Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

CUH
Ospidéal Ollscoile Chorcaí
Cork University Hospital

POLICY AND PROCEDURE FOR

THE PRESCRIBING, ORDERING AND ADMINISTRATION OF PROTHROMBIN COMPLEX CONCENTRATE (PCC) OCTAPLEX®

IN CORK UNIVERSITY HOSPITAL

Reference Number: PPG-CUH-CUH-42	**Revision No:** 2	**Review Cycle:** 2 years
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Approver (Lead): Quality Safety Policy and Evaluation	**Approval Date:** July 2022	

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1 Policy Statement

To ensure the safe prescribing, ordering and administration of Prothrombin Complex Concentrate (PCC) to patients for the emergency reversal of Warfarin in life threatening or major and/ or prior to emergency surgery (within 6 hours).

2 Purpose

The purposes of this policy are:

- To educate clinical staff in the appropriate use of prescribing, ordering and administration of Prothrombin Complex Concentrate PCC (Octaplex® is the PCC product in use in CUH).
- To provide a framework for the training of relevant staff and act as a resource for staff to deal with queries they may have with regard to the use of Prothrombin Complex Concentrate.
- To ensure that care complies with the European Union Directive 2002/98/EC, which sets standards of quality and safety for blood and blood components.

3 Scope

This Policy applies to all healthcare professionals who are involved in the prescribing, ordering and administration of Prothrombin Complex Concentrate, Octaplex®.

4 Legislation/Related Policies

- European Union Directive 2002/98/EC which sets standards of quality and safety for blood and blood components ED-C-BTR_D0298EC
- Infection prevention and control policies procedures and guidelines, Cork University Hospital Group (PPG-CUH-PAT-871)
- Policy and Procedure on Providing Blood Transfusion Patient Information Leaflets and prescribing blood components/products in CUH & CUMH (PPG-CUH-CUH-80)
- Having a blood transfusion, patient information leaflet (INF-CUH-CUH-9)
- Policy and procedure on collection and administration of blood components/products in Cork University Hospital and Cork University Maternity Hospital (PPG-CUH-CUH-13).
- Policy and Procedure on transfusion management of major haemorrhage in Cork University Hospital and Cork University Maternity Hospital (PPG-CUH-CUH-210).
- Policy and Procedure on Recognising, Investigating and Managing a Suspected Transfusion Reaction in the Cork University Hospital Group: PPG-CUH-CUH-30).

- Policy and Procedure for the management of patients presenting with excessive anticoagulation (INR>5.0) while on Vitamin K antagonists (e.g. warfarin) at the Cork University Hospital Group. (PPG-CUH-CUH-242)
- Policy and procedure on the management of adult patients on direct oral anticoagulants (DOACs) in Cork University Hospital Group (PPG-CUH-CUH 267)

5 Glossary of Terms and Definitions

- **Prothrombin Complex Concentrate (PCC)** is a pooled plasma coagulation factor concentrate containing the vitamin K dependant coagulation Factors II, VII, IX and X. It also contains Protein C and Protein S. The product in use at CUH is Octaplex®. It is licensed for the treatment of bleeding and perioperative prophylaxis in acquired deficiency of the prothrombin complex coagulation factors, such as deficiency caused by treatment with Vitamin K antagonists (of which Warfarin is the most common) or in the case of overdose of vitamin K antagonists, when rapid correction of the deficiency is required.

  Octaplex® is also licensed for treatment of bleeding and perioperative prophylaxis in congenital efficiency of the vitamin K dependant coagulation factors II and X when purified specific coagulation products are not available.

  Octaplex® is **not licensed** for the reversal of anticoagulation due to the anti-Xa inhibitors (e.g. Apixaban, Rivaroxaban, and Edoxaban) and is not recommended for this purpose. However, it is occasionally used in life threatening haemorrhage in the absence of a specific reversal agent. (See Policy and procedure on the management of adult patients on direct oral anticoagulants (DOACs) in Cork University Hospital Group (PPG-CUH-CUH 267)

- **International Normalised Ratio (INR)**
  The international normalised ratio (INR) is a laboratory measurement of how long it takes blood to form a clot. It is used to determine the effects of oral anticoagulants on the clotting system.

