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Guidelines on the use of OCTAPLEX® (Prothrombin complex concentrate/PCC) for rapid reversal of warfarin in association with life threatening bleeding.

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<th>Clinical Policies and Guidelines</th>
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<td>Quality Governance Operational Committee</td>
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<td>Date Endorsed</td>
<td>16th December 2014</td>
</tr>
<tr>
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<td>Hospital Transfusion Committee</td>
</tr>
<tr>
<td>Date Approved</td>
<td>23rd April 2014</td>
</tr>
<tr>
<td>Name of author and job title</td>
<td>Dr Kanchan Rege Consultant Haematologist</td>
</tr>
<tr>
<td>Key words (for search purposes)</td>
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CAUTION: You must refer to the intranet for the most recent version of this procedural document.

DOCUMENT VERSION CONTROL SCHEDULE

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<td>May 2014 / Quality Governance Operational Committee</td>
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<td>4</td>
<td>2014</td>
<td>Inclusion of instructions for new mix 2 vial</td>
<td>December 2014 / Quality Governance Operational Committee</td>
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Key Points:- This document

- Provides guidance for clinicians on rapid reversal of warfarin therapy in cases of life threatening bleeding.

- Outlines the indications and contraindications for the use of Octaplex (Prothrombin Complex Concentrate)
CAUTION: You must refer to the intranet for the most recent version of this procedural document.

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<td>2 - Summary of procedure for use of Octaplex</td>
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<tr>
<td>3- Mix2vial needle free reconstitution and transfer system</td>
<td>14</td>
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<tr>
<td>4 – Quality assurance checklist</td>
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Guidelines on the use of OCTAPLEX® (Prothrombin complex concentrate/PCC) for rapid reversal of warfarin in association with life threatening bleeding.

1. Introduction
1.1 Octaplex is licensed in the UK for treatment of bleeding disorders including reversal of oral anticoagulation.
1.2 It contains freeze dried human derived Factors II, VII, IX, X and Proteins S and C.
1.3 It provides very effective, rapid reversal of warfarin.
1.4 Octaplex is potentially thrombogenic and may provoke arterial or venous thrombosis. Its use should therefore be restricted to life threatening situations when the thrombotic risks are relatively less than the risk of continued bleeding.
1.5 Although the risk of bleeding on warfarin increases when the international normalised ratio (INR) >4.5 most bleeds (including intracranial bleeds) occur with the INR in the therapeutic range.

2. Purpose of the document
2.1 These guidelines have been produced to ensure that Octaplex is used appropriately when clinically indicated, in cases of life threatening bleeding.

3. Scope
3.1 These guidelines should be referred to by all staff responsible for requesting, prescribing, and administering Octaplex, and are based on British Committee for Standards in Haematology guidelines.

4. Definitions
4.1 PCC - Prothrombin Complex Concentrate
4.2 Octaplex PCC - Octaplex Prothrombin Complex Concentrate contains freeze dried human derived Factors II, VII, IX, X and Proteins S and C
4.3 iu - International unit
4.4 SHOT- Serious Hazards of Transfusion a UK wide reporting system for adverse transfusion events and ‘near misses’
4.5 SABRE- Serious Adverse Blood Reactions and Events. This system allows reporters to electronically submit reports of serious adverse events or serious adverse reactions directly to the Medicines and Healthcare Products Regulatory Agency (MHRA)

5. Process
5.1 The request, prescription and administration of Octaplex PCC (see following sections and also see appendix 2).

6. Indications for use
6.1 Life threatening haemorrhage.
6.2 Intracranial haemorrhage (this carries a 50% mortality in patients on warfarin).
6.3 Prior to emergency surgery in patients on Warfarin (if delaying surgery plus giving vitamin K is not clinically reasonable).
CAUTION: You must refer to the intranet for the most recent version of this procedural document.

6.4 May not be suitable for treatment of Jehovah’s Witnesses as it contains human material.

6.5 It is not indicated for less serious bleeding or for preparation for elective surgery.

7. **Dose**

<table>
<thead>
<tr>
<th>Wt (kg)</th>
<th>INR 2-2.5</th>
<th>INR 2.5-3</th>
<th>INR 3-3.5</th>
<th>INR &gt;3.5</th>
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</thead>
<tbody>
<tr>
<td>50</td>
<td>1500iu</td>
<td>2000iu</td>
<td>2500iu</td>
<td>2500iu</td>
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<td>60</td>
<td>2000iu</td>
<td>2000iu</td>
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<tr>
<td>100</td>
<td>3000iu</td>
<td>3000iu</td>
<td>3000iu</td>
<td>3000iu</td>
</tr>
</tbody>
</table>

