This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited.[1]

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

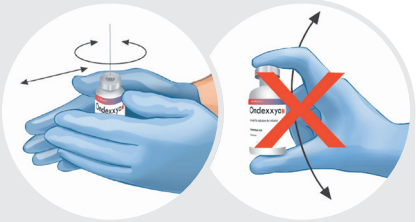
Per vial

- 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

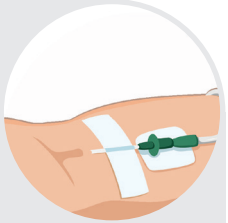
IMPORTANT

- **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.

For full handling information, please refer to sections 6.3 and 6.6 of the SmPC.

1. Ondexxya® Summary of Product Characteristics. January 2021. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/ondexxya.

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 

For full dosing information, please refer to section 4.2 of the SmPC

1. Ondexxya® Summary of Product Characteristics. January 2021. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/ondexxya.

Abbreviated prescribing information

ONDEXXYA® ▼ (andexanet alfa) 200 mg Powder for Solution for Infusion
This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. Refer to SmPC Section 4.8 for how to report adverse events.
Presentation: Each vial contains 200 mg of andexanet alfa. After reconstitution, each mL of solution contains 10 mg of andexanet alfa.
Indication: 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.
Dosage and method of administration: *Recommended dosage:* Ondexxya is initially administered as an IV bolus at a target rate of approximately 30 mg/min over 15 to 30 minutes, followed by a continuous infusion of 4 mg (low dose) or 8 mg (high dose) per minute for 120 minutes. Please refer to the SmPC for instructions on reconstitution before administration. *Reversal of apixaban:* The recommended dose regimen of Ondexxya 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. Where the last dose of apixaban was ≤ 5 mg the low dose is used. Where the last dose of apixaban was > 5 mg or unknown and was given < 8 hours or an unknown time before Ondexxya administration the high dose is used. Where the last dose of apixaban was > 5 mg or unknown but was known to be given ≥ 8 hours before Ondexxya administration the low dose is used. *Reversal of rivaroxaban:* The recommended dose regimen of Ondexxya 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. Where the last dose of rivaroxaban was ≤ 10 mg the low dose is used. Where the last dose of rivaroxaban was > 10 mg or unknown and it was given < 8 hours or an unknown time before Ondexxya administration the high dose is used. Where the last dose of rivaroxaban was > 10 mg or unknown but was known to be given ≥ 8 hours before Ondexxya administration the low dose is used. *Restarting antithrombotic therapy:* Following administration of Ondexxya and cessation of a major bleed, re-anticoagulation should be considered to prevent thrombotic events due to the patient's underlying medical condition. Antithrombotic therapy can be re-initiated as soon as medically indicated following treatment if the patient is clinically stable and adequate haemostasis has been achieved. Medical judgement should balance the benefits of anticoagulation with the risks of re-bleeding. *Elderly patients (≥ 65 years):* No dose adjustment is required. *Renal impairment:* The effect of renal impairment on andexanet alfa exposure levels has not been evaluated. Based on the existing data on clearance, no dose adjustment is recommended. *Hepatic impairment:* Based on the existing data on clearance of andexanet alfa, no dose adjustment is recommended. The safety and efficacy have not been studied in patients with hepatic impairment. *Paediatric population:* The safety and efficacy of andexanet alfa in children and adolescents have not been established. No data are available. *Method of administration: Intravenous use:* After an appropriate number of vials of Ondexxya has been reconstituted, the reconstituted solution (10 mg/mL) is transferred to a suitable empty IV polyolefin (PO) or polyvinyl chloride (PVC) bag without further dilution, prior to administration by IV infusion using a 0.2 or 0.22 micron in-line polyethersulfone (PES) or equivalent low protein-binding filter. For instructions on reconstitution of the medicinal product before administration, refer to full SmPC.
Contraindications: Hypersensitivity to active substance or any excipient. Known allergic reaction to hamster proteins. **Warnings and precautions:** *Limitations of use:* Clinical efficacy is based upon reversal of anti-FXa-activity in healthy volunteers dosed with apixaban or rivaroxaban. Andexanet alfa is not suitable for pre-treatment of urgent surgery. Use for edoxaban- or enoxaparin-reversal is not recommended due to lack of data. Andexanet alfa will not reverse the effects of non-FXa inhibitors. Treatment monitoring should be based mainly on 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). Treatment monitoring of andexanet alfa should not be based on anti-FXa-activity. Commercial anti-FXa-activity assays are unsuitable for measuring anti-FXa activity following administration of andexanet alfa as these assays result in erroneously elevated anti-FXa activity levels, thereby causing a substantial underestimation of the reversal