The Walton Centre NHS Foundation Trust

Excellence in Neuroscience

MANAGEMENT OF BLEEDING AND REVERSAL OF ANTICOAGULATION IN ANTICOAGULATED PATIENTS

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Responsible Director:	Medical Director	
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1.0 Introduction

Major haemorrhage with oral antithrombotic drugs is infrequent but management can be difficult especially with antithrombotic for which there are no specific reversal agents.

Bleeding during antithrombotic therapy is associated with high morbidity and mortality. Before any antithrombotic treatment is started, the risks and benefits should be carefully considered.

In this guideline we consider the management of bleeding in patients on the more widely used antithrombotic agents including heparin, oral vitamin K antagonists such as warfarin and direct oral anticoagulants (DOACs).

2.0 Objective

This guideline provides clinical staff with guidance on the management of bleeding in those taking antithrombotic drugs and reversal of the action of these drugs.

3.0 Scope of Guideline

This guideline applies to the management of all patients who experience bleeding with antithrombotic drugs, and all clinical staff caring for this patient group should be aware of this guideline.
This guideline does not apply to the perioperative management of anticoagulated patients – please refer to the separate Trust guideline.

4.0 Guideline

4.1 General Measures to Manage Bleeding

In many cases, simple non-pharmacological measures and stabilization of the patient whilst the antithrombotic is eliminated are sufficient to treat or prevent bleeding. The general non-pharmacological measures that should be taken include:

- Stop the antithrombotic drug
- Document the time and amount of last drug dose and presence of hepatic or renal impairment
- Assess the source of bleeding
- Request FBC, coagulation screen, fibrinogen, renal function & liver function
- If available, request a specific laboratory test to measure the effect of the drug.(ie INR for warfarin, anti Xa for LMWH, DOAC levels if available)
- Correct haemodynamic compromise with intravenous fluids/blood products
- Apply mechanical pressure, if appropriate
- Use endoscopic, radiological or surgical measures to arrest haemorrhage

Pharmacological measures are specific to the antithrombotic, see tables/sections below.

4.2 Unfractionated Heparin

Given the short plasma half-life of unfractionated heparin (UFH), treatment or prevention of bleeding can often be achieved by stopping UFH and the use of general measures. UFH can be rapidly reversed with protamine sulphate, which is derived from fish sperm and forms a stable, inactive salt with heparin.

Table 1: Guidance on Reversal of Unfractionated Heparin

Antithrombotic Agent	Unfractionated Heparin
Half Life	Short
Initial Management	Stop Heparin Infusion
Reversal Agent	Protamine Sulphate
Dose of Reversal Agent	• Calculated from the quantity of UFH administered in the 2 hours prior to reversal • 1mg protamine reverses 80-100 units of UFH. • This should be given no faster than 5mg/min to minimize the risk of adverse reactions • The maximum recommended dose of 50mg protamine is sufficient to reverse UHF in most settings. • If heparin has been stopped >15 minutes, discuss with haematology and refer to protamine summary of product characteristics (SPC) as a lower dose may be required.
Reversal Agent location	Pharmacy/emergency medicines store/ward stock
Monitoring	APTT Ratio Note- APTT ratio of 0.8-1.2 suggests no heparin effect In the context of continued life-threatening bleeding discuss other haemostatic measures with the on-call haematologist.
Cautions	Protamine can cause severe allergic reactions including anaphylaxis, hypotension, bronchospasm and skin reactions in up to 10% of patients.

4.3 Low Molecular Weight Heparin

Low Molecular Weight Heparins (LMWH) are derived from UFH through chemical or enzymatic degradation. Although LMWH may prolong the APTT this should not be used in monitoring the degree of anticoagulation.

Table 2: Guidance on Reversal of Low Molecular Weight Heparin

Antithrombotic Agent	Low Molecular Weight Heparin
Half Life	This can vary depending on their chain length; however the half-life of the anticoagulant effect of LMWH is approximately 4 hours. This is prolonged in renal impairment.
Initial Management	Apply general measures listed above. Consider if reversal agent is needed.