6 Roles and Responsibilities

6.1 Consultants and Doctors in Training

- Medical staff must be aware of the policy and have easy access and adhere to the policy.

6.2 Clinical Nurse/Managers

- To ensure that nurses/midwives are aware of the policy and that they have easy access
- To ensure this policy is implemented.
- To ensure that staff are facilitated to attend training in support of this policy.

6.3 Staff Nurses

- Staff nurses/midwives must read and adhere to this policy and procedure when caring for patients requiring treatment with Fibrinogen concentrate.
- Complete Haemovigilance education
- Complete IV policy training
  Complete Anaphylaxis training within the last 2 years

7 Procedure

7.1 Health and Safety

- When handling blood and blood components always wear personal protective equipment and any exposure to blood or blood products through spillage and or exposure must be reported using a "blood/body fluid" exposure report form.

- All blood samples must be treated as potentially infectious. Needle stick injuries must be reported using a "Blood/body Fluid" exposure report form to the Occupational Health Department (routine hours) and Emergency Department (out of hours).

7.2 Clinical indications & Contraindications

- Octaplex® prothrombin complex concentrate (PCC) is licensed for the treatment of bleeding and perioperative prophylaxis in acquired deficiency of the prothrombin complex coagulation factors, such as deficiency caused by treatment with Vitamin K antagonists (of which Warfarin is the most common) or in the case of overdose of vitamin K antagonists, when rapid correction of the deficiency is required.

- Clinical judgement should be exercised on a case-by-case basis to decide if the potential benefit of treatment with PCC outweighs that of the potential thromboembolic complications in the following patients:

  - Patients with a history of coronary artery disease.
  - Patients with liver disease.
  - Peri- or post-operative patients.

- Patients at risk of thromboembolic phenomena.
- Patients with Disseminated Intravascular Coagulation (DIC).
- Patients with prosthetic heart valves.

- It is recommended that vitamin K is administered intravenously in addition to PCC. For patients with **mechanical heart valves** overcorrection of the INR should be avoided. A low dose of Vitamin K should be used such as 1mg to 2 mgs of the IV paediatric preparation given sublingually. If overcorrection does occur and INR <2 contact cardiothoracic team.

- PCC should **NOT** be used for reversal of Warfarin in **non-emergency situations**. Administration of vitamin K and/or reduction or discontinuation of Warfarin is usually sufficient in this situation. See *Policy and Procedure for the Management of Excessive Anticoagulation (INR>5.0) while on Vitamin K antagonists e.g. Warfarin at Cork University Hospital Group (PPG-CUH-CUH-242).*

- PCC (Octaplex®) is **NOT** licenced for the reversal of anticoagulation due to the anti-Xa inhibitors (e.g. Apixaban, Rivaroxaban, Edoxaban) and is **NOT** recommended for this purpose. However, it is occasionally used in life threatening haemorrhage, in the absence of a specific reversal agent. (See Policy and procedure on the management of adult patients on direct oral anticoagulants (DOACs) in Cork University Hospital Group (PPG-CUH-CUH-267).

- PCC (Octaplex®) **should not** be used in patients with:
  - Known hypersensitivity to the active substance or any of the excipients (see product package insert).
  - Known hypersensitivity to heparin or history of heparin induced thrombocytopenia.

7.3 Prescribing PCC (Octaplex®)

- PCC (Octaplex®) should be prescribed on the Cork University Hospital Blood component and Blood Product Prescription and Transfusion Record (Form 15A) or equivalent using the MN-CMS Millennium System in CUMH.

- The reason for transfusion should be clearly documented in the patient's medical notes, and the patient information leaflet "You may need a blood transfusion" should be given to the recipient or, in the case of minors or incompetent adults, to parents, guardians or next of kin.

7.4 Dosage

- Dosage and duration of therapy depend on the INR level, the severity of the coagulation disorder, the location and extent of bleeding and the clinical condition of the patient.

