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Prothrombin Complex Concentrates: Reversal of Warfarin Therapy

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Disclosures

Advisory Boards: Bayer, Boehringer-Ingelheim, Octapharma, CSL-Behring, Alexion

Research funding: Boehringer-Ingelheim, Pfizer-BMS

Speaker’s honoraria: Octapharma, Pfizer, CSL-Behring
Blood Coagulation Cascade

**Intrinsic-PTT**

- XIa \(\xrightarrow{\text{PL, Ca}^{++}, \text{VIIIa}}\) XII
- Xla \(\xrightarrow{\text{X}}\) Xa
- IX \(\xrightarrow{\text{Xa}}\) IXa

**Extrinsic-PT**

- VIIa/TF \(\xrightarrow{\text{VII}}\) VIIa
- PT(II) \(\xrightarrow{\text{PL, Ca}^{++}, \text{Va}}\) IIa

Fibrinogen \(\xrightarrow{\text{PL, Ca}^{++}, \text{Va}}\) Fibrin
NEW Blood Coagulation Cascade

Initiation

Tissue Factor/VIIa

Propagation

X

IX

VIIIa → IXa

Xa

II

Va

IIa

Fibrinogen

Fibrin
Vitamin K dependent Factors

Propagation

Tissue Factor/VIIa

Initiation

X

IX

Xa

IXa

VIIIa

II

IIa

Va

Fibrinogen

Fibrin

Thrombin Activity
Each vitamin K dependent protein contains 9-12 Gla residues.
What is $\gamma$-carboxylation?

Glutamic acid $\rightarrow \gamma$-carboxyglutamic acid

Carboxylase
Glutamic acid, CO\textsubscript{2} \rightarrow \gamma\text{-}carboxyglutamic acid

Vitamin K-dependent carboxylase

O_{2}

Vitamin K reductase

Vitamin K epoxide reductase

Warfarin inhibition
Propagation

Thrombin Activity

Initiation

Tissue Factor/VIIa

Coumadin

Fibrinogen

Fibrin

Coumadin

Fibrinogen

Fibrin

Coumadin

Fibrinogen

Fibrin

Coumadin

Fibrinogen

Fibrin

Coumadin

Fibrinogen

Fibrin

Coumadin

Fibrinogen

Fibrin

Coumadin

Fibrinogen

Fibrin
What do we Anticoagulate?

1. VTE (DVT/PE) Treatment
2. VTE Prevention
   A. Surgery (esp. orthopedics)
   B. Medical patients
3. Stroke prevention i.e. Atrial Fibrillation
4. Prosthetic Heart Valves
Problems with Coumadin:

1. Requires ~3-4 days for its effect and 3-4 days to wear off making it impractical for patients who require procedures
2. Many drug and food interactions that interfere with its pharmacokinetics
3. Narrow toxic-to-therapeutic window
4. Requires monitoring
Meta-analysis: Antithrombotic Therapy to Prevent Stroke in Patients Who Have Nonvalvular Atrial Fibrillation

Robert G. Hart, MD; Lesly A. Pearce, MS; and Maria I. Aguilar, MD

29 different trials over a period of 30 years involving 29,000 patients

60-70% risk reduction
From: Meta-analysis: Antithrombotic Therapy to Prevent Stroke in Patients Who Have Nonvalvular Atrial Fibrillation


29 different trials over a period of 30 years involving 29,000 patients

60-70% risk reduction
Warfarin, INR and Mortality

1.1-1.5 % major bleeds/pts-y (30 000 emergencies/y [G])

Analysis of 1 250 000 INR-values
42 451 patients: 3 533 death

Indications:
- AF 58%
- VTE 25%
- Stroke/TIA 22%
- Heart valves 18%
- Myocardial Infarction 3%

Another > 30 000/y non-hemorrhagic induced urgent interventions [G]

Mortality in matched non OAT pts

Target INR: 2.0-3.0
Optimal INR: 2.2-2.3

Thromboembolism
Hemorrhage

Odén, A, BMJ 2002; 325: 1073-75
Go, AS, JAMA 2003;290:2685-2692
Treatment option for reversal of OAT