Reversal Agent	Protamine Sulphate- Reverses approximately 60% of LMWH, and may be used in the context of bleeding.
Dose of Reversal Agent	• **LMWH administered within 8 hours of the time of requirement for correction of anticoagulation**: give protamine sulphate (1mg per 100 anti-Xa units of LMWH). If ineffective, consider further protamine sulphate 500 micrograms per 100 anti-Xa units. Maximum dose in 24 hours is 50mg. Maximum infusion rate of 5mg/min to minimize the risk of adverse reactions. • **LMWH administered greater than 8 hours from the time of requirement of correction of anticoagulation:** consider giving a half dose of protamine.
Reversal Agent location	Pharmacy/emergency medicines store/ward stock
Monitoring	Anti-Xa assay (untimed). Guidance on the interpretation of results may be obtained from the on-call Haematologist. In the context of continued life-threatening bleeding discuss other haemostatic measures with the on-call haematologist.
Cautions	Protamine can cause severe allergic reactions including anaphylaxis, hypotension, bronchospasm and skin reactions in up to 10% of patients.

4.4 Vitamin K Antagonists (e.g. Warfarin)

The management of bleeding and reversal of anticoagulation with vitamin K antagonists such as warfarin depends on the urgency of which reversal of anticoagulation is required, which is dictated by the clinical situation.

There are two agents which can be used for the reversal of Vitamin K Antagonists –

- Vitamin K (phytomenadione)- Available as both IV and oral preparations from pharmacy and ward stock in some areas.
- Prothrombin Complex Concentrate (PCC) - Octaplex. This is issued by the Hospital Transfusion Laboratory

The management of warfarin associated bleeding is summarised in Figure 1, further information can be found in Table 3.