- In cases of severe haemorrhage requiring emergency reversal of warfarin, initial bolus doses of Octaplex ranging from 25 IU to 50 IU per kg body weight (depending on the INR), are recommended. As a guideline, the recommended dose of Octaplex is based on the factor IX (FIX) content of Octaplex and the patient's International Normalised Ratio (INR) as follows:

Patient's INR	**Recommended dose of Octaplex based on FIX content**
INR 2.0 – 3.9	25 IU/Kg **#**
INR 4.0 – 6.0	35 IU/Kg **#**
INR > 6	50 IU/Kg **#**

- **# A single dose of Octaplex should NOT exceed 3000 IU (*i.e.* 120 mL Octaplex)** *(SmPC, 2021).* In case of overdose, the risk of development of thromboembolic complications or disseminated intravascular coagulation is enhanced *(MIMS, 2022)*.

- If the calculated dose exceeds 3000 IU, administer the 3000 IU, then repeat the INR and seek advice from the haematology team.

- If using PCCs for treatment of major or life threatening bleeding associated with certain direct oral anticoagulants (DOACs) (e.g. apixaban, rivaroxaban, edoxaban etc.), refer to PPG-CUH-CUH-267, as dosing guidelines differ from those for warfarin reversal described in this document.

7.5 Ordering

- The CUH blood component / product requisition form must be completed fully. Include the following details: patient's name, medical record number, date of birth, date and time of request, indication for transfusion and dose required. In CUMH, PCCs can be ordered using the MN-CMS Millennium System.

- Send the requisition form to the Blood Transfusion Laboratory.

- The prescribing doctor should telephone the laboratory for urgent requests.

7.6 Administration Process

7.6.1 Reconstitution

- The following supplies are required for reconstitution:

- Vial of Octaplex® PCCs (500 IU or 1000 IU)
- Vial of sterile water (provided with Octaplex®: 20 mL with 500 IU & 40 ml with 1000 IU)
- Nextaro® transfer device (provided with Octaplex®)
- Syringe (not provided)
- Antiseptic solution (not provided)

	• Reconstitution and withdrawal should be carried out under aseptic technique. • Ensure both the solvent and the powder (in unopened vials) is at room or body temperature (not above 37ºC). • Octaplex® should be reconstituted with the sterile water for provided.
	• Remove the plastic tamper proof caps from the powder vial and the sterile water to expose the central portions of the infusion stoppers. • Disinfect the rubber stoppers of both vials with antiseptic solution and allow to dry.
	• Peel away the lid on the outer package of the Nextaro® transfer device, but do not remove it from the plastic outer packaging and do **NOT** touch the exposed surface of the Nextaro® device.
	• Place the water vial on an even surface and hold it firmly. • Without removing the outer package, place the blue part of the Nextaro® on top of the water vial and press firmly down until it snaps into place. Do **NOT** twist as you push down.

	• While holding onto the solvent vial, carefully remove the outer package from the Nextaro®, being careful to leave the Nextaro® attached firmly to the solvent vial.
	• Take the water vial with the attached Nextaro® transfer device and turn it upside down. • Place the white part of the Nextaro® connector on top of the powder vial and press firmly down until it snaps into place. The water flows automatically into the vial.
	• With both vials still attached, gently <u>swirl</u> the powder vial until the product is dissolved. Avoid shaking the vial, as it causes foam formation. • Octaplex® dissolves quickly at room temperature to a colourless to slightly blue solution. It should be completely reconstituted within 15 minutes (generally 5 – 10 minutes).
	• Unscrew the Nextaro® mixing device into two parts. Dispose of the empty water vial with the blue part of the Nextaro®. • If the powder fails to dissolve completely or an aggregate is formed, do **<u>NOT</u>** use the preparation.
	• Attach the syringe to the leur lock outlet on the white part of the Nextaro®, which contains an in-built filter.

	• Turn the vial upside down and draw the solution into the syringe. • Once the solution has been transferred, firmly hold the plunger of the syringe and remove the syringe from the Nextaro®. • The reconstituted product should be administered immediately.

7.6.2 Pre-Administration Checks

- The patient must wear a hospital identification wristband, which must contain:
  - Surname, first name, date of birth and MRN.

- Two health care professionals must undertake uninterrupted identity checks, aloud at the intended recipient's side. Whenever possible, the intended recipients should be requested to actively participate in the identification process and state their name and date of birth on order to exclude the possibility of misidentification and administration errors.

