Andexanet alfa (Ondexxya®)

For adult patients treated with a direct factor Xa (FXa) inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

This document is intended for use by healthcare professionals only.

INDICATION FOR USE: [1]

TREATMENT	INDICATION	ICD10	PROTOCOL CODE
Andexanet alfa (Ondexxya®)	For adult patients treated with a direct factor Xa (FXa) inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.	D68.3	HAEM001

TREATMENT: [1]

CAUTION

Andexanet alfa should not routinely be used for the treatment of intracerebral haemorrhage in patients receiving oral Factor Xa inhibitors, though may be considered on a case-by-case basis after consultation with relevant local experts.

Dose Table 1

Andexanet alfa	Initial Intravenous Bolus	Continuous Intravenous Infusion	Total number of 200 mg vials needed
Low dose	400 mg at a target rate of 30 mg/minute	4 mg/min for 120 minutes (480 mg)	5
High dose	800 mg at a target rate of 30 mg/minute	8 mg/min for 120 minutes (960 mg)	9

Dose Table 2

FXa inhibitor	Last dose (FXa inhibitor)*	Timing of last dose before andexanet alfa initiation**	
		Less than 8 hours	Greater than or equal to 8 hours***
Apixaban	Less than or equal to 5 mg	Low dose	Low dose
	Greater than 5 mg	High dose	
Rivaroxaban	Less than or equal to 10 mg	Low dose	Low dose
	Greater than 10 mg	High dose	

***If the strength of the last dose of FXa inhibitor is unknown, no dose recommendation is available*[1]
***If the interval between the last dose of FXa inhibitor and the bleeding episode is unknown, no dose recommendation is available.*[1]
****Only patients who had acute major bleeding within 18 hours after administration of an FXa inhibitor were included in studies. Therefore it may NOT be clinically appropriate to administer andexanet alfa in patients where administration of an FXa inhibitor is greater than 18 hours as benefit in this patient cohort has not been demonstrated.*[2]

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ELIGIBILITY:

- Administration of **apixaban or rivaroxaban**

  AND

- have an **acute, life threatening, uncontrolled bleeding** associated with any of the following:
  - Signs and symptoms of haemodynamic compromise e.g. severe hypotension, poor skin perfusion, mental confusion or low cardiac output not otherwise explained
  - Drop in haemoglobin (Hb) greater than 2 g/dL OR Hb less than or equal to 8 g/dL if no baseline Hb available
  - Bleeding in a critical area or organ e.g. retroperitoneal, intra-articular, pericardial, epidural or intracranial, intramuscular with compartment syndrome

EXCLUSION CRITERIA:

- Patients less than 18 years of age
- Patients who do not meet the eligibility criteria above

CONTRAINDICATIONS: [1, 2]

- Hypersensitivity to active substance or to any other ingredients
- Known allergic reaction to hamster proteins
- Intracranial haemorrhage (ICH) with Glasgow Coma Scale (GCS) <7

SPECIAL WARNINGS AND PRECAUTION FOR USE [1, 2, 3, 4]

Post-authorisation studies of Andexanet alfa, have identified that in treatment of patients with intracerebral haemorrhage who received factor Xa inhibitors, "*Andexanet resulted in better control of hematoma expansion than usual care but was associated with thrombotic events, including ischemic stroke.*" [3]

Caution is advised when deciding on treatment options to reverse anti-coagulation due to life-threatening or uncontrolled bleeding. Clinicians are recommended to consider an individual patient's benefit-risk assessment, to determine suitability for treatment with Andexanet alfa.

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Caution should be used when prescribing andexanet alfa for patients who meet the eligibility criteria AND have one or more of the following clinical criteria:

- Require emergency surgery within the next 12 hours. Consider discussion with relevant Consultant if vascular or cardiothoracic emergency surgery is likely to be required.
- Require treatment with unfractionated heparin within the next 24 hours e.g. an invasive procedure for ICH with a secondary vascular cause, cardiothoracic surgery (refer to Adverse Effects / Regimen Specific Complications section below for further information).
- Who have received Prothrombin Complex Concentrate (PCC) within the previous 7 days or recombinant FVIIa within 12 hours.
- Refer to the Summary of Product Characteristics (SmPC) for further information.

DOSE MODIFICATIONS:

- See dose tables 1 and 2 above

SUPPORTIVE CARE: [1]

- Andexanet alfa can be used in conjunction with standard haemostatic supportive measures, which should be considered as medically appropriate

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS: [1, 5]

The adverse effects listed are not exhaustive. Please refer to the Summary of Product Characteristics for full details. **This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions**.

- **Infusion Reactions:**
  - Mild infusion reactions can usually be managed with clinical monitoring.
  - Moderate infusion reactions can be managed by slowing or stopping the infusion temporarily and use of an antihistamine can be considered.
  - Severe infusion reactions should be managed by stopping the infusion and managing the patient specific symptoms.

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- **Temporary heparin resistance:**
  - Following treatment with andexanet alfa, unfractionated or low molecular weight heparin will be ineffective for 24 hours.[6]
  - This is especially relevant for patients likely to require an invasive procedure/surgery for which unfractionated heparin will be needed. In this setting, if andexanet alfa has been administered, the patient **will be unresponsive to heparin and there is a significant risk of acute, severe thrombosis.**

- **Elevation in D-dimers post infusion of andexanet alfa:**
  - Elevation in D-dimers is expected post infusion of andexanet alfa and D-dimers should not be used in the evaluation of possible thrombosis.

