li> <li>2. 3F-PCC 25-50 Units/Kg IV +/- rFVIIa 30 mcg/kg IV</li> </ol>

# Use of Prothrombin Complex Concentrates (PCC)

TABLE C	
Lab findings / clinical situation	Treatment
<b>INR GREATER Than 1.5</b>	
Volume status: Euvolemic or hypovolemic	<ul style="list-style-type: none"> <li><input type="checkbox"/> Discontinue warfarin</li> <li><input type="checkbox"/> Vitamin K 5-10 mg IV (given IVPB over 60 mins) every 8 hours x 3 doses</li> <li><input type="checkbox"/> FFP: <u>10 mL/kg*</u> <ul style="list-style-type: none"> <li>- Check INR immediately after infusion of initial dose.</li> <li>- Repeat dose as needed until goal INR obtained.</li> <li>- Check INR after each dose</li> <li>- <u>Note:</u> Higher volumes of FFP are associated with TRALI</li> </ul> </li> </ul>
Volume status: Hypervolemic OR Persistent coagulopathy despite FFP	<ul style="list-style-type: none"> <li><input type="checkbox"/> Discontinue warfarin</li> <li><input type="checkbox"/> Vitamin K 5-10 mg IV (given IVPB over 60 mins) every 8 hours x 3 doses</li> <li><input type="checkbox"/> 3F PCC 25 IU/kg IV X 1 +/- FFP 3 to 10 mL/kg*                             <ul style="list-style-type: none"> <li>- Recheck INR 15-30 min after each dose and consider further therapy based on response</li> </ul> </li> </ul>
<b>INR LESS Than 1.5</b>	
aPTT GREATER than 50 seconds without therapeutic heparin	<ul style="list-style-type: none"> <li><input type="checkbox"/> Discontinue warfarin</li> <li><input type="checkbox"/> No FFP is indicated</li> <li><input type="checkbox"/> There has probably been a heparin contaminant introduced or lab error. Send STAT aPTT sample with request for Hepzyme/Hepsorb                             <ul style="list-style-type: none"> <li>- If aPTT corrects, then give Protamine 50 mg IV x 1</li> <li>- If aPTT still GREATER than 50 sec, then check:                                     <ul style="list-style-type: none"> <li>o aPTT Mixing study</li> <li>o Factor VIII activity</li> <li>o Factor VIII inhibitor</li> </ul> </li> </ul> </li> </ul>
Heparin use with PTT > 50 seconds	<ul style="list-style-type: none"> <li><input type="checkbox"/> Protamine 50 mg IV x 1                             <ul style="list-style-type: none"> <li>- If aPTT still GREATER than 50 sec, then check:                                     <ul style="list-style-type: none"> <li>o aPTT Mixing study</li> <li>o Factor VIII activity</li> <li>o Factor VIII inhibitor</li> </ul> </li> </ul> </li> </ul>
Low Molecular weight heparin use	<ul style="list-style-type: none"> <li><input type="checkbox"/> Protamine 50 mg IV (partial reversal only)</li> </ul>
Fibrinogen < 150 mg / dL	<ul style="list-style-type: none"> <li><input type="checkbox"/> Cryoprecipitate: 10 pack (Initial dose = 10 pack) Check FBGN after cryoprecipitate</li> </ul>
Platelets < 50,000 or current use of P2Y12-inhibitor (e.g., clopidogrel) / Aggrenox	<ul style="list-style-type: none"> <li><input type="checkbox"/> Platelets: <u>Two 5-packs</u> If going to OR, give one 5-pack pre-op, then repeat dose in OR; recheck platelet count after 15 mins</li> </ul>

\* FFP dose should be calculated by volume rather than units (**1 unit FFP is approx. 200 ml**). Plasma is available in both frozen and thawed forms; Hoxworth will send whichever is readily available. There is no difference in efficacy of the 2 forms.

