Guidance for rivaroxaban and apixaban rapid reversal using andexanet

Clinical Guidance for the Use of Andexanet in the Rapid Reversal of Rivaroxaban and Apixaban			
Date effective from:	10/07/2023	**Review date:**	10/07/2025
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Approved by:	Drugs & Therapeutic Committee		
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Executive Lead:	Julia Anderson		
Target Audience:	All medical, nursing and pharmacy staff involved in the care of adult patients in clinical areas		
Keywords (min. 5):	Anticoagulant reversal, apixaban, rivaroxaban, andexanet		

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Version Control: Review and Amendment Log

Date	Author	Version/Page	Reason for change
May 21	Julia Anderson	1.0	New guideline to outline indication and use for andexanet as a reversal agent for specific life-threatening bleeding associated with Apixaban or Rivaroxaban use.
May 23	Julia Anderson/Reshma Chhana	1.1	Adjusted guidance in line with UK National Clinical Guideline for Stroke April 2023. Andexanet not to be used for intracranial bleeding except within context of clinical trial Timing of last dose of Xa inhibitor prior to Andexanet changed to 18 hours to be in line with ANNEXA4 clinical trial Site drug and filter locations specified and summary flowchart added Documentation details for approval of use

Dissemination Plan

Audience	Method	Paper/Electronic	Responsible staff member
All staff	Upload - intranet	Electronic	D&T/Consultant Haematologist
A&E Leads	E-mail to all sites	Electronic	Consultant Haematologist
Pharmacists	E-mail / Site leads	Electronic	Clinical Lead Pharmacist WGH
Thrombosis Committee	Discussed and circulated; including haem at HYCP	Electronic	Consultant Haematologist

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Contents

1.0 Introduction

Andexanet alfa is recommended as an option for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled gastrointestinal bleeding. Due to lack of clinical trial data, andexanet alfa is not licensed for use in patients taking edoxaban. Andexanet binds to factor Xa (FXa) inhibitors and allows restoration of native FXa activity, thus increasing thrombin generation. After binding, andexanet dissociates from the FXa inhibitor and both agents are eliminated. The elimination half-life of andexanet ranges from four to seven hours.

Definition of life/limb-threatening bleeding

any of the following conditions (taken from *Annexa-4 phase III study* of andexanet):

- Retroperitoneal (CT or MRI documented)
- Epidural (CT or MRI documented)
- Intra-ocular (excludes conjunctival)
- Intramuscular with compartment syndrome
- Pericardial
- Non-traumatic intra-articular
- Any invasive procedure to stop bleeding
- Active bleeding from any orifice plus BP≤90mmHg systolic, or oliguria, poor skin perfusion, or associated decrease in haemoglobin ≥20g/L
- Any other bleeding that the clinician deems to be life-threatening

Exclusion

- Peri-operative use: there is no evidence to support use of andexanet alfa in the elective or emergency surgery setting. The recommendation for andexanet use for anti-coagulation reversal in the peri-operative setting is not supported.
- Age < 18years

Safety and efficacy

The safety and efficacy of andexanet alfa is not established for children below age of 18, in pregnancy or lactation. The effectiveness of andexanet alfa for intracranial bleeding has not yet been established and NHS Lothian is not currently involved in clinical trial for use. There is no evidence directly comparing andexanet alfa with established clinical management (including prothrombin complex concentrate i.e. beriplex) and indirect comparison has limitations. There is a potential thrombotic risk from andexanet and/or from reversing rivaroxaban or apixaban in prothrombotic patients. There is minimal data on re-exposure to andexanet alfa.

2.0 Purpose &Scope

The purpose of this document is to provide guidance for rapid reversal of apixaban and rivaroxaban using andexanet alfa (Ondexxya©) in adults (≥ 18 years old) who have taken either drug in the last 18 hours, presenting with life/limb-threatening bleeding or requiring emergency surgery.

*This guidance should only be used in consultation with haematology. This guidance is **NOT APPLICABLE** for use with any other anticoagulants, nor for reversal prior to elective surgery. Andexanet alfa is restricted to hospital use only.*

The cost of andexanet alfa is significant (from £13,875 to £24,975 per dose).

Before considering use of andexanet please consider:

- Maintain key principles of major haemorrhage to achieve haemostasis
- Check FBC, coagulation screen and renal function
- Ascertain time the Xa inhibitor was last taken, the type of Xa inhibitor, and the dose being taken, and withhold until safe to restart. If less than 2 hours, consider administration of oral activated charcoal to further inhibit drug absorption. Please note that these Xa inhibitors are not dialysable
- Treat any additional causes of coagulopathy and administer platelet transfusion if platelet count < 75 x 10^9/L.