**Withhold VKA:**

- Half lifes: 11 h Acenocoumarol (Sintrom)
- 40 h Warfarin (Coumadin)
- 31 h Fluindione (Previscan)
- 140 h Phenprocoumon

**Application of vitamin K:**

- oral: slow decrease of INR, start within 12-24 h
- i.v.: slow decrease of INR, start within 6-8 h
- s.c.: ???role

**Factor replacement:**

- immediate increase in factor activities

Ansell, J, Chest 2004;126:204S-233S
Baglin, TP, Br J Haematoll 2006;132:277-285
Aguilar, MI, Nayo Clin Proc 2007;83:82-92
Oral Vitamin K Lowers the International Normalized Ratio More Rapidly Than Subcutaneous Vitamin K in the Treatment of Warfarin-Associated Coagulopathy

A Randomized, Controlled Trial

Mark A. Crowther, MD, MSc; James D. Douketis, MD; Terri Schnurr, RN; Luigi Steidl, MD; Valentina Mera, MD; Carolina Ultori, MD; Achille Venco, MD; and Walter Ageno, MD
In a double blind randomized trial of 763 non-bleeding patients, oral vitamin K did not reduce bleeding when INRs were between 4 and 10
Treatment, time and INR

What are prothrombin complex concentrates (PCCs)?

Concentrated product of the vitamin dependent coagulation factors
  • Prothrombin
  • Factor VII
  • Factor IX
  • Factor X
  • Protein C
  • Protein S
  • Heparin

Two commercial products in Canada: Octaplex (Octapharma) and Beriplex (CSL Behring)
octaplex manufacturing process

- Cryoprecipitate-poor plasma
- Heparin and pH adjustment
- Ion Exchange Chromatography
- S/D Virus inactivation
- Ion exchange chromatography
- Virus removal: Nanofiltration
- Diafiltration
- Ultrafiltration
- Heparin and pH adjustment
- Sterile filtration, filling
- Lyophilisation
- octaplex®
Benefits of prothrombin complex concentrate (PCC) over fresh frozen plasma (FFP) for reversal of warfarin

### PCC vs Plasma

<table>
<thead>
<tr>
<th>FFP</th>
<th>PCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood group specific</td>
<td>Not blood group specific</td>
</tr>
<tr>
<td>Slow process to achieve target INR</td>
<td>Fast application: 10 mins</td>
</tr>
<tr>
<td>Takes time to thaw</td>
<td>Room temperated</td>
</tr>
<tr>
<td>Large volumes needed</td>
<td>Small volume</td>
</tr>
<tr>
<td>Varying content of coagulation factors</td>
<td>Standardised content of coagulation factors (1:1:1:1 ratio of FII, FVII, FIX, FX)</td>
</tr>
<tr>
<td>Unpredictable effect</td>
<td>Predictable effect</td>
</tr>
<tr>
<td>Not virus inactivated</td>
<td>Virus inactivated</td>
</tr>
<tr>
<td>Risk of TRALI</td>
<td>No risk of TRALI</td>
</tr>
</tbody>
</table>

**1.5 liter**  
**60 ml**
12 patients given FFP and 14 patients given PCC Not a randomized trial…. PCCs resulted in a lower INR

~800 ml FFP or 25-50 U/kg PCC
FFP n=12/ PCC n=14

Median Value at 0 and 15 min

MakrisM et al; Thromb Hamost 1997; 77:477-480
## Clinical studies: LEX-202

<table>
<thead>
<tr>
<th>Study number</th>
<th>LEX-202</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study centres (Number)</strong></td>
<td>Israel and Russia (n=6)</td>
</tr>
<tr>
<td><strong>Number of patients</strong></td>
<td>20 patients with major bleedings (INR&gt;5) or surgical/invasive procedures during treatment with oral anticoagulants (INR&gt;3)</td>
</tr>
<tr>
<td><strong>Treatment period</strong></td>
<td>Bleeding or procedure related</td>
</tr>
<tr>
<td><strong>Study drug (Batches used)</strong></td>
<td>Octaplex (n=3)</td>
</tr>
<tr>
<td><strong>Amount of study drug used</strong></td>
<td>37,250 IU</td>
</tr>
</tbody>
</table>
Clinical studies: LEX-202

n = 20
(10 bleeding, 10 surgery)
Median dose: 26.1 IU/kg
Clinical studies: LEX-202

Clinical efficacy rating

Mean dosage: 26.1 IU FIX/kg BW
Dosage range: 13.7-43.8 IU FIX/kg BW

Clinical studies: LEX-203

Efficacy and Safety of OCTAPLEX® in Patients Under Oral Anticoagulant Therapy and Undergoing Surgery or Invasive Procedures
A Prospective, Non-Randomised, Non-Controlled, Open-Label, Multi-Centre Phase III – Study (N = 60)
Correction of INR.