Figure 1. Flow chart for the management of warfarin associated bleeding

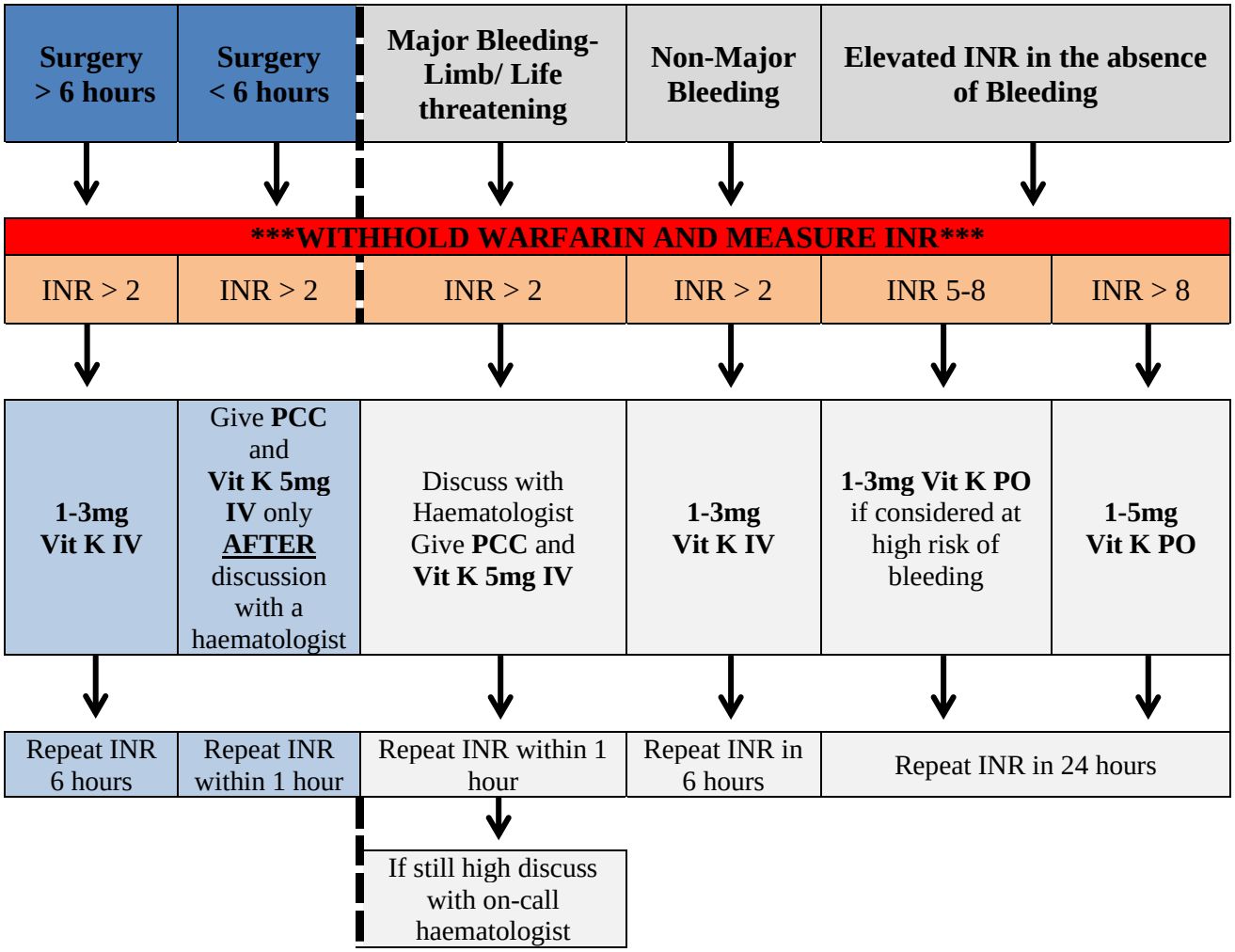


Table 3: Guidance on Reversal of Warfarin

Major Bleeding with Warfarin- Life threatening bleeding
• Resuscitate and utilise non-pharmacological measures to manage bleeding as necessary • Withhold Warfarin • Send samples for INR, FBC, group and save/ plasma cross match • Discuss with haematologist • Administer **Vitamin K (Phytomenadione- Konakion MM) 5mg by slow IV injection over 2 minutes.** Alternatively Vitamin K can be diluted in 50ml Glucose 5% and administered over 10 minutes. • **Administer **PCC (Octaplex) 25-50 units/kg (maximum dose 3000 units).** Instructions for the reconstitution of PCC are found in Appendix 2 and with the issued product. The infusion should start at a speed of 1 mL per minute, followed by 2-3 mL per minute, using an aseptic technique. Batch number must be recorded. • Recheck INR within 1 hour of administering PCC

• If repeat INR remains elevated – discuss with on-call Haematologist • Consider activating the Massive Haemorrhage Pathway. **'Octaplex (Prothombin Complex Concentrate) – check dose ordered. If the dose requested is less than 1,500IU or more than 3,000IU ask the prescriber to speak to a Haematology registrar for guidance. (Maximum dose is 3,000IU). So there is no requirement for Haematologist authorisation for issues of the product between 1500 and 3000IU.'
Non-Major Bleeding with Warfarin- Less Severe Haemorrhage- Haematuria, Epistaxis
• Withhold Warfarin and check INR • Non-pharmacological measures to manage bleeding • Discuss with a clinical haematologist • If INR >3.0, administer **Vitamin K 1-3mg via slow IV injection** • Recheck INR 6 hours after administration of Vitamin K
Elevated INR due to Warfarin in absence of bleeding
• Check INR • INR 5-8 – administer **Vitamin K 1-3mg PO** (paediatric injection to administered orally) - if considered to be at high risk of bleeding • INR >8 – administer **Vitamin K 1-5mg PO** (paediatric injection to administered orally) • Repeat INR in 24 hours.
Unexpected bleeding or headache at therapeutic levels of INR
• Cause of bleeding should be investigated as for patients who are not taking warfarin • Modify warfarin dose as appropriate • If cerebral haemorrhage is suspected INR should be reversed as soon as possible as in major bleeding

4.5 *Direct Oral Anticoagulants (DOACs) - Dabigatran, Rivaroxaban, Apixaban, Edoxaban*

The management of bleeding in the presence of these drugs is largely through cessation of treatment and general haemostatic measures.

