Andexanet alfa Intravenous for Adults

Who can administer

- May be administered by registered competent doctor or nurse/midwife

Important information

Available in: Dispensary, Pharmacy Department, University College Hospital (location Fridge 2, Shelf 10)

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PRODUCT MUST BE STORED IN FRIDGE UNTIL POINT OF PREPARATION (to avoid wastage of very high cost item)

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See HSE prescribing guidelinesÂ for details on the use of this drug (also listed under Further Information below)
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Management of acute, life threatening, uncontrolled bleeding in patients on apixaban or rivaroxaban (ref 1)

- **Caution: Increased risk of thrombosis**
    - The U.S. Food and Drug Administration (FDA) initially granted accelerated approval for andexanetÂ
    - However, since then the FDA has received post-marketing safety data from ANNEXA-I which demonstrated an **increased incidence of thrombosis (14.6% versus 6.9%) and thrombosis-related deaths at Day 30 (2.5% versus 0.9%)** in the Andexanet arm compared with the Usual Care arm, respectively.Â Based on this data, the FDA considers the risks of the product to outweigh its benefits. The company subsequently submitted a request to voluntarily withdraw the license for the product in the USA for commercial reasons
    - 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
- **The use of this product must be Consultant approved**
- **This is not a blood product but reversal of anticoagulation should be discussed with**

the Haematology Registrar/ Consultant Haematologist

- **STORED IN: University Hospital Galway:Â Main pharmacy fridge (Fridge 2, shelf 10)- nursing admin have access out of hours**
- **In order to improve the traceability of biological medicinal products, the name, batch number and expiry date of each vial should be clearly recorded in the patient's record**

Available preparations

Ondexxya 200mg vial

Reconstitution

Water for Injection

20ml per 200mg vial (10mg per mL)

- EXPENSIVE ++. Reconstitute ONLY when dose is prescribed and patient fit for treatment
- Use 20 gauge (or smaller) needles during preparation
- Inject 20ml Water for Injection into each vial, directing the stream down the wall of the vial
- Gently swirl the vial (do not shake) until the powder is completely dissolved (this takes approximately 3 to 5 minutes per vial)
- Prepare all vials needed before the next step
  - Low dose: will require 5 vials
  - High dose: will require 9 vials

Methods of intravenous administration

- After reconstitution, the drug solution is transferred to 50mL syringes for use in a syringe pump (no further dilution required) - and is administered as follows
- **Filter: The administration set must include a filter**
  - Coiled giving set (Lectrospiral ref 1155.80) administration set or similar is attached to the syringe containing the drug
  - Then attach a Sterifix 0.2 micron filter set (Braun 4099303 - available from pharmacy) to the end of the coiled giving set administration set, before it is connected to the patient

Methods of administration - using neat injection solution (no dilution required)

Â	**Total number of 200mg vials needed**	**Initial Intravenous bolus**	**Intravenous infusion**
Low dose	Five	Give 400mg over 15 minutes (160mL/hour**)Â** Â **Follow IMMEDIATELY with intravenous infusion**	Give 480mg over 120 minutes (24mL/hour) Â (Note: 12 ml will remain unused out of the 3rd vial)
High dose	Nine	Give 800mg over 30 minutes (160mL/ hour) (will need to use 2 syringes) **Follow IMMEDIATELY with intravenous infusion**	Give 960mg over 120 minutes (48mL/hour) (will need to use 2 syringes) (Note: 4 mL will remain unused out of the 5th vial)

Filter: The administration set must include a filter- see above for further detail

Flushing: See below for detail

Flushing

- A volume of the medicine remains in the infusion set at the end of the infusion
- To minimise medicine losses, the infusion set should not be changed when connecting syringes for administration of the initial bolus dose or the intravenous infusion
- Once the final syringe of the IV infusion has been administered the infusion line must be flushed with sodium chloride 0.9% at the same rate the medicine was administered
- Flushing can be undertaken by using the syringe pump to administer a syringe containing 20 mL of sodium chloride 0.9% at a rate of 24 mL/hour if on the low dose regimen or 48 mL/hour if on the high dose regimen

Infusion-related reactions - see under Monitoring

Dose in adults

For reversal of apixaban or rivaroxaban due to life-threatening or uncontrolled bleeding

Choose the required dosage regimen - depends on TIMING OF LAST DOSE of apixaban/rivaroxaban- see Table 1 below

