Nova Scotia Provincial Blood Coordinating Program

Guideline for
Prothrombin Complex Concentrate Utilization in Nova Scotia

Version 3.0
April 2016

PROMOTING EXCELLENCE IN TRANSFUSION MEDICINE
http://novascotia.ca/dhw/nspbcp
Developed by the Prothrombin Complex Concentrate Working Group (2016)

Principal Compiler: Susan Cairns BN RN
Utilization Transfusion Practice Coordinator
Nova Scotia Provincial Blood Coordinating Program
1673 Bedford Row
Room 2123
Halifax, Nova Scotia B3J 1T1
Phone: (902) 487-0508
susan.cairns@nshealth.ca

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Recommended Citation:
Table of Contents

1 Background ........................................................................................................................................... 4

2 Introduction ........................................................................................................................................... 4
   Table 1: Product Composition ....................................................................................................... 5

3 Guideline Development and Implementation Process ................................................................. 5
   3.1 Definitions ...................................................................................................................................... 5
   3.2 Development .................................................................................................................................. 5
   3.3 Impact assessment .......................................................................................................................... 6
   3.4 Endorsement ................................................................................................................................... 6
   3.5 Implementation ............................................................................................................................... 6
   3.6 Dissemination ................................................................................................................................... 6
   3.7 Monitoring, reporting and evaluation ............................................................................................. 6
   3.8 Review and revisions ....................................................................................................................... 6

4 Guideline ............................................................................................................................................... 6
   4.1 Indications for Use ......................................................................................................................... 6
      Table 2: CHEST Guidelines for the Management of Elevated INRs while on Vitamin K Antagonist (Warfarin) therapy ........................................................................................ 7
   4.2 Recommended Dosing .................................................................................................................. 7
      Table 3: PCC Dosing for Adults: ................................................................................................... 7
      Monitoring Requirement ................................................................................................................ 8
   4.3 Contraindications .......................................................................................................................... 8

5 References ............................................................................................................................................. 9

Appendix A – Prothrombin Complex Concentrates Working Group Members ........................................ 10
Appendix B – Data Collection Tool ..................................................................................................... 11
1 Background

The Nova Scotia Provincial Blood Coordinating Program (NSPBCP) provides leadership in collaborating with health care providers across the province and Canadian Blood Services (CBS) to maximize the safe and appropriate management of blood and blood products for patients in Nova Scotia. The NSPBCP maintains a surveillance program for adverse events related to transfusion therapy while ensuring appropriate standards for blood-transfusion therapy are being implemented and maintained within Nova Scotia health-care facilities.

Oral vitamin K antagonists, such as Coumadin®, are in widespread use for the prevention and treatment of thromboembolic disorders. “The major adverse effect of warfarin is bleeding. On average, the annual rate of major bleeding is 1-2% in patients on chronic warfarin, while minor bleeding events occur in 10-20% of warfarin users per year.” (Thrombosis Canada 2015) Rapid reversal of anticoagulation in bleeding patients or prior to urgent surgery or other interventional treatment is critical in mitigating morbidity and mortality. When indicated, the administration of PCCs with Phytonadione (Vitamin K₁) supplementation is the most effective method for rapid reversal of anticoagulation therapy.

Prothrombin complex concentrates (PCCs) (octaplex® and Beriplex®P/N), derived from human plasma and having undergone solvent/detergent treatment and/or nanofiltration for viral, bacterial and parasite inactivation/removal, have been licensed for use in Canada by Health Canada.

2 Introduction

The objective of the Guideline for Prothrombin Complex Concentration Utilization in Nova Scotia is to provide clinical guidance to healthcare professionals with patient conditions who may benefit from the rapid reversal of vitamin K antagonists while providing standardization of care on the appropriate use of PCCs. Guidelines provide evidence-based information and consensus-based recommendations for consideration when making individual decisions. Guidelines should not replace the case-by-case decisions for individual patient care which are unique to each circumstance.

PCCs are indicated for patients who require rapid correction of prothrombin complex coagulation factors, i.e. the patient is taking oral vitamin K antagonists (anticoagulants) and is bleeding or requiring urgent surgery/invasive procedure. It requires, however, careful risk benefit evaluation with awareness of contraindications and laboratory follow-up for dose adjustment¹.