Each box contains 500 iu. Max single dose 3000iu (6 Boxes). Once a vial is reconstituted please use complete vial. **DO NOT discard part used vials.**

8. **Contraindications**

8.1 Known hypersensitivity to plasma proteins
8.2 Disseminated Intravascular Coagulation
8.3 Recent arterial thrombosis
8.4 Previous history of heparin associated thrombocytopenia type II
8.5 Uncompensated liver disease

9. **Relative contraindications**

9.1 Patients with history of Ischaemic Heart Disease
9.2 Liver disease
9.3 Safety in pregnancy not established

10. **Risks**

10.1 Thrombosis (arterial and venous) and may provoke DIC
10.2 Anaphylaxis
10.3 Viral transmission

11. **Consequences of not administering the drug**

11.1 Fresh Frozen Plasma may also be used for the same indication as Octaplex. It, however, is associated with the risk of transfusion transmitted infection, anaphylaxis, Transfusion Related Acute Lung Injury, volume overload and other potential hazards of transfusion. It is also likely to correct the INR more slowly and less predictably.

11.2 The British Committee for Standards in Haematology recommend that all hospitals managing patients on warfarin should stock a licensed four-factor prothrombin complex concentrate (eg: Octaplex), as Fresh Frozen Plasma produces suboptimal anticoagulation reversal and should only be used if PCC is not available.
CAUTION: You must refer to the intranet for the most recent version of this procedural document.

12. Reconsitution

12.1 The clinical decision to use Octaplex should be approved by a Haematology Consultant (please see appendix 1). It should then be administered as soon as possible.

12.2 Octaplex is stocked in the Transfusion Laboratory, and should be collected as soon as it is available after being requested.

12.3 Octaplex is provided as a dried powder (available vial size is 500 IU/vial) along with sterile water. It will need to be reconstituted in the clinical area by the nurse or doctor responsible for the patient.

12.4 One box of Octaplex contains:
   - Octaplex 500IU powder in a vial with a stopper and flip off cap
   - 20ml Water for injection with a stopper and flip off cap
   - A needle free transfer set (Mix2vial™ device)

12.5 Multiple boxes will be issued to provide the correct dose.

12.6 Octaplex is stored refrigerated at 4°C. The vials will need to be warmed (by the nurse or doctor gently rolling the bottle in their hands) prior to administration.

12.7 To reconstitute, follow the instructions provided in the pack (see appendix 3) - i.e.
   - Remove the caps from the powder vial and the water vial and clean the rubber stoppers with an alcohol swab.
   - Remove the top of the Mix2vial package. Do not remove the device from the package.
   - Seat the blue end of the device on the water vial, using the blister pack as a holder. Push down until the spike penetrates the stopper and the device snaps into place.
   - Remove the plastic package and discard it. Take care not to touch the exposed end of the device.
   - Turn the water vial upside down and insert the clear end into the powdered octaplex vial, pushing down until the spike penetrates the stopper and the device snaps into place.
   - The water will automatically flow into the octaplex vial. Gently swirl the vial to make sure the octaplex is thoroughly mixed.
   - Remove the water vial by turning it anti-clockwise. Attach a 60 ml luer lock syringe to the octaplex vial. Under most circumstances, two 60 ml syringes will be required to administer the total dose, up to a maximum of 120ml. The syringes must be clearly labelled with the name and strength of the drug.

12.8 Octaplex® dissolves quickly at room temperature to a colourless / slightly opalescent solution. If the powder fails to dissolve completely or a deposit is formed, do not use the preparation.

12.9 The total number of vials required to give the final dose can be reconstituted at the same time.
13. **Administration**

13.1 Administer the reconstituted Octaplex solution by the intravenous route using a syringe pump.

13.2 In the summary of product characteristics issued by the manufacturer, the recommended administration rate is 2 to 3mls/minute, but this relates to treatment in non-emergency situations when immediate reversal is unnecessary - this is not practical in cases of life threatening haemorrhage. There is evidence to show that faster administration rates of up to 10ml/minute have been used without any adverse reactions (Reiss et al 2007, Franken et al 2007). In life threatening situations, using an administration rate of 4 to 8ml/minute means that a dose of 3000 iu (120mls) can be given over a total of 15 to 30 mins.

