



RECOMMENDATIONS FOR USE OF PROTHROMBIN COMPLEX CONCENTRATES IN CANADA



NATIONAL ADVISORY COMMITTEE ON BLOOD AND BLOOD PRODUCTS RECOMMENDATIONS FOR USE OF PROTHROMBIN COMPLEX CONCENTRATES

BACKGROUND:

The National Advisory Committee on Blood and Blood Products (NAC) is an interprovincial medical and technical advisory body to the provincial and territorial health ministries and the blood supplier Canadian Blood Services (CBS). Its mandate is to provide professional leadership in assisting in identifying, designing and implementing cost-effective blood utilization management initiatives for the optimization of patient care throughout Canada. In 2008, NAC was approached by CBS and the Provinces to develop national recommendations for appropriate use and distribution of the first prothrombin complex concentrate (PCC) available in Canada, octaplex®. Since that first recommendation document, two national audits of octaplex® and licensure of a second product, Beriplex® P/N has occurred.

Both octaplex® and Beriplex® P/N can be classified as four factor prothrombin complex concentrates. They are both human plasma derived products that have undergone solvent/detergent treatment and/or nanofiltration for viral, bacterial and parasite inactivation and removal. They contain not only the procoagulant Vitamin K dependent factors – II, VII, IX and X – but also contain the anticoagulant factors Protein C, Protein S and Heparin to varying degrees. In addition, Beriplex® P/N also contains Antithrombin. This group is not recommending one product over the other but do recommend not mixing the two products within the same infusion. There is however no evidence to suggest that infusing a second dose of the alternate product would be detrimental. Both of the manufacturers recommend their product when rapid correction of prothrombin complex levels is necessary, such as major bleeding or emergency surgery. For management of vitamin K antagonist treatment with an elevated INR but without bleeding, clinicians are referred to the American College of Chest Physicians (ACCP) 2008 recommendations. In most of these cases, reduction of the dose of the vitamin K antagonist and/or administration of Vitamin K₁ is usually sufficient for patient management.

The first review in 2009 targeted 20 institutions that had received the most issues of octaplex® from CBS. Ten responses were received reflecting 14 of the institutions. Only two out of the ten respondents adopted the 2008 NAC recommendations as written. The majority of sites altered the dosing recommendations prompting a second broader scope review in fall of 2010 and the following modifications to the NAC recommendations for the use of prothrombin complex concentrates in Canada.

The audit data from 2010, literature review and ongoing concerns regarding inventory distribution, cost and potential for thrombotic complications were considered during the PCC working group's revision of the 2008 recommendations. The working group continues to advocate the use of this product under the supervision of physicians who have access to expertise in thrombosis/hemostasis/transfusion medicine and to adequate diagnostic and treatment facilities to ensure appropriateness of indication, dosing of the product and management of its potential complications. 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. These recommendations consider available literature, audit data and consensus opinion of the working group. The lack of strong randomized control trial evidence on clinical effectiveness, morbidity and mortality highlights



the need for ongoing data collection on outcome data to ensure best practice. Conflict of interest disclosures of the working group members are available on the NAC website (www.nacblood.ca).

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 hours) surgical procedures.

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 or Disseminated Intravascular Coagulation (DIC)

** There may be extenuating clinical circumstances necessitating use of prothrombin complex concentrates in these clinical situations. They should be evaluated on a case-by-case basis with a physician experienced in the use of this product. If the decision is to use the product off-label in liver dysfunction and DIC, please consult the product monograph for further recommendations (e.g. the need for antithrombin levels or replacement)*

Special patient populations:

A. Pregnant and lactating women - there is insufficient evidence available to allow a recommendation for use of this product in this patient population. Caution should be exercised if used in pregnancy, particularly in the peripartum/early postpartum period because of heightened tendency to thrombosis.

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.

D. Reversal of Direct Thrombin Inhibitors (DTI) and other warfarin alternatives- there is insufficient evidence available to allow a recommendation for use of these products for the reversal of DTI (ie. Dabigatran, Rivaroxaban) therapy.



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.

	INR <3.0	INR 3.0-5.0	INR >5.0
Dose of Prothrombin Complex	40 mL (1000 IU)	80 mL (2000 IU)	120 mL (3000 IU)

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.

Vitamin K: Vitamin K₁ (10 mg IV) co-administration is strongly recommended if a reversal is required for longer than 6 hours (the half life of PCC). The onset of action of Vitamin K₁ is 4-6 h IV.

The working group recognizes that institutional policy may preclude the use of intravenous Vitamin K₁ administration. Although oral administration will correct Vitamin K deficiency, this route of administration may be less effective due to a delayed onset of action particularly if lower doses are used. The working group recommends review of policy to include administration of IV Vitamin K₁ at slow infusion rates to reduce concerns about reactions. Intramuscular and subcutaneous Vitamin K₁ are not recommended.

Post dose monitoring: 1. INR values - Since dose effect is not universally applicable, efficacy of dosing must be determined using the surrogate marker of an **INR - 10-30 minutes post PCC administration**. If correction to an INR <1.5 has not been achieved and there is insufficient time to wait for Vitamin K to take effect, a subsequent dose of PCC may be required if the patient continues to demonstrate clinical bleeding.

2. Clinical outcome - including evaluation of mortality and thrombotic events, at 24 hours and 30 days post dose.



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