In Canada, the PCCs contain 4 coagulation factors (Factors II, VII, IX, X).
Table 1: Product Composition\(^1,2\)

One 20 mL (500 IU) vial of PCC (reconstituted) contains the following:

<table>
<thead>
<tr>
<th>Factor</th>
<th>octaplex(^1)</th>
<th>Beriplex P/N(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human Coagulation Factor II</td>
<td>280-760 IU</td>
<td>380-800 IU</td>
</tr>
<tr>
<td>Human Coagulation Factor VII</td>
<td>180-480 IU</td>
<td>200-500 IU</td>
</tr>
<tr>
<td>Human Coagulation Factor IX</td>
<td>500 IU</td>
<td>400-620 IU</td>
</tr>
<tr>
<td>Human Coagulation Factor X</td>
<td>360-600 IU</td>
<td>500-1020 IU</td>
</tr>
<tr>
<td>Antithrombin III</td>
<td></td>
<td>4-30 IU</td>
</tr>
<tr>
<td>Protein C</td>
<td>140-620 IU</td>
<td>420-820 IU</td>
</tr>
<tr>
<td>Protein S</td>
<td>140-640 IU</td>
<td>240-680 IU</td>
</tr>
<tr>
<td>Heparin</td>
<td>80-310 IU</td>
<td>8-40 IU</td>
</tr>
<tr>
<td>Sodium citrate</td>
<td>17-27 mmol/L</td>
<td>~3 mmol/L</td>
</tr>
</tbody>
</table>

Due to the potential for thrombotic complications, treatment with PCCs should be initiated under the supervision of a clinician experienced in the treatment of coagulation disorders (i.e. emergency clinicians, hematologists, anesthetists). This caveat will ensure appropriate use, dosing and management of potential complications\(^1\).

3 Guideline Development and Implementation Process

3.1 Definitions

Coagulopathy - “a condition in which the blood’s ability to clot is impaired.” Some clinicians will also refer to coagulopathy in terms of thrombotic states. “…because of the complexity of the hemostatic pathways, the two conditions can exist simultaneously.”\(^7\)

INR (International Normalized Ratio) – a standardized way to report prothrombin time (PT) normalized for the different types of PT reagents available in laboratories

Vitamin K Antagonist (VKA) - an anticoagulant inhibiting the synthesis of vitamin K dependent clotting factors (Factors II, VII, IX and X, and the anticoagulant proteins C and S). The vitamin K antagonists referred to in this guideline are oral medications.

Prothrombin Complex Concentrate (PCC) – a lyophilized plasma protein product (PPP) derived from human plasma containing the vitamin K dependent coagulation factors.

3.2 Development

In 2009, the NSPBCP convened a physician working group for the development of the Utilization Guidelines for Prothrombin Complex Concentrates (octaplex\(^\circ\)). At the same time, the NSPBCP began collecting utilization data for PCCs within Nova Scotia. These guidelines were revised in 2012 and 2013 when the National Advisory Committee on Blood and Blood Products (NAC) provided updated versions of their recommendations. In 2014, NAC revised their Recommendations for Use of Prothrombin Complex Concentrates in Canada. The PCC WG (Appendix A) was reconvened in 2015 and the following guideline has been adapted from the 2014 NAC recommendations with the dosing recommendations based on data results from PCC utilization in Nova Scotia.
3.3 Impact assessment
The following guideline has not changed the appropriate dosing recommendations in Nova Scotia therefore this guideline would not impact appropriate current practice.

3.4 Endorsement
The Prothrombin Complex Concentrate Working Group has served as the advisory body to the NSPBCP for the development of these guidelines.

3.5 Implementation
The Guideline for the Utilization of Prothrombin Complex Concentrates in Nova Scotia is intended for provincial implementation.

3.6 Dissemination
The Guideline for the Utilization of Prothrombin Complex Concentrates in Nova Scotia guidelines will be disseminated to the NSHA and IWK for implementation.