13.3 There is a small risk of allergic reactions – if these occur the infusion should be stopped immediately and standard allergy/anaphylaxis therapy should be instituted. As a precautionary measure, the patients pulse rate should be measured before and during the infusion. If a marked increase in the pulse rate occurs the infusion speed must be reduced or the administration must be interrupted.

13.4 No blood must flow into the syringe due to the risk of formation of fibrin clots.

13.5 Once reconstituted, the solution should be used immediately.

14. **Post administration**

14.1 Repeat PT/INR 30-60 minutes post administration and at 6 hours + 18 hours (may need further therapy).

14.2 Monitor clinical response and for evidence of disseminated intravascular coagulation DIC/thrombosis.

14.3 Daily full blood counts (FBCs) and INRs/clotting screens required for 2-3 days.

14.4 Some severely over anticoagulated patients may need further doses of vitamin K if clinical need to maintain complete reversal.

14.5 Once acute event treated and patient stable it may be appropriate to consider prophylactic heparin in some situations e.g.: mechanical heart valve.

14.6 Record efficacy of Octaplex in patient notes.

15. **Endorsement**

15.1 The policy will be approved by the Hospital Transfusion Committee. Final endorsement will be by the Quality Governance Operational Committee.

16. **Distribution**

16.1 The guideline will be stored on SharePoint. Staff will be made aware of the guideline during induction and clinical update sessions.
**CAUTION**: You must refer to the intranet for the most recent version of this procedural document.

17. References


17.3 Octaplex ® (human prothrombin complex )- Summary of Product Characteristics (UK Specific) 2010. Octapharma Ltd.

17.4 Reiss, HB et al. (2007), Prothrombin Complex Concentrate (Octaplex) in patients requiring immediate reversal of oral anticoagulation. Thrombosis Research. 121 (1) 9-16
Appendix 1
FLOWCHART FOR EMERGENCY REVERSAL OF ORAL VITAMIN K ANTAGONISTS in LIFE THREATENING EMERGENCIES

<table>
<thead>
<tr>
<th>Step 1:</th>
<th>ASSESS URGENT INDICATION FOR OCTAPLEX</th>
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<tr>
<td>Is there a life threatening or other urgent indication for emergency reversal of oral vitamin K antagonists?</td>
<td>Yes / No</td>
</tr>
<tr>
<td>Head injury with neurological symptoms or signs of deterioration</td>
<td></td>
</tr>
<tr>
<td>Intracranial bleed proven on CT</td>
<td></td>
</tr>
<tr>
<td>Major obstetric or gynaecological / major post surgical bleed with shock</td>
<td></td>
</tr>
<tr>
<td>Major Traumatic Injuries with haemodynamic instability</td>
<td></td>
</tr>
<tr>
<td>Intra-ocular bleed, pericardial bleed or compartment syndrome</td>
<td></td>
</tr>
<tr>
<td>Requires surgery/procedure in &lt;6 hours</td>
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If yes: complete Step 2 & proceed IMMEDIATELY to actions 1-5 overleaf

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<tr>
<td>Is the patient currently taking Aspirin / Clopidogrel / other anti-platelet medication e.g. NSAIDs?</td>
<td>Yes / No</td>
</tr>
<tr>
<td>Has the Major Transfusion Protocol been started for significant haemorrhage?</td>
<td></td>
</tr>
<tr>
<td>Are there any contra-indications to Octaplex: Does the patient have liver disease or DIC?</td>
<td></td>
</tr>
<tr>
<td>Are there any cautions for Octaplex administration: Mechanical heart valve / thrombotic disease MI/thrombotic stroke/venous thromboembolism in past 3/12</td>
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**CAUTION:** You must refer to the intranet for the most recent version of this procedural document.

<table>
<thead>
<tr>
<th>ACTIONS</th>
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</table>
| **1: Investigation** | | Insure intravenous access  
Send urgent bloods  
INR, clotting/fibrinogen, FBC, cross match, U&E & LFT |
| **2: Initial treatment & advice** | | Administer vitamin K 5mg intravenous, stat  
Contact duty Haematologist to authorise Octaplex (based on patient weight) & to agree INR to aim for  
Provide significant history & confirm  
- **dose authorised:** ____________ IU  
- **INR to aim for** ____________ |
| | Ring blood bank 8452 to request issue  
(out of hours duty Haematology BMS bleep 1151) |
| **3: Octaplex** | | Prescribe Octaplex on blood product prescription chart  
Send staff to blood bank to collect Octaplex urgently  
Reconstitute IMMEDIATELY & administer at a rate of 8ml / minute via syringe pump |
| **4: Assess therapeutic effect** | | As soon as Octaplex infusion complete, take & send a repeat INR from a separate venepuncture site  
Inform Dr responsible for patient of INR result:  
Dr ____________________ informed of INR result  
INR = ____________  
If desired INR not achieved Dr to discuss need for additional Octaplex with duty Haematologist (unless additional dose previously agreed) & repeat step 3  
**NOTE:** maximum total Octaplex dose = 3000IU in 24 hours  
Repeat INR 6 hrs after vitamin K given to assess if more required  
INR ________ result after 6 hours  
Additional vitamin K required? Yes ☐ No ☐ |
| **5: Handover** | | It is imperative to handover the next time critical intervention if the patient is transferred to another ward / department / hospital  
Next step ________________________________  
due at: ____________ hrs |