INR results pre and up to 1 hour post first infusion

Mean +/- standard deviation

Per-protocol population, N=56
Dosing recommendations

The dose will depend on the INR before treatment and the targeted INR. In the following table approximate doses (mL / kg body weight of the reconstituted product) required for normalisation of INR (≤1.2 within 1 hour) at different initial INR levels are given.

<table>
<thead>
<tr>
<th>Initial INR</th>
<th>2.0 - 2.5</th>
<th>2.5 - 3.0</th>
<th>3.0 - 3.5</th>
<th>&gt;3.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approximate dose* (mL octaplex® / kg body weight)</td>
<td>0.9 - 1.3</td>
<td>1.3 - 1.6</td>
<td>1.6 - 1.9</td>
<td>&gt;1.9</td>
</tr>
</tbody>
</table>

One vial of octaplex is 20 mL and contains 500 IU FIX

For example:
Recommended dose of octaplex for a 70 kg patient with starting INR of 2.5:
1.3 mL x 70 kg = 91 mL octaplex
91 mL octaplex / 20 mL per vial = 4.55 vials octaplex (2275 IU octaplex)
PRODUCT COMPOSITION:
- One 20 mL vial of octaplex® contains the following:

<table>
<thead>
<tr>
<th>Product</th>
<th>IU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human Coagulation Factor II</td>
<td>220-760</td>
</tr>
<tr>
<td>Human Coagulation Factor VII</td>
<td>180-480</td>
</tr>
<tr>
<td>Human Coagulation Factor IX</td>
<td>400-620</td>
</tr>
<tr>
<td>Human Coagulation Factor X</td>
<td>360-600</td>
</tr>
<tr>
<td>Protein C</td>
<td>140-620</td>
</tr>
<tr>
<td>Protein S</td>
<td>140-640</td>
</tr>
<tr>
<td>Heparin</td>
<td>80-310</td>
</tr>
<tr>
<td>Sodium citrate</td>
<td>17-27 mmol/L</td>
</tr>
</tbody>
</table>

- Reconstituted solution contains approximately 25 IU of prothrombin complex per mL.

INDICATIONS:
Recommended in:
- A. Reversal of warfarin therapy or vitamin K deficiency in patients exhibiting major bleeding manifestations.
- B. Reversal of warfarin therapy or vitamin K deficiency in patients requiring urgent (<6 hour) surgical procedures.

If a study is available all qualified patients should be encouraged to participate in the study rather than receiving open-label product.

Contraindicated in:
- A. Patients with a history of Heparin Induced Thrombocytopenia

Not recommended* for:
- A. Elective reversal of oral anticoagulant therapy pre - invasive procedure.
- B. Treatment of elevated INRs without bleeding or need for surgical intervention. For management of vitamin K antagonist overdose with elevated INR but without bleeding, please refer to the ACCP 2008 recommendations.
- C. Massive transfusion
- D. Coagulopathy associated with Liver dysfunction
- E. Patients with recent history of thrombosis, myocardial infarction, recent ischemic stroke or Disseminated Intravascular Coagulation (DIC)
B. Pediatric patients – there is insufficient evidence available to allow a recommendation for use of this product in this patient population.

C. Congenital factor II or X deficient patients – use of the product should be at the discretion of the local Hemophilia clinic.

DOsing, administration & monitoring:
The following recommendation is based on review of literature and the desire to prevent thrombotic complications. The subcommittee is aware that it may be less than the manufacturer’s recommended dose in many individuals.

For adult patients:

40 mL octaplex® (1000 IU Factor IX activity*) and 10 mg Vitamin K IV

*A higher or second dose may be needed in extremes of INR or weight, suggest consultation with a specialist in hematology or transfusion medicine in these situations.