3.0 Definitions

DOAC – direct oral anticoagulant

FBC – full blood count

GCS – Glasgow coma scale

GI – gastrointestinal

ICH – intracranial haemorrhage

OOH – out of hours

RIE – Royal Infirmary of Edinburgh

SJH – St John's Hospital

WGH – Western General Hospital

4.0 Roles and responsibilities

Medical team: to ensure that appropriate indication for use and safe prescribing of andexanet is confirmed at consultant grade and that the consultant confirms this by direct discussion with the on-call Consultant Haematologist (RIE) – *contactable 24 hours a day via switchboard.*

Haematology team: To confirm appropriate indication for use of andexanet at consultant grade when contacted by consultant responsible for patient care and to authorise provision by pharmacy.

Nursing team: To ensure administration and prescribing is in place.

Pharmacy team: to ensure appropriate haematology approval, indication, dosing and subsequent medication supply provision provided in a timely manner as outlined by this guidance. To ensure record keeping on dose use maintained in pharmacy for each use.

5.0 Main content

5.1 Indication

The decision to use andexanet alfa (Ondexxya©) should be made by the physician-in-charge at consultant grade following risk:benefit consideration, and must be discussed with the on-call Haematology Consultant (RIE).

When considering the use of andexanet alfa, the consultant responsible should take the individual circumstances of the patient into account, including the likely prognosis following a catastrophic bleeding event.

It may be necessary to consider checking drug levels if the timing of the last dose is unknown. Urgent factor Xa levels (apixaban, and rivaroxaban) are available by request from the specialist coagulation laboratory and require approval from the on-call haematologist.

For intracranial bleeding, it has been agreed that NHS Lothian will follow the National Clinical Guideline for Stroke, updated in April 2023; see recommendation 3.6B that states *"Patients with intracerebral haemorrhage in association with direct oral anticoagulant (DOAC) treatment should have the anticoagulant urgently reversed. …….For those taking factor Xa inhibitors, 4-factor prothrombin complex concentrate should be considered and andexanet alfa may be considered in the context of a randomised controlled trial".*

5.2 Contraindications:

- Previous life-threatening reaction to andexanet alfa.
- Not licensed for use in under 18 years old.

- Most frequently observed adverse reactions are mild or moderate infusion-related reactions with symptoms such as flushing, feeling hot, cough, dysgeusia and dyspnoea occurring within a few minutes to a few hours of the infusion.

Cautions:

- Pregnant/lactating female: due to a lack of information for use of andexanet alfa, treatment is not recommended in this patient group. In the case of life-threatening bleeding, the potential risks and benefits should be considered with caution on an individual case basis for use in specific situations.

5.3 NHS Lothian site storage location:

Authorisation for approval of use must be obtained by the on-call Consultant Haematologist (RIE) prior to prescribing for use. For pharmacy medication supply during working hours (Mon-Fri 08:45 – 17:00; Sat-Sun 09:00 – 12:00), clinical pharmacists must be contacted; out-of-hours the on-call pharmacist via switchboard.

Sufficient vials for one dose (low/high as per table 2) of andexanet along with the appropriate PALL filter will be available from the following locations at respective sites:

Table 1: Location for Andexanet Alfa and filter supply

Site	Working-Hours *(Mon-Fri 08:45 – 17:00; Sat-Sun 09:00 – 12:00)*		Out-Of-Hours	
	Andexanet	**PALL filter***	**Andexanet**	**PALL filter***
RIE	Main RIE pharmacy store	A&E, ICU	HAN Emergency Drug Cupboard (EDC) refrigerator	EDC
WGH	Main WGH pharmacy store	MAU, ICU	Emergency Drug Cupboard (EDC) refrigerator	EDC *(in basket on top of fridge-sign attached)*
SJH	Resuscitation cupboard refrigerator, A&E Department	A&E	Resuscitation cupboard refrigerator, A&E Department	A&E
PALL filter supply should be maintained by relevant location and ordered directly via PECOS as a "device"				
Storage: must be stored in a refrigerator between 2°C – 8°C				

5.4 Dose and mode of administration:

The dose of andexanet is based on the dose of factor Xa inhibitor and time of last dose. No dose adjustments are necessary for elderly patients or patients with renal or hepatic impairment.