3.7 Monitoring, reporting and evaluation
In order to monitor adherence to the Guideline for the Utilization of Prothrombin Complex Concentrates in Nova Scotia, PCC utilization is reported to the NSPBCP on a quarterly basis using the data collection tool in Appendix B. Annual and quarterly utilization is reported to the NSHA and IWK and strategies to optimize appropriate use are implemented in collaboration with the NSPBCP.

3.8 Review and revisions
The following guideline will be reviewed and revised as per NSPBCP policy or as new evidence and/or national guidelines become available.

4 Guideline

4.1 Indications for Use
PCCs are recommended in the following situations:

1. Rapid reversal of warfarin therapy, i.e. Coumadin®/Sintrom® or vitamin K deficiency in patients exhibiting major bleeding manifestations.
2. Rapid reversal of warfarin therapy, i.e. Coumadin®/Sintrom® or vitamin K deficiency in patients requiring urgent surgical (less than 6 hours) or other interventional procedures.

NOTE – the 6 hour recommendation reflects the half life of the product and does not apply to the urgency of the surgery/procedure.

PCCs should only be administered to patients with an INR (International Normalized Ratio) greater than or equal to 1.7. It is recommended the INR be available prior to administering PCCs, however, in emergent situations (i.e. major bleeding or intracranial hemorrhage) where the INR result is delayed or not available and it is known the patient is taking a vitamin K antagonist, the administration of PCCs is acceptable with the understanding the INR will be collected prior to PCC administration.
For management of vitamin K antagonist treatment with an elevated INR in the absence of bleeding, it is recommended clinicians refer to the American College of Chest Physicians (ACCP) 2012 recommendations. In most of these instances, reduction of the dose of the vitamin K antagonist and/or administration of Phytonadione (Vitamin K₁) is usually sufficient for patient management.

**Table 2: CHEST Guidelines for the Management of Elevated INRs while on Vitamin K Antagonist (Warfarin) therapy**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR 4.5 to 10 No evidence of bleeding</td>
<td>Do not administer vitamin K. Hold or lower the dose of VKA</td>
</tr>
<tr>
<td>INR greater than 10 No evidence of bleeding</td>
<td>Administer oral vitamin K. Hold or lower the dose of VKA</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>Rapid reversal of anticoagulation with PCC and slow administration of vitamin K 5-10 mg IV. Do not administer plasma.</td>
</tr>
</tbody>
</table>

“It is critical to recognize that the use of prothrombin complex concentrates may unmask thrombotic risk factors that were being managed through the use of Vitamin K antagonists.”

**4.2 Recommended Dosing**

The following dosing recommendations are based on utilization data results received from Nova Scotia hospitals since the implementation of the previous guideline (Version 2.3) - April 2013 to March 2015.

**Table 3: PCC Dosing for Adults**

<table>
<thead>
<tr>
<th>INR 1.7 – 5.0</th>
<th>INR ≥ 5.1 OR Intracranial Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose of PCC</td>
<td></td>
</tr>
<tr>
<td>40 mL (1000 IU)</td>
<td>80 mL* (2000 IU)</td>
</tr>
</tbody>
</table>

*The recommended PCC dose of 80 mL (1000 IU) may be administered
  o to patients who are on a vitamin K antagonist with an INR greater than or equal to 5.1 and the patient is bleeding, or requiring urgent surgery or invasive procedure within 6 hours
  o to patients who are taking vitamin K antagonist but the INR is not known and the patient has a major bleed
  o to patients who are taking a vitamin K antagonist and have an intracranial hemorrhage

For pediatric patients, consultation with a pediatric hematologist is recommended.

**NOTE:** The above dosing may be less than the manufacturer’s recommendations contained in the product monograph. The product monograph “recommendations aim to correct factor levels to normal despite the fact normal hemostasis does not require 100% factor levels.”
Phytonadione (Vitamin K₁) 10 mg administered intravenously is strongly recommended.³,⁴ Intramuscular and subcutaneous administration of Phytonadione (Vitamin K₁) is not recommended.⁴

**Monitoring Requirement**¹

*Pre-dose monitoring:* The pre-dose INR is required. There may be situations where the clinician cannot wait for the INR result prior to administering the PCC dose however the pre-PCC INR should be drawn and calculated.

