Reversal of Apixaban, Edoxaban and Rivaroxaban in Major Haemorrhage or Prior to Emergency Procedures

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- Policy Distribution List (as held by [job title or department]
- NHS Ayrshire and Arran Intranet
- Others, as relevant

Guideline Content

1.0 Introduction

Andexanet alfa has recently been approved by Scottish Medicine Consortium for restricted use in context of reversal of apixaban and rivaroxaban in life-threatening or uncontrolled bleeding. Due to a lack of published data, andexanet alfa has not been licensed for use in patients on edoxaban. Due to the similarity of the mechanism of action of apixaban and rivaroxaban, it has been agreed locally within NHS Ayrshire and Arran that andexanet alfa should be used “off label” for patients presenting with life-threatening or uncontrolled bleeding on edoxaban.

Andexanet alfa should not be prescribed without prior discussion with the on-call haematology consultant and instances where its use is considered should be discussed with the most senior member of the parent team on-site.

Andexanet alfa should not be used routinely for reversal of apixaban, rivaroxaban or edoxaban prior to surgical procedures. This is due not only to its lack of evidence in this context, but also due to the short half-life (1 hour) of andexanet alfa compared to the DOACs (9-12 hours), increasing the risk of significant post-operative bleeding. Andexanet alfa can be considered at the discretion of the haematology consultant in cases where an emergency procedure would proceed irrespective of the availability of a reversal agent.

It should be noted that the use of andexanet alfa for reversal of edoxaban is an off label indication. Please refer to the NHS Ayrshire & Arran Code of Practice for Medicines Governance Section 9(a) – unlicensed medicines for further information:

Definition of life-threatening/ uncontrolled bleeding

(Based on ANNEXA-4 study)

- *Bleeding in critical area or organ: e.g. retroperitoneal, epidural, pericardial, intramuscular with compartment syndrome, intracranial**

  **Evidence for reversal of DOACs with andexanet in intracranial haemorrhage was limited in the trial data and further research is ongoing this area.*

- *Clinically overt/apparent bleeding associated with decrease in haemoglobin to <20g/L*
- *Signs/symptoms of haemodynamic instability (e.g. hypotension)*
- *Any other clinical bleeding considered life threatening.*

2.0 Purpose of guideline

The purpose of the guideline is to assist all staff when dealing with a major haemorrhage in a patient taking a DOAC such as apixaban, edoxaban or rivaroxaban. A Consultant Haematologist should always be consulted when dealing with a major haemorrhage.

3.0 Scope of guideline

All clinical practitioners within NHS Ayrshire and Arran who are dealing with a major haemorrhage in a patient taking a DOAC.

4.0 Definition of terms

DOAC	direct acting oral anticoagulant (apixaban, edoxaban, rivaroxaban)
IV	intravenous
LMWH	Low molecular weight heparin e.g. dalteparin (Fragmin®)

5.0 Management in the setting of life threatening/uncontrolled bleeding

- Stop all anticoagulants.
- Check coagulation screen, full blood count and renal function.
- If DOAC administered < 2 hours previously consider activated charcoal.
- Consider IV tranexamic acid 1g three times daily (clinician discretion in upper GI bleed given HALT-IT trial data).
- Treat any additional causes of coagulopathy.
- Consider appropriateness of andexanet alfa with senior in parent team and thereafter haematology consultant. Andexanet alfa cannot be released for use without discussion with the on Haematology Consultant on-call.
- In intracranial haemorrhage, please discuss with stroke physician on call prior to discussion with haematology consultant.
- Andexanet alfa is administered as IV bolus over 15-30 minutes and thereafter as IV infusion over 2 hours. Dosing information is located within section 6.0.
- In instances where andexanet alfa is not felt to be clinically appropriate, discussion with on call haematologist may still be appropriate to discuss alternate treatments, such as Beriplex 50 IU/kg.
- Bleeding may reoccur even after andexanet alfa administration, and again in these situation please discuss with on-call haematologist to discuss potential for additional administration of Beriplex at 50 IU/kg.
- Anti-Xa should not be reassessed post administration as levels did not correlate with clinical effectiveness.

6.0 Dosing schedules for andexanet alfa, preparation, administration and monitoring

6.1. Dosing regimens for DOAC reversal

DOAC	Last dose of DOAC	Timing of last dose before andexanet alfa initiation		
		<8 hours or unknown	8 hours-18 hours	More than 18 hours
Apixaban	5mg or less	Low dose	Low dose	Not recommended-outwith a clinical trial
	More than 5mg or dose unknown	High dose		
Rivaroxaban	10mg or less	Low dose	Low dose	
	More than 10mg or dose unknown	High dose		
Edoxaban	30mg or less	Low dose	Low dose	
	More than 30mg or dose unknown	High dose		

	Initial intravenous loading dose of	Continuous intravenous infusion	Total number of vials required
Low dose regimen	400mg at target rate of 30mg/minute (approximately 15 minutes)	4mg/minute over 120 minutes (480mg)	5
High dose regimen	800mg at target rate of 30mg/minute (approximately 30 minutes)	8mg/minute over 120 minutes (960mg)	9

6.2 Andexanet alfa preparation and administration

- For instructions on the preparation and administration of andexanet alfa infusion refer to the information above and the monograph within the Medusa Injectable Medicines Guide available on AthenA.
- A syringe pump (Agilia pump).is recommended for administration of both the loading and maintenance doses.
- An in-line filter is required for the administration. Recommended that 0.2µm air eliminating, low protein filter is used i.e the PALL AEF1E filter.
- Andexanet alfa is kept in the Emergency Pharmacy cupboard, within the fridge at both University Hospital Ayr and Crosshouse sites. The PALL AEF1E filter required for administration is located on the shelf beside andexanet alfa medication.
    - Please contact the pharmacy department or clinical pharmacist in working hours to access stock or hospital co-ordinator out-of-hours.
- Due to cost, wastage should be minimised. As andexanet alfa is a fridge item, **please request the exact number of vials required.**

6.3 Monitoring

- Anti Xa monitoring pre and post infusion is not required as subsequent dosing is not dependant on this. If timing of last DOAC is uncertain, anti-Xa of particular DOAC can be requested to assist future decision making for other potential products (e.g. Beriplex®) but administration of andexanet alfa should not be delayed to facilitate this.

7.0 Haemostasis

- Monitor for evidence of bleeding and discuss with haematology if patient re-bleeds.
- Give LMWH thromboprophylaxis as soon as appropriate (due to risk of thrombosis with Andexanet Alfa estimated at 10.3% in trial, but unclear if related to drug or patients underlying risk of thrombosis).
- Do not reintroduce DOAC until at least 24 hours after LMWH thromboprophylaxis given successfully without re-bleeding or discussed with haematology consultant
- Andexanet alfa is a black triangle medicine therefore all suspected adverse effects from treatment must be reported to the MHRA (Medicines and Healthcare products Regulatory Agency) using the Yellow Card Reporting system. These can be completed online at www.mhra.gov.uk/yellowcard. Alternatively the yellow cards found inside a BNF can be completed and posted to FREEPOST YELLOW CARD (no other address details required).

Adapted with kind permission from NHS Greater Glasgow and Clyde Guideline dated September 2020

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