

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.