- The following four identifiers must be checked: surname, first name, date of birth and MRN.

- These must be identical with the recipient's details on:
  - The recipient's ID band.
  - The prescription and administration record
  - Compatibility tag attached to the PCCs

- If a discrepancy has been detected or if you are unsure about something, **do NOT administer the product** and contact blood transfusion lab or haemovigilance staff immediately.

7.6.3 Product Administration

- Reconstituted product should be administered immediately by a separate injection/infusion line. The suggested rate of administration of PCC (Octaplex®) is 1mL/minute initially, then increasing to 2-3 mL/min if tolerated by the patient (SmPC, 2021). It can be given by slow IV push or by syringe driver.

- Take care that no blood enters the syringe filled with the PCCS, as there is a risk that the blood will coagulate in the syringe.

7.6.4 Traceability

- On administration of the product in CUH, remove the pink peelable sticker from the compatibility tag and stick it into the patient's blood administration record (Form-15A/form-15).

- In CUMH, the batch number barcode on the compatibility tag, must be scanned into the blood product administration section of the patient's MN-CMS electronic record. In the event of MN-CMS downtime, the transfusion will be documented as for CUH above.

- In CUH and CUMH, if the pre-administration checks were performed manually, the yellow section of the compatibility tag must be detached, signed and dated, then attached to the original yellow collection slip and placed in the designated area for collection and return to the blood transfusion lab, as described in PPG-CUH-CUH-13, LI-C-BTR-BLOOREQ and LI-C-BTR-EBTSLIP.

7.7 Patient Observation and Monitoring

- Perform standard blood transfusion observations, as described in PPG-CUH-CUH-13.

- If a marked increase in the patient's pulse rate occurs the infusion speed must be reduced or the administration must be interrupted (SmPC, 2021).

- Patients should be monitored closely for signs or symptoms of intravascular coagulation or thrombosis, especially if they have a history of coronary heart disease, liver disease, are already at risk of thromboembolic events or DIC, are neonates or they are peri- or post op. (SmPC, 2021)

7.8 Suspected Adverse Reactions and Events

- The most common adverse reactions reported following PCC Octaplex® treatment are deep vein thrombosis and allergic/anaphylactic reactions. Refer to the Octaplex® product insert for a full list of possible adverse reactions and their incidence.

- If allergic or anaphylactic type reactions occur, the injection/infusion should be stopped immediately. In the case of anaphylactic shock, treat the patient as per PPG-CUH-NUR-21.

- All suspected adverse reactions/events involving PCCs must be reported to the blood transfusion laboratory/haemovigilance staff for review and if applicable, reporting to the manufacturer who will then notify the HPRA.

7.9 Monitoring Effectiveness

- An INR must be taken within thirty minutes to one hour after administration of PCC (Octaplex®). There will usually be an initial correction of the INR shortly after administration of PCC. The INR should be checked again 6 hours after administration of PCC (Octaplex®) because of the relatively short half-life of Factor VII in the Prothrombin Complex Concentrate. Additional doses of PCC (Octaplex®) may be required

- The INR should be monitored every 4-24 hours until the patient's INR is within their target range. The doctor must ensure that the INR samples are obtained (clearly labelled) and sent to the laboratory he/she must then follow up on these results and act accordingly.

8 References

1. Octapharma Ltd., (2004). *Octaplex Republic of Ireland Product Characteristics.* Coventry: Octapharma Ltd.
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3. Preston F.E. et al. (2002). Rapid Reversal of Oral Anticoagulation with Warfarin by a Prothrombin Complex Concentrate (Beriplex): efficacy and safety in 42 patients. *British Journal of Haematology*.116, p.619-624.
4. Evans G. et al. (2001). Beriplex P/N Reverses Severe Warfarin-induced Overanticoagultion Immediately and Completely in Patients Presenting with Major Bleeding. *British Journal of Haematology*. 115, p. 998-1001.
5. Makris M. et al. (2001). The Management of Coumarin-induced Over-Anticoagulation. Annotation. *British Journal of Haematology*. 114, p. 271-280.
6. Octapharma: Octaplex® Prothrombin Complex Concentrate (PCC) Summary of product characteristics (SmPC), January 2021.