- **Low dose**
  - **Initial intravenous bolus:** 400mg, followed by...
  - **Intravenous infusion:** 480mg
- **High dose**
  - **Initial intravenous bolus:**800mg, followed by...
  - **Intravenous infusion:Â** 960mg

Table 1: Choose the dosage regimen

The size and timing of the last dose of apixaban or rivaroxaban taken determines whether the high dose or low dose regimen is used

Â	**Last dose**	**Timing of last dose of apixaban or rivaroxaban before andexanet administration**	
		less than 8 hours or unknown	**8 hours or more***
Apixaban	5mg or less	Low dose	Low dose
	greater than 5mgÂ	High dose	
Rivaroxaban	10mg or less	Low dose	Low dose
	greater than 10mg	High dose	

If the strength of the last dose is unknown, no dose recommendation is available [(ref 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 [(ref 1)]

Elderly patients: No dosage adjustments required

Renal impairment: No dosage adjustments required

Hepatic impairment: No dosage adjustments required

Record the batch number and expiry date of each vial in the patient's record

Monitoring

Infusion-related reactionsÂ [ref 1]

- 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.

Further information

The information below is taken from: HSE Prescribing Guideline (ref 1)Â

Indications

- For use in patients who have taken apixaban or rivaroxaban
- **AND**
- have an acute, life threatening or uncontrolled bleeding associated with one or more 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) >2 g/dL OR Hb 8 g/dL or less 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

Contra-indications:

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

Use with caution

- Patients requiring emergency surgery within the next 12 hours
- Patients requiring treatment with unfractionated heparin within the next 24 hours e.g. an invasive procedure for ICH with a secondary vascular cause, cardiothoracic surgery
- Patients 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 for further information.

Temporary heparin resistance:

- Following treatment with andexanet alfa, unfractionated or low molecular weight heparin will be ineffective for 24 hours
- 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 with and Restarting anticoagulation

- Reversal of anticoagulation can be associated with an increase in risk of thrombosis for up to 30 days post-reversal. 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. The 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 the 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

Management of bleeding and surgery if andexanet alfa is contra-indicated or not clinically appropriate:

- Andexanet alfa is not currently licensed for:
    - the treatment of life-threatening bleeding in patients on edoxaban
    - prevention of bleeding prior to emergency surgery
- For patients on edoxaban or patients needing reversal for emergency surgery, please discuss treatment options with local haematology or a 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 the management of acute bleeding in patients on anticoagulation.

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Important safety informationÂ

MRHA/CHM advice: part 1

- Commercial anti-FXa activity assays are unsuitable for measuring anti-FXa activity following administration of andexanet alfa (July 2020)
- Treatment monitoring after administration of andexanet alfa should not be based on anti-FXa activity assays
- In these assays, the FXa inhibitor dissociates from andexanet alfa, resulting in the detection of falsely elevated anti-FXa activity levels, and consequently a substantial underestimation of the reversal activity of andexanet alfa

- Healthcare professionals are advised to monitor treatment using clinical parameters indicative of appropriate response (i.e. achievement of haemostasis), lack of efficacy (i.e. re-bleeding), and adverse events (i.e. thromboembolic events).

MHRA/CHM advice: part 2

- Avoid use of andexanet prior to heparinisation (November 2020)
- Off-label use of andexanet alfa to reverse FXa anticoagulation prior to surgery with intended heparin anticoagulation has been reported to cause unresponsiveness to heparin and healthcare professionals are advised to avoid such use
- In-vitro data suggest binding of andexanet alfa to the heparin-antithrombin III (ATIII) complex and neutralisation of the anticoagulant effect of heparin
- Results of coagulation tests might be misleading when andexanet alfa and heparin are given within a short time of one another
- The effect of andexanet alfa has not been validated while heparin is active, and its use for anti-FXa reversal before urgent surgery has not been evaluated.

Storage

- **PRODUCT MUST BE STORED IN FRIDGE UNTIL POINT OF PREPARATION (to avoid wastage of very high cost item)**
- All stock kept in: Dispensary, Pharmacy Department, University College Hospital (location Fridge 2, Shelf 10)
- **Store between 2 and 8^{0}C**

References

SPC 4th April 2025

Injectable Medicines guide- downloaded from Medusa, 22nd May 2023

1: HSE Prescribing Guideline for Andexanet Alfa 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 Oct 2023

Therapeutic classification

Antidote - Apixaban or rivaroxaban ONLY