### Prescribing and Monitoring

1. No minimal effective dose of PCC has been established; therefore, the lowest possible dose should be used.
2. The dose of PCC should be determined based on hemostasis and clinical symptoms. Standard laboratory parameters for non-warfarin oral anticoagulants unreliably correlate with proportional changes in plasma drug concentrations.
3. Prothrombin time (PT), activated partial thromboplastin time (PTT), fibrinogen, thromboelastography (TEG), and platelets should be monitored
4. All patient cases in which PCC is administered for off-label indications described herein will undergo post-hoc quality review under the direction of the Chief Quality Officer for UC Health. Results and conclusions of the review will be presented to the UC Health Drug Policy Development Committee as appropriate.

### Dispensing

1. All orders received by the pharmacy shall be verified for appropriateness of use prior to dispensing (using this guideline)
2. In the event that the drug is being ordered for an indication not covered by this guideline, the clinical pharmacist on-call will evaluate the appropriateness of use in discussion with the ordering physicians.
3. All doses will be rounded to the nearest vial size.
4. Delivery of PCC will be as follows:  
The PCC will be hand delivered to the nurse or appropriate physician. (Do not send via pneumatic tube station)

### **Cautions<sup>6</sup> -Consider Hematology / Oncology consult**

1. Patients with a history within the last 6 months, of disseminated intravascular coagulation (DIC), or hyperfibrinolysis.
2. Patients with a known congenital coagulation disorder.
3. Patients with known antiphospholipid antibody syndrome or have known lupus anticoagulant antibodies, as this may be indicative of a hypercoagulable state.
4. Patients with present or past specific factor inhibitor activity.
5. Patients with a history of hypersensitivity to plasma-derived products.
6. Pregnant or nursing women.

### **Warnings**

Increased risk of thrombotic events. Risk factors include:

- a. Septicemia, rule out DIC
- b. Crush injury, rule out DIC
- c. Active venous or arterial thrombosis
- d. Disseminated intravascular coagulation (DIC)
- e. Advanced atherosclerotic disease
- f. Concomitant treatment with activated or nonactivated prothrombin complex concentrates (aPCCs / PCCs), tranexamic acid (TXA), or aminocaproic acid
- g. History of coronary heart disease
- h. Liver disease
- i. Post-operative immobilization
- j. Elderly ( $\geq 65$  years old)
- k. Neonates

# Use of Prothrombin Complex Concentrates (PCC)

## Summary / Background

### Summary:

1. The US market currently has nonactivated 3 factor PCC products (Profilnine and Bebulin) and an activated 4 factor PCC (Feiba) product available. The literature though has utilized nonactivated 4 factor PCC products for oral anticoagulation reversal. The increasing use of warfarin and newer oral anticoagulants like dabigatran, rivaroxaban and apixaban require us to carry appropriate products for reversal of these agents.
2. The 3F PCC products have a smaller amount of factor VII than the 4F PCC products.
3. Formulary recommendation is to have a nonactivated 3 factor PCC (Profilnine) AND activated 4 factor PCC (Feiba) available.
4. Reconsider our formulary products when the 4 factor PCC product is available (estimated September 2013).
5. Continuous ongoing review of requests for PCC products. A review of PCC use within 1- 2 years with results presented to the DPD committee for further formulary / policy changes.

### Background

1. Prothrombin complex concentrates or PCC (aka. factor IX complex) were originally developed and FDA approved for the treatment of hemophilia B (deficiency in factor IX). PCCs contain the vitamin K dependent clotting factors (II, VII, IX and X) and are derived from human plasma. PCCs are categorized as 3-factor or 4-factor products. The 3-factor PCC products available in the USA are Bebulin<sup>®</sup> and Profilnine<sup>®</sup>, which contain inactivated factors II, IX, and X, and a very low amount of inactivated factor VII. FEIBA NF<sup>®</sup> is a 4-factor product that contains a higher amount factor VII mainly in the activated form. Four-factor inactivated PCCs (Beriplex<sup>®</sup>, Octaplex<sup>®</sup>, and Prothromplex<sup>®</sup>) are available in Europe and Canada.<sup>1</sup> PCCs are dosed based on the amount of factor IX activity.