In the context of major bleeding there may be a role for pro-haemostatic agents. Their use must be guided by a haematologist on the basis of the published evidence. **Note: Vitamin K and protamine administration will be ineffective in the reversal of these agents and have no role in reversal of bleeding under DOACs**

Table 4: Guidance on Reversal of Direct Oral Anticoagulants

<table>
<tr><td rowspan="3">Antithrombotic Agent</td><td colspan="4">Direct Oral Anticoagulants</td></tr>
<tr><td colspan="3">Factor Xa Inhibitor</td><td>Direct Thrombin Inhibitors</td></tr>
<tr><td>Apixaban</td><td>Rivaroxaban</td><td>Edoxaban</td><td>Dabigatran</td></tr>
<tr><td>Half Life</td><td>12 hours</td><td>5-13 hours</td><td>10-14 hours</td><td rowspan="2">12-18hours. Normalisation of plasma levels depends on CrCl
Normal Function- 12-24 hours
CrCl 50-80ml/min- 24-36hours
CrCl 30-50ml/min- 36-48hours
CrCl <30ml/min- >48hours</td></tr>
<tr><td colspan="3">Normalisation of plasma levels within 12-24 hours</td></tr>
<tr><td>Initial Management</td><td colspan="4">• Cessation of treatment- Confirm prescribed regime and timing of last dose
• General haemostatic measures
• Fluid replacement
• Consider stopping antiplatelet therapy and other factors which may influence plasma concentration
• Request FBC, Group & Save, eGFR, APTT, PT, fibrinogen
• Request drug levels
• Consider activated charcoal if ingested within 2 hours</td></tr>
<tr><td rowspan="2">Reversal Agent</td><td colspan="3">Andexanet Alfa
(off label for edoxaban)</td><td rowspan="2">Idarucizamab
(Praxbind©)</td></tr>
<tr><td colspan="3">Only for life threatening or uncontrolled GI bleeding</td></tr>
<tr><td>Dose of Reversal Agent</td><td colspan="3">See dosing tables below</td><td>5g IV over two consecutive infusions of 2.5g no more than 15 minutes apart</td></tr>
<tr><td>Monitoring</td><td colspan="4">Routine coagulation tests for these agents are difficult to interpret, and often do not reflect the bleeding tendency. Interpretation should be guided by a Haematologist.
The haematology laboratory has the ability to assay Rivaroxaban, Apixaban, Edoxaban and Dabigatran levels –these should be discussed with a clinical Haematologist.</td></tr>
<tr><td>Cautions</td><td colspan="4">In the context of continued life-threatening bleeding discuss other haemostatic measures with the on-call haematologist.</td></tr>
</table>

The management of DOAC associated bleeding is summarised in table 5:-

Table 5: Guidance on management of bleeding for patient taking Direct Oral Anticoagulants

Life threatening
• Call consultant Haematologist • Initiate Trust Massive Haemorrhage pathway • Discuss the use of haemostatic agents • Consider haemodialysis • Consider reversal agent ** Even after direct reversal significant DOAC concentrations may reappear in some patients and contribute to recurrent or continued bleeding.***
Non life-threatening Major Bleeding

• Supportive measures
  o Mechanical compression
  o Endoscopic Haemostasis if gastrointestinal bleed
  o Surgical Haemostasis
  o Fluid replacement
  o RBC Substitution aiming for Hb >7g/dl
  o Platelet transfusion aiming for platelets >50 x 10^9 or >100 x 10^9 if CNS bleeding
  o Maintain BP and urine output
• Consider Tranexamic acid 1g IV bolus over 10mins
• For Dabigatran-Consider idarucizumab or haemodialysis

Minor Bleeding
• Mechanical Compression • Delay next dose or discontinue drug • Reconsider choice of DOAC • Reconsider concomitant medication aimed at treating the cause of bleeding e.g.- PPI for gastric ulcers

Dabigatran Reversal

Idarucizumab (Praxbind©) is a licensed humanised monoclonal antibody which binds specifically to dabigatran to block its anticoagulant affects and its metabolites. It neutralises anticoagulant activity by forming a stable complex which is then excreted.