activity of andexanet alfa. Dosage recommendation is based upon data-modelling in healthy volunteers. Validation has not been successful, yet. Data from bleeding patients are limited. Preliminary data suggest higher risk of thrombosis for patients receiving the higher dose of andexanet, previous lower dose of the anti-FXa inhibitor, and patients on rivaroxaban. In ANNEXA-4, intracranial haemorrhage (ICH) patients (GCS > 7 and haematoma volume < 60 mL) have been included. Treatment of patients with more severe ICH with andexanet alfa has not been studied. *Thrombotic events:* Thrombotic events have been reported following treatment with andexanet alfa. Patients being treated with FXa inhibitor therapy have underlying disease states that predispose them to thrombotic events. Reversing FXa inhibitor therapy exposes patients to the thrombotic risk of their underlying disease. In addition, independent pro-thrombotic effect of andexanet alfa cannot be ruled out. Duration of this effect in bleeding patients is not known. Laboratory parameters as anti-FXa activity, endogenous thrombotic potential (ETP), or markers of thrombosis might not be reliable for guidance. To reduce this risk, resumption of anticoagulant therapy should be considered as soon as medically appropriate after completion of treatment. In healthy volunteers, dose-dependent increases in coagulation markers F1+2, TAT, and D-dimer after administration of andexanet alfa were observed, but no thromboembolic events were reported. These markers were not measured in patients enrolled in the ANNEXA-4 study, but thromboembolic events have been observed. Monitoring for signs and symptoms of thrombosis is, therefore, strongly recommended. *Use of andexanet alfa in conjunction with other supportive measures:* Andexanet alfa can be used in conjunction with standard haemostatic supportive measures, which should be considered as medically appropriate. The safety of andexanet alfa has not been evaluated in patients who received prothrombin complex concentrates, recombinant factor VIIa, or whole blood within seven days prior to the bleeding event, as they were excluded from clinical trials. Pro-coagulant factor treatments (e.g., 3- or 4-factor prothrombin complex concentrate (PCC)/activated PCC, recombinant factor VIIa, fresh frozen plasma) and whole blood should be avoided unless absolutely required, due to lack of data in combination with these treatments. *Interaction with heparin:* Use of andexanet prior to heparinization e.g. during surgery should be avoided as andexanet causes unresponsiveness to heparin. Use of andexanet as an antidote for heparin or low-molecular weight heparin has not been evaluated and is not recommended. *Infusion-related reactions:* In case of mild or moderate infusion reactions, careful observation may be sufficient. For moderate symptoms, consideration may be given to a brief interruption or slowing of the infusion with resumption of the infusion after symptoms subside. Diphenhydramine may be administered.
Interaction with other medicinal products and other forms of interaction: In vitro data suggest interaction of andexanet alfa with the heparin- anti-thrombin III (ATIII) complex and neutralization of the anticoagulant effect of heparin. Off-label use of andexanet alfa pre-surgery with intended heparin-anticoagulation has been reported to cause unresponsiveness to heparin.
Adverse reactions: The most frequently reported adverse reactions in clinical trials in healthy subjects with Ondexxya were mild or moderate infusion-related reactions comprising symptoms such as flushing and feeling hot (very common), and cough, dysgeusia and dyspnoea (common). Transient elevations of D-dimer and F1+2 fragments were also very common in healthy subjects. Other common side effects observed in healthy subjects were urticaria, dizziness postural, headache, palpitations, abdominal discomfort or pain, dry mouth, nausea, pruritus (generalised), back pain, muscle spasms, chest discomfort, hyperhidrosis and peripheral coldness. Amongst bleeding patients commonly reported side effects were ischaemic stroke and pyrexia, with uncommonly reported side effects of cerebral infarction, cerebrovascular accident, transient ischaemic attack, acute myocardial infarction, cardiac arrest, myocardial infarction, deep vein thrombosis, iliac artery occlusion and pulmonary embolism. **Refer to full SmPC for additional information and other adverse reactions**.
Legal Category: POM **Package quantities & Basic NHS costs** £11,100 (4 vials per pack) **Marketing Authorisation Holder:** Alexion Europe SAS, 103-105 rue Anatole France, 92300 Levallois-Perret, France. **Marketing Authorisation Number:** EU/1/18/1345/001 **Further information available from:** Alexion Pharmaceuticals e-mail: MedInfo.EMEA@alexion.com. **Date of First Authorisation:** 26th April 2019. **Doc Ref:** M/UK/AnXa/0028. **Last revised:** January 2021

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/ Adverse events should also be reported to Alexion Pharma UK Ltd on 0800 321 3902 or uk.adverseevents@alexion.com.