Maximum total dose: 120 mL or 3000 IU Factor IX activity.

Administration: Must be administered intravenously.
The rate of infusion should not exceed 2-3 mL/min.

Post dose monitoring: INR – 10-15 minutes
Clinical outcomes (incl. thrombotic events) – 24 hour and 30 day
Jewish General Hospital (JGH) Experience

- Approval from Thrombosis and Hematology not needed
- Use reviewed retrospectively
- 1000 FIX units for ‘everyone’
  - Easier to implement
  - Scientific evidence for using BW and INRs not robust
  - Guide dose by INR 15-30 minutes post infusion

- NEED TO BE ON WARFARIN
JGH Experience: Issues

- Use of vitamin K
- Protocol stipulates that 10 mg IV vitamin K be given
- Should be given in most circumstances except when reversal is needed only temporary e.g. surgical procedures such as pacemakers, cardiac cath,
- Preparation of product
Treatment, time and INR

JGH Experience

- **Cost:**
  - $750 per 1000 FIX units vs. $200-250 per unit of FFP
    - i.e. same cost, maybe even cheaper than FFP
  - Definite reduction in costs of administration such as nursing costs
The effectiveness and safety of fixed low-dose prothrombin complex concentrates in patients requiring urgent reversal of warfarin

Cindy Varga, Sultan Al-Touri, Stella Papadoukakis, Stephen Caplan, Susan Kahn, and Mark Blostein
• Retrospective chart review of 103 patients who received PCCs for bleeding or need for an urgent procedure while patient on coumadin

• Received 1000 U (~16.7 U/kg) regardless of size and INR

• INR checked 30 minutes after infusion with the option of administering more if needed as judged by the treating physician

• Assessed clinical efficacy, INR response and toxicity within 30 days
Message 1: INR response not great (~50%<1.5) to PCC but clinical response excellent

INR Response

INR ≤1.5
50 patients (48.5%)

INR 1.6 – 2.0:
45 patients (43.7%)

INR 2.1 – 3.0:
7 patients (6.8%)

INR 3.1 – 5.0:
1 patients (0.97%)

Clinical Response

Excellent: 44 patients
Moderate: 0 patients
No response: 6 patients

Excellent: 36 patients
Moderate: 5 patients
No response: 3 patients
Unknown: 1 patient*

Excellent: 5 patients
Moderate: 1 patient
No response: 1 patient

Excellent: 1 patient
Moderate: 0 patients
No response: 0 patients

Excellent Clinical Response in 86/103 = 83%

Transfusion, 53:1451, 2013
Message 2: Intracranial Haemorrhage (ICH) do poorly despite PCCs

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>No. (N = 103)</th>
<th>Clinical Response No. (%)</th>
<th>Deaths due to bleeding (no.)</th>
<th>No. pts &gt; 1 dose</th>
<th>Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Excellent</td>
<td>Moderate</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>ICH</td>
<td>22</td>
<td>14 (63.6)</td>
<td>0 (0.0)</td>
<td>8 (36.4)</td>
<td>7</td>
</tr>
<tr>
<td>Extracranial Bleed</td>
<td>54</td>
<td>47 (87.0)</td>
<td>5 (9.3)</td>
<td>2 (3.7)</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>34</td>
<td>28 (82.4)</td>
<td>5 (14.7)</td>
<td>1 (2.9)</td>
<td>1</td>
</tr>
<tr>
<td>Traumatic</td>
<td>8*</td>
<td>6 (75.0)</td>
<td>0 (0.0)</td>
<td>1 (12.5)</td>
<td>0</td>
</tr>
<tr>
<td>Genito-urinary</td>
<td>7</td>
<td>7 (100.0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mucosal bleed</td>
<td>2</td>
<td>2 (100.0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>1</td>
<td>1 (100.0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hemothorax</td>
<td>1</td>
<td>1 (100.0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1</td>
<td>1 (100.0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Procedure</td>
<td>27</td>
<td>26 (96.3)</td>
<td>1 (3.7)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Transfusion, 53:1451, 2013
**Message 3**: Toxicity low
- Of 103 patients, 5 thrombotic events within 30 days
- All patients had other comorbidities