It is licensed for use in adults treated with dabigatran etexilate (Pradaxa), when rapid reversal of anticoagulation is required, such as for:-

- Emergency surgery or urgent procedures
  - Stop dabigatran
  - Consider deferring surgery for > 12 hours
  - Optimise Hb and platelets
  - Inform anaesthetist
- Life threatening, uncontrolled bleeding
  - Stop dabigatran and anti-platelets
  - Initiate local/ supportive measures
  - Follow Trust Massive Haemorrhage Pathway

IMPORTANT- Idarucizumab will NOT reverse the action of other anticoagulants. Its action is specific to dabigatran. It must NOT be given unless the patient has taken dabigatran.

Dose- 5 grams IV as two consecutive infusions of 2.5grams in 50ml over 5 – 10 minutes each or as two 2.5gram bolus injections.

Supply- Idarucizumab is available from the transfusion laboratory. If a dose is given, the pharmacy department should be informed to ensure replacement stock is ordered.

Administration of a second 5 gram dose may be considered in the following situations only when approved by a haematologist:-

- Recurrence of clinically relevant bleeding together with a prolonged APTT
- If potential re-bleeding would be life threatening or a prolonged APTT is observed
- Patients require a second emergency surgery or urgent procedure and have a prolong APTT

Absence of antithrombotic therapy exposes patients to the thrombotic risk of their underlying disease or condition.

Apixaban, rivaroxaban and edoxaban reversal

Andexanet Alfa (Ondexxya) is a recombinant form of human factor Xa which binds specifically to apixaban, rivaroxaban and edoxaban thereby reversing their anticoagulant effects.

It is licensed for reversal of apixaban or rivaroxaban in life-threatening or uncontrolled bleeding. However, it is only commissioned for use in with life-threatening or uncontrolled bleeding if the bleed is in the gastrointestinal tract. Andexanet alfa is recommended only in research for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled bleeding in the skull (intracranial haemorrhage; ICH), in the form of an ongoing randomised trial mandated by the regulator. If a patient taking a DOAC presents with another source of life-threatening bleeding this should be discussed urgently with the on-call haematology consultant and a decision may be made to administer andexanet alfa in exceptional circumstances.

The use of andexanet alfa for reversal of edoxaban is off-label however there is evidence to support its use. At the time of writing the preliminary results of the ANNEXA-4 study show that andexanet alfa significantly decreased anti-factor Xa activity and excellent or good haemostasis at 12 hours was observed in 75.0% of patients.

See appendix 3 for details of reconstitution and administration of andexanet alfa and appendix 4 for further dosing information.

Dose-

The dose of andexanet alfa should be calculated using the patient's regular dose of apixaban, rivaroxaban or edoxaban.

Table 6: Andexanet alfa dosing regimens

	Initial intravenous bolus	**Continuous intravenous infusion**	**Total number of 200mg vials needed**
Low dose	400mg at a target rate of 30mg/min	4mg/min for 120mg minutes (480mg)	5
High dose	800mg at a target rate of 30mg/min	8mg/min for 120mg minutes (960mg)	9

Reversal of apixaban

The recommended dose regimen of andexanet alfa is based on the dose of apixaban the patient is taking at the time of anticoagulation reversal, as well as on the time since the patient's last dose of apixaban (see table 7).

Table 7: Summary of dosing for reversal of apixaban

FXa inhibitor	**Last dose**	**Timing of last dose before andexanet alfa initiation**	
		< 8 hours or unknown	**≥ 8 hours**
Apixaban	≤ 5 mg	Low dose	Low dose
	> 5 mg/ Unknown	High dose	

Reversal of rivaroxaban

The recommended dose regimen of andexanet alfa is based on the dose of rivaroxaban the patient is taking at the time of anticoagulation reversal, as well as on the time since the patient's last dose of rivaroxaban (see table 8).