*Post-dose monitoring:* Efficacy of dosing must be determined by testing the INR 10 - 30 minutes post PCC administration.⁴

The post-PCC administration target INR is 1.7 however for intracranial hemorrhage, the target INR is less than 1.3.⁵ If the target INR is not obtained after initial or subsequent doses or if there is insufficient time to wait for the vitamin K to take effect and the patient continues to bleed or to require urgent surgery or invasive procedure, consider administering an additional PCC dose of 20 mL (500 IU Factor IX activity).

It is recommended clinical outcomes (including thrombotic events) be assessed at 24 hours and upon hospital discharge or 30 days post PCC administration, whichever comes first.

### 4.3 Contraindications

**PCCs are not indicated for the following:**⁴

i. in patients with a history of heparin induced thrombocytopenia (HIT)

ii. those who have shown hypersensitivity to any ingredient in the product

iii. for the treatment of intracranial hemorrhage or other bleeding occurring as a complication of thrombolytic therapy.

**PCCs are generally not recommended* for:**⁴

i. elective reversal of oral anticoagulant therapy pre – invasive procedure

ii. treatment of elevated INRs without bleeding or need for surgery or other interventional treatment (refer to the ACCP 2012 recommendations)

iii. massive transfusion

iv. coagulopathy associated with liver dysfunction

v. disseminated intravascular coagulopathy (DIC)

vi. utmost caution should be used in patients with a recent (within three months) history of thrombosis (myocardial infarction, ischemic stroke or thromboembolism)

**Special patient populations*:**⁴

i. There is insufficient published evidence to recommend for use of PCCs in pediatric patients, pregnant and lactating women. Caution should be exercised if used in pregnancy, particularly in the peripartum/early postpartum period because of the heightened tendency for thrombosis.

ii. The use and dosing of the product for congenital factor II or X deficient patients should be at the discretion of the bleeding disorder/hemophilia clinic.

iii. There is insufficient published evidence to recommend PCCs for the reversal of direct thrombin inhibitors⁴ (i.e. Argatroban, Bivalirudin, Dabigatran) or factor Xa inhibitors (i.e. Apixaban, Dalteparin, Danaparoid, Enoxaparin, Tinzaparin, Fondaparinux, Rivaroxaban). There is published evidence suggesting PCCs may be effective in the reversal of direct anti-Xa (Rivaroxaban) therapy in animal studies and in healthy volunteers however no consensus on the appropriateness and dosing has been determined.⁴
*There may be extenuating clinical circumstances necessitating the use of PCCs in these clinical situations where the benefit outweighs the risk. They should be evaluated on a case-by-case basis with a clinician experienced in the use of this product. If the decision is made to use the product off-label in liver dysfunction and DIC, consult the product monograph for further recommendations (e.g. the need for antithrombin levels or replacement).  

5 References


Appendix A – Prothrombin Complex Concentrates Working Group Members

The NSPBCP acknowledges the tremendous and diligent work of the provincial PCC WG for providing valuable expertise and contributions in the development of this guideline.

<table>
<thead>
<tr>
<th>Prothrombin Complex Concentrates Working Group</th>
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</thead>
<tbody>
<tr>
<td>Dr. Frank Cragg</td>
</tr>
<tr>
<td>Dr. Brian Jollymore</td>
</tr>
<tr>
<td>Dr. Eiad Kahwash</td>
</tr>
<tr>
<td>Dr. Blaine Kent</td>
</tr>
<tr>
<td>Dr. Jean F. Legare</td>
</tr>
<tr>
<td>Dr. Stephen Phillips</td>
</tr>
<tr>
<td>Dr. Victoria Price</td>
</tr>
<tr>
<td>Dr. Irene Sadek</td>
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<thead>
<tr>
<th>Nova Scotia Provincial Blood Coordinating Program (NSPBCP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. Sudeep Shivakumar</td>
</tr>
<tr>
<td>Marina Hamilton</td>
</tr>
<tr>
<td>Susan Cairns</td>
</tr>
</tbody>
</table>
# Appendix B – Data Collection Tool