<table>
<thead>
<tr>
<th>Thrombosis</th>
<th>Days post PCC</th>
<th>Dose (IU)</th>
<th>Pre INR</th>
<th>Post INR</th>
<th>Management/ Clinical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep Venous Thrombosis</td>
<td>4</td>
<td>2000 IU</td>
<td>3.2</td>
<td>1.9</td>
<td>Bridged to warfarin</td>
</tr>
<tr>
<td>Non ST-elevation myocardial infarction</td>
<td>1</td>
<td>1500 IU</td>
<td>8.3</td>
<td>1.9</td>
<td>Treated conservatively. Good cardiac outcome.</td>
</tr>
<tr>
<td>Non ST-elevation myocardial infarction</td>
<td>1</td>
<td>1000 IU</td>
<td>4.4</td>
<td>3.2</td>
<td>Treated conservatively. Good cardiac outcome.</td>
</tr>
<tr>
<td>Bilateral Deep Venous Thrombosis</td>
<td>30</td>
<td>1000 IU</td>
<td>2.00</td>
<td>1.60</td>
<td>Bridged to warfarin</td>
</tr>
<tr>
<td>Non ST-elevation myocardial infarction</td>
<td>1</td>
<td>1000 IU</td>
<td>2.90</td>
<td>1.40</td>
<td>Treated conservatively. Good cardiac outcome.</td>
</tr>
</tbody>
</table>

Transfusion, 53:1451, 2013
DOSING, ADMINISTRATION & MONITORING:
The following recommendation is based on review of literature and the desire to prevent thrombotic complications. The working group is aware that it is less than the manufacturer’s recommended dose in many individuals. This is in part due to the fact the package insert recommendations will correct factor levels to normal despite the fact that normal hemostasis does not require 100% factor levels. The working group would also like to highlight that 50% of patients in the audit responded to the previously recommended standardized dose of 1000 IU (40 mL octaplex®).

For adult patients:

Dosing of prothrombin complex concentrate should be based on the INR as per the table below. If the INR is unknown and major bleeding is present, 80 mL should be administered.

<table>
<thead>
<tr>
<th>Dose of Prothrombin Complex</th>
<th>INR &lt;3.0</th>
<th>INR 3.0-5.0</th>
<th>INR &gt;5.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 mL (1000 IU)</td>
<td>80 mL (2000 IU)</td>
<td>120 mL (3000 IU)</td>
<td></td>
</tr>
</tbody>
</table>

Administration: Must be administered intravenously.
May be administered by direct IV push, syringe pump or minibag.
The manufacturer’s recommended maximal rates of infusion are:
- octaplex® = 3mL/min
- Beriplex® P/N = 8 mL/min.
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
Ravi Sarode, Truman J. Milling, Jr, Majed A. Refaai, Antoinette Mangione, Astrid Schneider, Billie L. Durn and Joshua N. Goldstein

- Randomized open label- 4 Factor PCC vs FFP
- 200 patients, ~100 per arm
- Non-surgical

<table>
<thead>
<tr>
<th>Baseline INR</th>
<th>4F-PCC Dose, IU of Factor IX per kg Body Weight*</th>
<th>Plasma Dose, mL per kg Body Weight*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 to &lt;4</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>4–6</td>
<td>35</td>
<td>12</td>
</tr>
<tr>
<td>&gt;6</td>
<td>50</td>
<td>15</td>
</tr>
</tbody>
</table>

4F–PCC indicates 4-factor prothrombin complex concentrate; and INR, international normalized ratio.

*Dose calculation based on 100 kg body weight for patients weighing >100 kg. Maximum dose ≤5000 IU of factor IX (4F-PCC) or ≤1500 mL (plasma).
Primary endpoint analysis

### Table 7. Rapid INR Reduction (Intention-to-Treat Efficacy Population)

<table>
<thead>
<tr>
<th>No. (%) of Patients [95% CI]</th>
<th>Difference 4F-PCC Minus Plasma, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4F-PCC (n=98)</td>
<td>Plasma (n=104)</td>
</tr>
<tr>
<td>61 (62.2)</td>
<td>10 (9.6)</td>
</tr>
<tr>
<td>[52.6 to 71.1]</td>
<td>[3.9 to 15.3]</td>
</tr>
</tbody>
</table>

4F-PCC indicates 4-factor prothrombin complex concentrate; CI, confidence interval; and INR, international normalized ratio.