- **Thrombotic Risk and Restarting Anticoagulation:**
  - Reversal of anticoagulation can be associated with an increase in risk of thrombosis for up to 30 days post reversal.[3] This may be related to changes in coagulation parameters due to the reversal agent or to the interruption of anticoagulation in a patient with prothrombotic risk factors.
  - This may be especially relevant for patients with a recent (<1 month) history of thrombosis and risks and benefits of the use of any reversal agent should be considered on an individual basis.

- **Risk mitigation measures for thrombosis:**
  - Monitor patients for signs and symptoms of thrombosis post reversal.
  - Consider restarting anticoagulation when safe to do so, having regard for the individual risks and benefits. Suggested timelines for reintroduction of anticoagulation:
    - 7-14 days following a severe, life threatening bleed or intracranial haemorrhage
  - Longer or shorter intervals to restarting anticoagulation may be appropriate according to clinical circumstances and/or neurosurgical advice

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OTHER INFORMATION:

Storage: Store in a refrigerator (2°C to 8°C)

Administration: Methods of administration include: syringe pump or suitable empty intravenous bags comprised of polyolefin (PO) or polyvinyl chloride (PVC) material. A 0.2 or 0.22 micron in-line polyethersulfone (PES) or equivalent low protein-binding filter should be used. See SmPC for further information.

The following administration devices are suggested examples of suitable equipment that may be used to administer andexanet alfa via a 0.2 or 0.22 micron in-line filter using the administration methods listed in the SmPC. Decision on method of administration to be made locally, depending on the availability of necessary consumables, staff skill set etc. This list is not exhaustive.

Syringe pump	Intravenous bag
Vygon lectrospiral administration set (1155.80)	Baxter administration set (VMC9627)
B. Braun Sterifix 0.2 micron filter set (4099303)	

- Andexanet alfa is not licensed for:
  - the treatment of life threatening bleeding in patients on edoxaban
  - prevention of bleeding during emergency surgery
- For patients on edoxaban or patients needing reversal for emergency surgery, please discuss treatment options with local haematology or relevant responsible consultant.
- Consider the use of PCC in patients on apixaban or rivaroxaban requiring reversal of anticoagulation where andexanet alfa is contra-indicated or not clinically appropriate. Refer to local guidance for management of acute bleeding in patients on anticoagulation.

DRUG INTERACTIONS:

Refer to SmPC

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ATC CODE:

Andexanet alfa V03AB38

REIMBURSEMENT CATEGORY:

Hospital Reimbursement

REFERENCES:

1. Summary of Product Characteristics Ondexxya 200 mg/mL powder for solution for infusion. Available from: https://www.ema.europa.eu/en/documents/product-information/ondexxya-epar-product-information_en.pdf Accessed online: 16.08.2024
2. Connolly SJ, Crowther M, Eikelboom JW, Gibson CM, Curnutte JT, Lawrence JH, Yue P, Bronson MD, Lu G, Conley PB, Verhamme P, Schmidt J, Middeldorp S, Cohen AT, Beyer-Westendorf J, Albaladejo P, Lopez-Sendon J, Demchuk AM, Pallin DJ, Concha M, Goodman S, Leeds J, Souza S, Siegal DM, Zotova E, Meeks B, Ahmad S, Nakamya J, Milling TJ Jr; ANNEXA-4 Investigators. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. N Engl J Med. 2019 Apr 4;380(14):1326-1335. doi: 10.1056/NEJMoa1814051. Epub 2019 Feb 7. PMID: 30730782; PMCID: PMC6699827.
3. S.J. Connolly, M. Sharma, A.T. Cohen et. al. Andexanet for Factor Xa Inhibitor-Associated Acute Intracerebral Hemorrhage. N Engl J Med. 2024 May 16; 390(19): 1745-1755. DOI: 10.1056/NEJMoa2313040
4. Summary of Product Characteristics NovoSeven powder and solvent for solution for injection. Available from: https://www.ema.europa.eu/en/documents/product-information/novoseven-epar-product-information_en.pdf. Accessed online: 12.06.2023
5. Witt DM. What to do after the bleed: resuming anticoagulation after major bleeding. Hematology Am Soc Hematol Educ Program. 2016 Dec 2;2016(1):620-624. DOI: 10.1182/asheducation-2016.1.620. PMID: 27913537; PMCID: PMC6142471.
6. "Clinical judgement" as per correspondence on file from Chair of Irish Haematology Society 13.6.2023.

APPENDIX

Contributors:

This guideline was based on original work by:
The Irish Haematology Society Coagulation Special Interest Group.

Subsequent clinical input and review was provided by:

- Irish Association for Emergency Medicine Clinical Guidelines Committee
- National Clinical Programme for Emergency Medicine
- National Clinical Programme for Surgery
- National Clinical Programme for Stroke
- Access & Integration Drug Management Programme (AIDMP)

With additional information provided by:

- St. James's Hospital Pharmacy Department

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- St. Vincent's University Hospital Drugs & Therapeutics Committee Short Life working group May/June 2023
- Galway University Pharmacy Department, "Andexanet alfa Intravenous for Adults" available from: http://medinfogalway/ivguides/andexanet-alfa-intravenous-adults. Accessed 21st of June 2023

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