## Massive Bleeding Data Collection Form

**Blood Components & Products/PCC/rFVIIa**

<table>
<thead>
<tr>
<th>Province ID#</th>
<th>Hospital ID#</th>
<th>Date</th>
<th>Patient HCN</th>
<th>Patient First &amp; Last Name</th>
<th>Birth date</th>
<th>Gender</th>
<th>Weight (kg)</th>
<th>Ordering Physician CPSNS #</th>
<th>Physician Name</th>
<th>Specialty</th>
<th>Location (circle): Emerg / ICU / OR / Floor / Clinic / Other (specify)</th>
</tr>
</thead>
</table>

### Massive Bleeding

- [ ] No
- [ ] Yes – specify

### On Anticoagulants

- [ ] No
- [ ] Yes – specify

#### MTP Activated

- [ ] No
- [ ] Yes

**Time activated:** _______ (hhmm)

#### MTP Activated by:

- [ ] Lab
- [ ] Physician

**Specify blood components issued at activation:**

- [ ] None
- [ ] RBC ________ units
- [ ] Plasma ________ mL
- [ ] Platelets ________ units
- [ ] Other

#### Tranexamic Acid

- [ ] No
- [ ] Yes

**Time administered:** _______ (hhmm)

### Total Blood Products/Components transfused

- [ ] None
- [ ] Yes – specify

<table>
<thead>
<tr>
<th>Category</th>
<th>Units/Doses</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC</td>
<td>________</td>
<td></td>
</tr>
<tr>
<td>Plasma</td>
<td>________ mLs</td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>________ doses</td>
<td></td>
</tr>
<tr>
<td>Cryo</td>
<td>________ units</td>
<td></td>
</tr>
</tbody>
</table>

**platelet doses requested from CBS** (for facilities where platelets are not inventoried) ________ doses

### PCC

- [ ] No
- [ ] Yes

**Product administered (circle):** octaplex® / Beriplex® P/N

**Concentrations Factor II or X Deficiency**

- [ ] No
- [ ] Yes (specify)

**Vitamin K Deficiency**

- [ ] No
- [ ] Yes

#### Patient on oral anticoagulants

- [ ] No
- [ ] Coumadin®
- [ ] Sintrom®
- [ ] Other

- [ ] Actively Bleeding
- [ ] Yes

**Specify procedure:**

**Date of Procedure:** _______ (YYYY/MM/DD)

#### Initial INR result

**INR result known prior to issuing PCC**

- [ ] Yes
- [ ] No

**Phytonadione (Vitamin K®) administered**

- [ ] Yes
- [ ] Dose _____ mg.

#### Initial PCC dose

<table>
<thead>
<tr>
<th>PCC Dose</th>
<th>mL</th>
<th>Time (hhmm)</th>
<th>Post INR</th>
<th>Time (hhmm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### PCC Dose 2

- [ ] mL
- [ ] Time (hhmm)
- [ ] Post INR
- [ ] Time (hhmm)

#### PCC Dose 3

- [ ] mL
- [ ] Time (hhmm)
- [ ] Post INR
- [ ] Time (hhmm)

#### PCC Dose 4

- [ ] mL
- [ ] Time (hhmm)
- [ ] Post INR
- [ ] Time (hhmm)

### rFVIIa

**If reporting rFVIIa use, complete the Massive Bleeding/Transfusion section.**

#### rFVIIa administered

- [ ] No
- [ ] Yes

**Total rFVIIa dose administered:** _____ mg

**Reason for administration:**

### Clinical Disposition

- [ ] Bleeding stopped
- [ ] Yes
- [ ] Unknown or N/A

- [ ] Patient discharged
- [ ] Yes
- [ ] Unknown or N/A

- [ ] Patient survived
- [ ] Yes
- [ ] Date of death _______ (YYYY/MM/DD)

**Did the patient develop arterial/venous thromboembolism during hospitalization?**

- [ ] No
- [ ] Yes
- [ ] Unknown or N/A

**Comments / Additional Information**

**Signature:**

Fax to NSPBCP 902-422-0893

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