*INR ≤1.3 at 0.5 h after end of infusion.

†4F-PCC noninferior to plasma: lower limit of 95% CI more than −10%

Farrington–Manning P value for noninferiority P<0.0001 rejecting null hypothesis of inferiority of 4F-PCC; 4F-PCC superior to plasma: lower limit of 95% CI >0.

### Table 5. Hemostatic Efficacy (Intention-to-Treat Efficacy Population)

<table>
<thead>
<tr>
<th>Primary Rating</th>
<th>4F-PCC (n=98)</th>
<th>Plasma (n=104)</th>
<th>Difference 4F-PCC Minus Plasma, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemostatic efficacy rating by category*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>44† (44.9)</td>
<td>45† (43.3)</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>27 (27.6)</td>
<td>23 (22.1)</td>
<td></td>
</tr>
<tr>
<td>Poor/none</td>
<td>27 (27.6)</td>
<td>36 (34.6)</td>
<td></td>
</tr>
<tr>
<td>Noneffective</td>
<td>25 (25.5)</td>
<td>33 (31.7)</td>
<td></td>
</tr>
<tr>
<td>Missing primary rating</td>
<td>2 (2.0)</td>
<td>3 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Effective hemostasis</td>
<td>71 (72.4)</td>
<td>68 (65.4)</td>
<td>7.1‡ (−5.8 to 19.9)</td>
</tr>
<tr>
<td>2.6 (18.1)</td>
<td>56.2 (71.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Effective hemostasis indicates hemostatic efficacy rated as excellent or good. 4F-PCC indicates 4-factor prothrombin complex concentrate; and CI, confidence interval.

*Hemostatic efficacy assessed by a blinded independent board.

†P=0.50 by Cochran–Mantel–Haenszel test.

‡4F-PCC noninferior to plasma: lower limit of 95% CI more than −10%

Farrington–Manning P value for noninferiority P=0.0045 rejecting null hypothesis of inferiority of 4F-PCC.
### Table 8. Summary of AEs (Intention-to-Treat Safety Population)

<table>
<thead>
<tr>
<th>AE</th>
<th>4F-PCC (n=103)</th>
<th>Plasma (n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any nonserious AE*</td>
<td>66 (64.1)</td>
<td>71 (65.1)</td>
</tr>
<tr>
<td>Related AE†</td>
<td>10 (9.7)</td>
<td>23 (21.1)</td>
</tr>
<tr>
<td>AE leading to treatment discontinuation</td>
<td>0</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Serious AE*</td>
<td>32 (31.1)</td>
<td>26 (23.9)</td>
</tr>
<tr>
<td>Related serious AE†</td>
<td>2 (1.9)</td>
<td>4 (3.7)</td>
</tr>
</tbody>
</table>

**AEs of interest**

<table>
<thead>
<tr>
<th>Event</th>
<th>4F-PCC (n=103)</th>
<th>Plasma (n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths to day 30</td>
<td>6 (5.8)</td>
<td>5 (4.6)</td>
</tr>
<tr>
<td>Deaths to day 45</td>
<td>10 (9.7)</td>
<td>5 (4.6)</td>
</tr>
<tr>
<td>Related deaths (to day 45)†</td>
<td>1 (1.0)</td>
<td>0</td>
</tr>
<tr>
<td>Thromboembolic AE</td>
<td>8 (7.8)</td>
<td>7 (6.4)</td>
</tr>
<tr>
<td>Related thromboembolic AE†</td>
<td>4 (3.9)</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Fluid overload or similar cardiac event</td>
<td>5 (4.9)</td>
<td>14 (12.8)</td>
</tr>
<tr>
<td>Related fluid overload or similar cardiac event†</td>
<td>0</td>
<td>7 (6.4)</td>
</tr>
</tbody>
</table>

4F-PCC indicates 4-factor prothrombin complex concentrate; and AE, adverse event.