Table 8: Summary of dosing for reversal of rivaroxaban

FXa inhibitor	**Last dose**	**Timing of last dose before andexanet alfa initiation**	
		< 8 hours or unknown	**≥ 8 hours**
Rivaroxaban	≤ 10 mg	Low dose	Low dose
	> 10 mg/ Unknown	High dose	

Reversal of edoxaban

The recommended dose regimen of andexanet alfa is based on the dose of edoxaban the patient is taking at the time of anticoagulation reversal, as well as on the time since the patient's last dose of rivaroxaban (see table 9).

Table 9: Summary of dosing for reversal of edoxaban

FXa inhibitor	Last dose	Timing of last dose before andexanet alfa initiation	
		< 8 hours or unknown	≥ 8 hours
Edoxaban	30 mg	Low dose	Low dose
	60 mg/ Unknown	High dose	

Supply- Andexanet alfa is available from the transfusion laboratory. If a dose is given, the pharmacy department should be informed to ensure replacement stock is ordered.

Administration- Andexanet alfa is administered as an intravenous bolus at a target rate of approximately 30 mg/min over 15 minutes (low dose) or 30 minutes (high dose), followed by administration of a continuous infusion of 4 mg/min (low dose) or 8 mg/min (high dose) for 120 minutes (see table 6).

4.6 Other anticoagulants

There is no specific reversal agent for fondaparinux, danaparoid or argatroban. If bleeding occurs whilst prescribed one of these agents, treatment should be stopped and general haemostatic measures taken. Contact the on-call clinical haematologist for further advice.

4.7 Restarting anticoagulation after bleeding

The reintroduction of anticoagulation following bleeding is clinically guided re-anticoagulation should be considered to prevent thrombotic events due to the patient's underlying medical condition. Medical judgement should balance the benefits of anticoagulation with the risks of re-bleeding

Dabigatran etexilate treatment can be re-initiated 24 hours after administration of idarucizumab, if the patient is clinically stable and adequate haemostasis has been achieved. Other anticoagulants may be re-introduced once clinically indicated/appropriate. Haematology advice can be sought for alternative anticoagulants and interventions (e.g IVC filter).

5.0 Roles and Responsibilities

This guideline applies to clinicians involved in the care of patients receiving antithrombotic drugs with bleeding or other reasons for reversal. Directorate Managers and Clinical Directors should disseminate the guideline and encourage its implementation.

6.0 Associated documentation and references

[redacted] Guideline on the management of bleeding in patients on antithrombotic agents. British Journal of Haematology, 160: 35–46

[redacted] British Committee for Standards in Haematology (2011), Guidelines on oral anticoagulation with warfarin – fourth edition. British Journal of Haematology, 154: 311–324

Management of the warfarinised patient requiring urgent surgery. Trust Policy ID 2054.

Trust Formulary. Chapter 2 Cardiovascular System- Reversal of anticoagulation. 02.08.03.

Electronic Medicines Compendium (eMC). Praxbind 2.5 g/50 mL solution for injection/infusion. 2019. https://www.medicines.org.uk/emc/product/5073

Electronic Medicines Compendium (eMC). Ondexxya 200mg powder for solution for infusion 2021 https://www.medicines.org.uk/emc/product/10933

Andexanet alfa for reversing anticoagulation from apixaban or rivaroxaban. Technology appraisal guidance [TA697]. 2021 https://www.nice.org.uk/guidance/ta697/chapter/1-Recommendations

Andexanet Alfa for Acute Bleeding During Treatment With Edoxaban. https://www.ahajournals.org/doi/10.1161/str.52.suppl_1.P3

7.0 Training & Resources

No specific training requirements identified.