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<table>
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<td>1. Overt bleed without shock</td>
</tr>
<tr>
<td>2. Traumatic bleed</td>
</tr>
<tr>
<td>3. Head or facial injury with no neurological signs and on oral vitamin K antagonists:</td>
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Assessment completed by:

<table>
<thead>
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<th>Signature</th>
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<tr>
<td>Date</td>
<td>Time</td>
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Appendix 2 Summary of procedure for use of Octaplex

Doctor makes clinical assessment of patient bleeding on warfarin

↓

Bleeding considered life threatening

↓

Send urgent INR, APTT, Fibrinogen, FBC and X match (as appropriate)
Weigh patient or make estimate of weight
Contact transfusion laboratory and request urgent results and inform laboratory that Octaplex may be required

↓

Review patient with INR/clotting screen
Clinical decision to use Octaplex approved by Haematology Consultant

↓

Request Octaplex via transfusion laboratory (dose based on body weight)
and administer vitamin K iv

↓

Transfusion laboratory contacts doctor/clinical area to inform Octaplex available – doctor/nurse arranges immediate collection from blood bank

↓

Reconstitute in clinical area

↓

Administer as slow iv bolus (see section 13 for details)

↓

Repeat INR/clotting screen at 30 – 60 minutes

↓

Repeat INR/clotting screen at 6 hours and 18 hours
Monitor for signs of thrombosis and DIC

↓

Record clinical efficacy of Octaplex in medical notes
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Appendix 3: Mix2Vial needle free reconstitution

octaplex® Product Update

Mix2Vial™ Introduction

Octapharma are introducing an octaplex® needle-free reconstitution and transfer system.

The Mix2Vial™ replaces the current double ended needle and separate filter in a single device, simplifying the steps in the reconstitution process.

This device represents a needle-free system that meets Sharps Instruments in Healthcare requirements under Health and Safety Regulations 2013.

The contents of the octaplex® pack have changed as follows: the pack now contains a 500 IU octaplex® powder vial, a 20ml water for injection vial and a Mix2Vial™ (this incorporates a filter). The pack no longer contains the double ended needle, filter needle, syringe, swabs or butterfly needle.

If you would like further information, we can arrange for your Key Account Manager to contact you and provide demonstration materials with reconstitution instructions.

For further information please contact Octapharma customer services:
Tel: 0161 837 3771
Email: customer.services@octapharma.co.uk
Website: www.octapharma.co.uk


Date of preparation: October 2013  OPX/13/13
CAUTION: You must refer to the intranet for the most recent version of this procedural document.

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Central Index Number: 0254

Version 4
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Compliance Team Approval:

1. Date of approval: 24th November 2014
2. Comments to author for any amendments
3. Date returned to author: 24th November 2014
4. Name of Approver: Caroline Sykes Compliance and Policies Assistant

Approval Committee / Group: Hospital Transfusion Committee

If the committee/group is happy to approve this document, would the chair please sign below and send the policy together with this document, the Equality Impact Assessment, and NHSLA checklist (if required) and the relevant section of the minutes to the author. (To aid distribution all documentation should be sent electronically wherever possible)

Name: B Appadu
Date: 23/04/14

Signature & Designation Needed

Hospital Transfusion Committee Chair

Comments

Endorsing Committee / Group: Quality Governance Operational Committee (QGOC)

If the committee/group is happy to endorse this document, would the chair please sign below and send the policy together with this document, the Equality Impact Assessment, and NHSLA checklist (if required) and the relevant section of the minutes to the Compliance Team. To aid distribution all documentation should be sent electronically wherever possible.

Name: [Signature]
Date: 16/11/14

If answers to any of the above questions is 'no', then this document is not ready for endorsement, it needs further review.

EqI/A form marked with appropriate Appendix number: N/A
Document Archived in PDF format: Yes □ No □