For major bleeding due to vitamin K antagonist and when rapid reversal is necessary the 2012 CHEST guidelines recommend administration of a 4-factor PCC and 5-10 mg IV vitamin K given as one time dose and may be repeated in 12 hours if INR is still elevated.<sup>2</sup>

Other recent guidelines that suggest the use of PCC's include the 2010 Guidelines for the Management of Intracerebral Hemorrhage (ICH).<sup>3</sup> The 2010 ICH guidelines state that patients with an elevated INR due to oral anticoagulants (OACs) should have their warfarin withheld, receive therapy to replace vitamin K-dependent factors and receive intravenous vitamin K (Class I; Level of Evidence: C). PCCs have not shown improved outcomes compared with FFP but may have fewer complications compared with FFP and are reasonable to consider as an alternative to FFP (Class IIa; Level of Evidence: B). Patients in which PCCs may be a reasonable alternative include patients who need emergent reversal of vitamin K dependent OAC bleeds, in which time to reversal and/or volume status preclude the use of FFP and vitamin K.

The approval of newer oral anticoagulants (e.g., dabigatran, rivaroxaban, apixaban), in the US market have also highlighted the need for appropriate antidotes for these medications. Currently, there are no effective reversal strategies for these agents. Emerging animal evidence suggests inactivated 4-factor or activated (e.g., FEIBA NF<sup>®</sup>) PCC may shorten hemorrhage time in the presence of dabigatran.<sup>4</sup> Although one healthy adult study with 12 patients suggested a 4-factor PCC may reverse the laboratory effects of rivaroxaban.<sup>5</sup> Dabigatran was not been shown to be affected by PCC administration in this study.

2. Because of their effects on the clotting cascade, PCCs have been used off-label for a variety of bleeding conditions.
3. Off-label uses are constrained by cost and limited clinical evidence.
4. The use of PCCs like other blood coagulation products (i.e., recombinant factor VIIa) carry the risk of thromboembolic adverse events. Concerns may be further heightened with the use of activated PCC.

### References

1. Patanwala AE, Acquisto NM, and Erstad B. Prothrombin complex concentrate for critical bleeding. *Ann Pharmacother*. 2011;45:990-9.
2. Holbrook A, Sculman S, Witt DM et al. Evidence based Management of anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9<sup>th</sup> ed: American College of Chest Physicians Evidence based clinical practice guidelines. *Chest* 2012; 141(2) (Suppl): e152S-e184S.
3. Morgenstern LB, Hemphill, III Claude, Anderson Craig et al. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage. *Stroke* 2010; 41: 00-11.
4. Zhou W, Schwarting S, Illanes S et al. Hemostatic Therapy in experimental intracranial hemorrhage associated with the direct thrombin inhibitor Dabigatran. *Stroke* 2011; 42: 3594-3599.
5. Eerenberg ES, Kamphuisen PW, Sijpkens MK et al. Reversal of Rivaroxaban and Dabigatran by PCC: A Randomized , Placebo-Controlled, Crossover Study in Healthy Subjects. *Circulation* 2011; 124: 1573-1579.
6. [www.clinicaltrials.gov/NCT00618098](http://www.clinicaltrials.gov/NCT00618098). Study of Octaplex and FFP in patients under vitamin K Therapy Antagonist needing urgent surgery or invasive procedures. Accessed 2-2-13.
7. Sarode R et al. Rapid warfarin reversal: a 3 factor PCC and rVIIa cocktail for intracranial hemorrhage. *J Neurosurg* 2012; 116: 491-497.
8. Dawlatshahi D et al. Poor prognosis in warfarin associated intracranial hemorrhage despite anticoagulation reversal. *Stroke* 2012; 43: 00-00.
9. Dager WE et al. Dabigatran effects on the INR, aPTT, TT and fibrinogen: A multicenter , In vitro study. *Ann Pharmacother* 2012; 46: 1627-1636.
10. Lambourne MD et al. Prothrombin complex concentrates reduce blood loss in murine coagulopathy induced by warfarin, but not in that induced by dabigatran etexilate. *J Throm & Haemost* 2012; 10: 1830-40.