Appendix 1 - Glossary of Terms used within Guideline

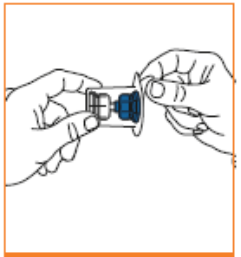
Antithrombotic	A drug where the mechanism of action inhibits the normal thrombotic pathway, such as Heparins, Warfarin and Novel Oral Anticoagulants
Anti- Xa	A test that monitors blood clotting in patients taking anticoagulant drugs, such as low molecular weight heparin or unfractionated heparin. Heparins bind to antithrombin, which inhibits clotting factor Xa.
APTT	Activated partial thromboplastin time
INR	International Normalised Ratio
IV	Intravenous
LMWH	Low Molecular Weight Heparin
DOAC	Direct Oral Anticoagulant. This group of drugs includes dabigatran, rivaroxaban, apixaban and edoxaban.
PCC	Prothrombin Complex Concentrate – a blood product containing Vitamin K dependant Coagulation Factors. The Trust stocks the 4-factor PCC Octaplex which contains Factors II, VII, IX, X, Protein C and Protein S.
PO	The expression is used in medicine to describe a treatment that is taken orally.
UFH	Unfractionated Heparin

1. Appendix 2 – Octaplex Reconstitution Instructions

octaplex® (500 IU coagulation factor IX per vial, powder and solvent for infusion, Human Prothrombin Complex)

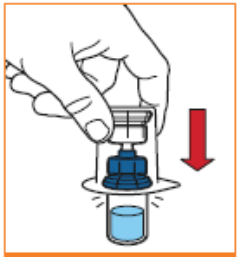
octaplex® Mix2Vial™ Instructions for reconstitution

Follow the hospital's aseptic procedures at all times. Working on a clean flat surface, remove the vials from the outer packaging and remove the flip top lids. Disinfect the vial injection sites with an alcohol swab.



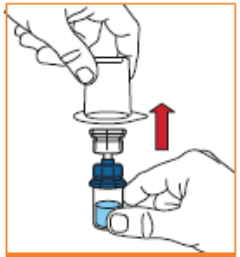
Step 1

Remove the top of the Mix2Vial™ package. Do not remove the device from the package.



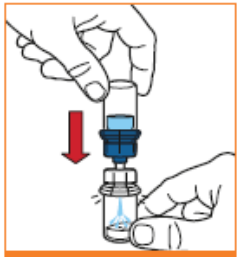
Step 2

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 in place.



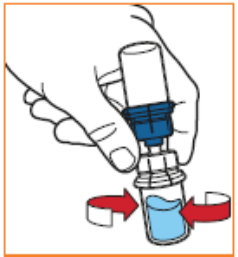
Step 3

Remove the plastic package and discard it. Take care not to touch the exposed end of the device.



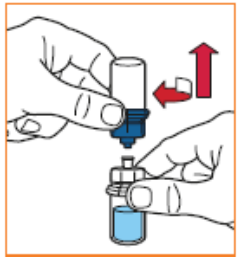
Step 4

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 in place.



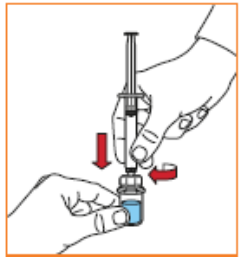
Step 5

The water will automatically flow into the octaplex® vial. Gently swirl the vial to make sure the octaplex® is thoroughly mixed.



Step 6

Remove the water vial by turning it anti-clockwise. Attach a syringe to the octaplex® vial.



Step 7

Turn the octaplex® vial upside down and withdraw the solution into the syringe. Remove the syringe by turning the barrel counter clockwise. octaplex® is now ready for administration.

The reconstitution guidelines above have been adapted from octaplex® Summary of product characteristics and reconstitution direction from Mix2Vial™ of West Pharmaceutical Services.

octapharma
For the safe and optimal use of human proteins

Date of preparation: October 2013 OPX/13/07

2. Appendix 3 – Andexanet alfa reconstitution and administration information

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited.[4]

Ondexxya® reconstitution and administration[1]

Ondexxya® andexanet alfa

▼This medicinal product is subject to additional monitoring.