Table 2: Dosing Andexanet Alfa based on timing of DOAC (apixaban/rivaroxaban)

Factor Xa Inhibitor	**Last dose taken**	**Timing of last dose before andexanet alfa infusion**	**Timing of last dose before andexanet alfa infusion**	**Timing of last dose before andexanet alfa infusion**
		< 8 hrs/unknown	**≥8 hours**	**>18 hours**
Apixaban	5 mg or less	Low dose	Low dose	Not recommended as not included in clinical trial
Apixaban	More than 5 mg or dose unknown	High dose	Low dose	Not recommended as not included in clinical trial
Rivaroxaban	10 mg or less	Low dose	Low dose	Not recommended as not included in clinical trial
Rivaroxaban	More than 10 mg or dose unknown	High dose	Low dose	Not recommended as not included in clinical trial

Response should be assessed clinically. Specific monitoring (e.g. factor Xa inhibitor level) is not indicated.

If bleeding recurs despite use of andexanet alfa, this should be discussed with the on-call haematologist to decide whether there is a role for additional use of Beriplex 25 – 50 units/kg.

5.5 Administration:

Andexanet alfa is administered as an intravenous bolus over 15-30 minutes followed by an intravenous infusion over 2 hours. The bolus and the maintenance infusion are prepared in separate large volume syringes.

In NHS Lothian, the use of a syringe infusion with PALL AEF1E low-protein binding filter and tubing is recommended. The filter will be issued with the dose. It is advised that both loading, and maintenance doses are reconstituted at the same time.

- Andexanet alfa 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.

	Initial Intravenous Bolus	**Continuous Intravenous Infusion *(maintenance dose)***	**Total Number of Vials required**
Low dose	**400 mg over 15 min** *At a target rate of 30 mg/min* *Infusion rate ~160 mL/hr*	4 mg/min for 120 mins (480 mg) Infusion rate 24mL/hr	5
High dose	**800 mg over 30 min** *At a target rate of 30 mg/min* *Infusion rate ~160 mL/hr*	8 mg/min for 120 mins (960 mg) Infusion rate 48 mL/hr	9

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Instructions for reconstitution/preparation of loading dose:

- Reconstitute the required number of vials of andexanet alfa for the low dose regimen or high dose regimen.
- Inject 20 mL sterile water for injections into each 200 mg vial. Use 20 gauge (or larger) safety hypodermic needles.
- Slowly direct the stream down the wall of the vial.
- Gently swirl the vial (do not shake, as this can lead to foaming) until the powder is completely dissolved (this takes approximately 3-5 minutes for each vial).
- Inspect the reconstituted solution for particulate matter and/or discolouration prior to administration.
- Do not use if opaque particles or discolouration are present. Prepare all vials before the next step.
- Withdraw the required volume of the reconstituted dose into 60 mL syringes. For the high loading dose, you will need 2 x 60 mL syringes.
- Add the in-line filter and administration set. Set the rate on the syringe pump to deliver 30 mg per minute (infusion rate approximately 160 mL/hr).

Maintenance dose (infusion should be commenced as soon as the loading dose is complete)

- Low dose – 480 mg given as 4mg/min for 120 mins (infusion rate 24 mL/hr)
- High dose – 960 mg given as 8mg/min for 120 mins (infusion rate 48 mL/hr)

Instructions for reconstitution/preparation of maintenance dose:

- Prepare vials as before.
- Withdraw the required volume of the reconstituted dose into 60 mL syringes. For the high maintenance dose, you will need 2 x 60 mL syringes.
- Add the in-line filter and administration set and set rate on the syringe pump to deliver low dose mg/min for 120 mins (infusion rate 24 mL/hr), or high dose 8 mg/min for 120 mins (infusion rate 48 mL/hr).

An ongoing audit of use of andexanet will be conducted in NHS Lothian due to treatment costs and ensure governance around appropriate clinical use. See section 6.2.

6.0 Associated materials

6.1 Summary flowchart on indication for use and supply of andexanet for rapid reversal of rivaroxaban or apixaban

Life-threatening bleeding or uncontrolled GI bleeding *(not ICH)* attributed to rivaroxaban/apixaban that is unsuitable for 1st line intervention i.e. interventional radiology/endoscopy as deemed by consultant in charge*

**as per sections 1, 3, 5.1, 5.2*

↓

On-call haematologist consultant (RIE) contacted via switchboard to confirm indication, dosing for prescribing and suitability to administer

↓ *Clinical/Medical team to complete approval details on TRAK (see section 6.2)*

Clinical pharmacist /on-call OOH pharmacist contacted to confirm dose and supply. Confirm clinical team looking after patient have documented details of approval on TRAK *(see section 6.2)*