*Defined in Table XIV in the online-only Data Supplement.
†Defined as events for which there was a relationship to study treatment in the opinion of the investigator. AEs with missing relationship were considered treatment related.
‡As assessed by the Safety Adjudication Board; no deaths in either group were classified as related by an investigator.
Kcentra (Prothrombin Complex Concentrate, Human)

STN: BL 1254210
Proper Name: Prothrombin Complex Concentrate (Human)
Trade Name: Kcentra

Indication:
- For urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients with acute major bleeding.

Product Information
- Product Labeling - Prothrombin Complex Concentrate (Human) (PDF - 1.5MB)

Supporting Documents
- April 29, 2013 Approval Letter - Prothrombin Complex Concentrate (Human)
- Summary Basis for Regulatory Action - Kcentra (PDF - 634KB)
- Approval History, Letters, Review, and Related Documents - Kcentra

Related Information
- FDA approves Kcentra for the urgent reversal of anticoagulation in adults with major bleeding

Page Last Updated: 05/21/2013
Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.
What about the New Oral Anticoagulants Dabigatran (Pradaxa) Rivaroxaban (Xarelto) Apixaban (Eliquis)?
Prothrombin complex concentrates reduce blood loss in murine coagulopathy induced by warfarin, but not in that induced by dabigatran etexilate

M. D. LAMBOURNE, * L. J. ELTRINGHAM-SMITH, † S. GATAIANE, † D. M. ARNOLD, * ‡
M. A. CROWTHER ‡ and W. P. SHEFFIELD * ‡
*Canadian Blood Services, Research and Development, †Department of Pathology and Molecular Medicine; and ‡Department of Medicine,
McMaster University, Hamilton, Ontario, Canada
Reversal of dabigatran anticoagulation by prothrombin complex concentrate (Beriplex P/N) in a rabbit model

I. PRAGST,* S. H. ZEITLER,* B. DOERR,* F. J. KASPEREIT,* E. HERZOG,* G. DICKNEITE* and J. VAN RYN†
*CSL Behring GmbH, Marburg; and †Boehringer Ingelheim Pharma GmbH & Co KG, Biberach, Germany

Fig. 4. Blood loss after kidney incision in dabigatran-treated rabbits receiving PCC doses in the range of 0–50 IU kg⁻¹. Graphic conventions as in Fig. 3. CI, 95% confidence interval; PCC, prothrombin complex concentrate.
Hemostatic Therapy in Experimental Intracerebral Hemorrhage Associated With Rivaroxaban
Wei Zhou, Markus Zorn, Peter Nawroth, Ulf Bütehorn, Elisabeth Perzborn, Stefan Heitmeier and Roland Veltkamp

B

Control
Rivaroxaban
Rivaroxaban + FVIIa
Rivaroxaban + FFP
Rivaroxaban + PCC

2 mm

C

Hematoma volume (mm³)

Control Rivaroxaban FVIIa FFP PCC

Blood volume (μL)

Control Rivaroxaban FVIIa FFP PCC

*
Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate: A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects

Elise S. Eerenberg, Pieter W. Kamphuisen, Meertien K. Sijpkens, Joost C. Meijers, Harry R. Buller and Marcel Levi

Circulation 124:1573, 2011

**Rivaroxaban**

- **PT**

- **Time**

- **Baseline**

- **T=0**

- **15 min**

- **30 min**

- **1 h**

- **2 h**

- **4 h**

- **6 h**

- **24 h**

- **Seconds**

- **Rivaroxaban 20mg BID for two and a half days**

- **PCC or placebo infusion**

- **placebo**

- **PCC**

**Dabigatran**

- **TT**

- **Time**

- **Baseline**

- **T=0**

- **15 min**

- **30 min**

- **1 h**

- **2 h**

- **4 h**

- **6 h**

- **24 h**

- **Seconds**

- **Dabigatran 150mg BID for two and a half days**

- **PCC or placebo infusion**

- **placebo**

- **PCC**
Current Protocols

Rivaroxaban:
- Cohort of patients with bleeding on rivaroxaban
- Multi center registry across Canada
- Funded by Octapharma
- *Use of Beriplex (PCC):* 25-50 U/kg

Dabigatran:
- Cohort of patients with bleeding on dabigatran
- Multi center registry across Canada
- Funded by Baxter
- *Use of FEIBA (activated PCC)*
  - Anecdotal cases