1. Preparing the (200 mg Ondexxya®) vials

- Ondexxya® does not need to be brought to room temperature before reconstitution or administration to the patient. Aseptic technique during the reconstitution procedure should be used.
- Remove the flip-top
- Wipe the rubber stopper of each vial with an alcohol swab

2. Reconstituting the lyophilisate in the vials

Per vial

- Using a 20 mL (or larger) syringe and a 20-gauge (or larger) needle, withdraw 20 mL of **water for injection**
- Insert the syringe needle through the centre of the vial's rubber stopper
- Push the plunger down **slowly** to inject the water for injections into the vial

IMPORTANT: Carefully direct the stream of water for injection toward the inside wall of the vial to **minimise** foaming.

Inject all required vials before proceeding to the next step.

3. Dissolve

- **Gently swirl** each vial until the powder is completely dissolved
- **Do NOT shake** the vial(s), as this can lead to foaming

IMPORTANT: The powder will have dissolved and the solution will be ready for use after approximately 3–5 minutes.

4. Inspect

- Prior to administration, inspect the reconstituted solution for particulate matter and/or discolouration
- Do not use if the solution contains opaque particles or is discoloured
- Solution after reconstitution: 10 mg/mL

IMPORTANT: The reconstituted solution is clear, colourless or slightly yellow.

5. Transfer

Withdraw the reconstituted solution from each vial into the large-volume (50 mL or larger) syringes (equipped with a 20-gauge or larger needle)

Administration by syringe pump

IMPORTANT

- **Low dose:** 1 infusion syringe intravenous (IV) bolus, 1 infusion syringe continuous IV infusion
- **High dose:** 2 infusion syringes IV bolus, 2 infusion syringes continuous IV infusion
- Hold the syringe needle upright and do not set the syringe down between multiple withdrawals from vials (to prevent air bubbles)

Use of IV bags

- Transfer the reconstituted solution from the syringe into an appropriate IV bag
- It is recommended to split the solution intended for bolus and continuous infusion into two separate bags to ensure the correct administration rate

6. Administration

The IV rate is the same whether using a syringe pump or IV bags.

- **IV bolus rate**
  Low dose: 400 mg, which corresponds to 40 mL, 180 mL/hr, administered over approximately 15 minutes.
  High dose: 800 mg, which corresponds to 80 mL, 180 mL/hr, administered over approximately 30 minutes.
- **Continuous IV infusion rate**
  Low dose: 480 mg, which corresponds to 48 mL, 24 mL/hr, for 120 minutes.
  High dose: 960 mg, which corresponds to 96 mL, 48 mL/hr, for 120 minutes.

The infusion should be administered using 0.2 µm (or 0.22 µm) in-line filters (polyethersulfone [PES] or a similar material with low protein binding).

All used syringes, needles, and vials, including any unused portion of reconstituted solution, should be disposed of in accordance with local requirements.

In-use stability after reconstitution

- In primary packaging/vial: 16 hours at 2–8°C
- Ready-to-use medication: a further 8 hours at room temperature (≤ 25° C)

From a microbiological point of view, once reconstituted, the product should be used immediately. If this is not the case, the user is responsible for the storage times and conditions prior to use.

3. Appendix 4 – Andexanet alfa dosing recommendation

Ondexxya® dosage recommendations[1]

Ondexxya® andexanet alfa

Two dosing regimens, individualised depending on the specific direct factor Xa (FXa) inhibitor, last individual dose of FXa inhibitor and time since last FXa inhibitor dose[1]

FXa inhibitor	Last individual dose	Time since last individual dose		
		< 8 hours	≥ 8 hours	Unknown
Apixaban	≤ 5mg	LOW	LOW	LOW
	> 5mg or unknown	HIGH	LOW	HIGH
Rivaroxaban	≤ 10mg	LOW	LOW	LOW
	> 10mg or unknown	HIGH	LOW	HIGH

	Initial intravenous bolus	Continuous intravenous infusion	Total number of Ondexxya® (200 mg) vials
LOW DOSE	400mg, which corresponds to 40 mL, 180 mL/hr, administered over 15 minutes	480mg, which corresponds to 48 mL, 24 mL/hr for 120 min	5 x
HIGH DOSE	800mg, which corresponds to 80 mL, 180 mL/hr, administered over 30 minutes	960mg, which corresponds to 96 mL, 48 mL/hr for 120 min	9 x

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