↓

Site	Working-Hours *(Mon-Fri 08:45 – 17:00; Sat-Sun 09:00 – 12:00)*		Out-Of-Hours	
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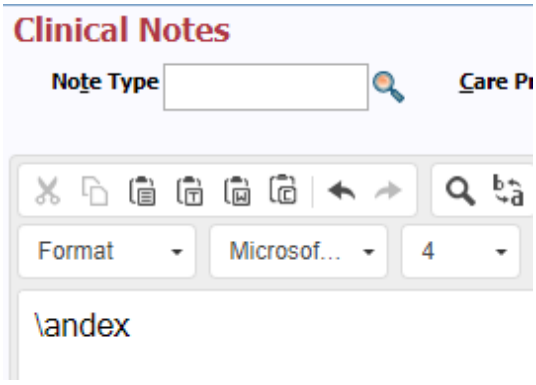
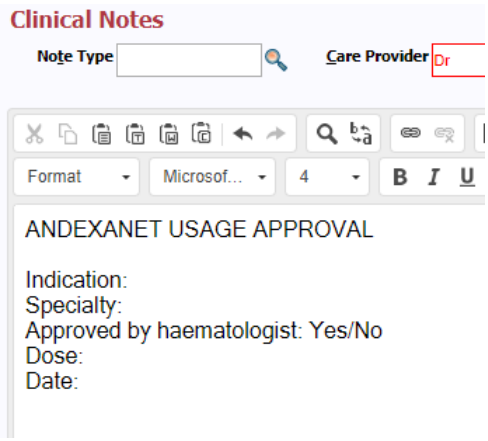
RIE	Main RIE pharmacy store	A&E, ICU	HAN Emergency Drug Cupboard (EDC) refrigerator	EDC
WGH	Main WGH pharmacy store	MAU, ICU	Emergency Drug Cupboard (EDC) refrigerator	EDC *(in basket on top of fridge-sign attached)*
SJH	Resuscitation cupboard refrigerator, A&E Department	A&E	Resuscitation cupboard refrigerator, A&E Department	A&E
PALL filter supply should be maintained by relevant location and ordered directly via PECOS as a "device"				
Storage: must be stored in a refrigerator between 2°C – 8°C				

6.2 Table to document usage of Andexanet

For andexanet approval of use, the following **MUST** be documented on TRAK (short-code "**\andex ")** by the requesting clinician/clinician team**:**

- Indication:
- Specialty:
- Approved by haematologist: Yes/No
- Dose:
- Date:





And the details documented on the table (appendix 1) when obtaining supply from EDC/A&E/Pharmacy.

Evidence base/references

References
Connolly SJ, Crowther M, Eikelboom JW et al. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. N Eng J Med 2019; 380: 1326-35. Accessed via: Final Study Report of Andexanet Alfa for Major Bleeding With Factor Xa Inhibitors | Circulation (ahajournals.org)
National Clinical Guideline for Stroke for the United Kingdom and Ireland. 2023 edition. Accessed via: National-Clinical-Guideline-for-Stroke-2023.pdf (strokeguideline.org)
Scottish Medicines Consortium; Healthcare Improvement Scotland. Accessed May 2023: andexanet alfa (Ondexxya) (scottishmedicines.org.uk)
Andexanet Summary of Product Characteristics. Accessed on electronic medicines compendium. Last updated Nov 2022. Ondexxya 200 mg powder for solution for infusion - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
Saja K; on behalf of the Haemostasis and Thrombosis Taskforce of the British Society for Haematology. Addendum to the guideline on peri-operative management of anti-coagulation and anti-platelet therapy. Br J Haematol.

2022;193:188-189. Addendum to the guideline on the peri-operative management of anti-coagulation and anti-platelet therapy - Saja - 2022 - British Journal of Haematology - Wiley Online Library
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Associated Documents	
Beriplex Administration	June 2019

7.0 Stakeholder consultation

Consultation
Stroke Medicine Neurosurgery Haematology Pharmacy

8.0 Monitoring and review

Element (s) to be monitored	**Person (position) responsible for the monitoring**	**Method**	**Monitoring frequency**	**Committee or group monitoring is reported to including responsibility for action plans and changes in practice**
Compliance to the guideline	*Thrombosis Committee*	*Audit* *Review of datix reports*	*Quarterly* *On-going*	*NHS Lothian Thrombosis committee – including neurosurgery, stroke, medicine, and pharmacy teams*

Appendix 1

Details of Andexanet Usage

The following details should be filled out for every occurrence of andexanet usage

Date	CHI number	Clinical Specialty	Indication	Dose	Approved by Haematology and Pharmacy
					Yes/No
					Yes/No
					Yes/No
					Yes/No
					Yes/No
					Yes/No
					Yes/No
					Yes/No
					Yes/No
					Yes/No
					Yes/No
					Yes/No
					Yes/No

This copy will be kept in the pharmacy department (one for each site) and filled out by the authorising pharmacist/on call pharmacist.