Andexanet

<table>
<tr><td colspan="3">CAUTION: High Administration Risk Rating</td></tr>
<tr><td>Form & Storage</td><td>Powder for concentrate for solution for infusion. Each vial contains 200mg andexanet alfa</td><td>Store in a refrigerator (2°C - 8°C) in the original package to protect from light.</td></tr>
<tr><td>Reconstitution</td><td colspan="2">• Add 20 mL water for injections, using a syringe with a 21-25 gauge needle, directing the liquid down the wall of the vial to avoid excessive foaming.
• Gently swirl the vial for at least 15 seconds. Do not shake vigorously or invert.
• Leave for 3- 5 minutes to allow foam to settle; the vial can be gently swirled occasionally during this time.
• The reconstituted solution is clear, colourless or slightly yellow.
• Solution after reconstitution: 10 mg/mL</td></tr>
<tr><td>Compatibility & Stability</td><td colspan="2">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.</td></tr>
<tr><td>Administration</td><td colspan="2">• Withdraw the reconstituted solution from each vial into the large-volume (50 mL or larger) syringes (equipped with a 20-gauge or larger needle)
• It is recommended to split the solution intended for bolus and continuous infusion to ensure the correct administration rate
• <u>Administration equipment required:</u>
• Pressure administration set is attached to the syringe containing the drug
• Then attach 0.2 micron filter to the end of administration set, before it is connected to the patient

Low Dose – Reconstitute 5 x 200mg vials
<table><tr><th>Administration</th><th>Dose</th><th>Volume</th><th>Rate</th><th>Time to administer</th></tr><tr><td>IV Bolus</td><td>400mg</td><td>40mL</td><td>160mL/hr</td><td>15 mins</td></tr><tr><td>IV Infusion</td><td>480mg</td><td>48mL</td><td>24 mL/hr</td><td>120 mins</td></tr></table>
High Dose – Reconstitute 9 x 200mg vials
Note: for high dose therapy, two syringes will be needed for the loading dose and two for the maintenance dose
<table><tr><th>Administration</th><th>Dose</th><th>Volume</th><th>Rate</th><th>Time to administer</th></tr><tr><td>IV Bolus</td><td>800mg</td><td>80mL</td><td>160mL/hr</td><td>30 mins</td></tr><tr><td>IV Infusion</td><td>960mg</td><td>96mL</td><td>48 mL/hr</td><td>120 mins</td></tr></table></td></tr>
<tr><td>Monitoring</td><td colspan="2">Treatment monitoring should be based mainly on clinical parameters indicative of appropriate response (i.e. achievement of haemostasis), lack of efficacy (i.e., rebleeding), and adverse events (i.e. thromboembolic events).</td></tr>
</table>

<table>
<tr><td>Adverse Drug Reactions</td><td>Common: Back pain; cerebrovascular insufficiency; chest discomfort; cough; dizziness postural; dry mouth; dyspnoea; feeling hot; fever; flushing; gastrointestinal discomfort; headache; hyperhidrosis; muscle spasms; nausea; palpitations; peripheral coldness; skin reactions; taste altered
Uncommon: Cardiac arrest; embolism and thrombosis; iliac artery occlusion; myocardial infarction</td></tr>
<tr><td></td><td>

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

<table>
<tr><td colspan="4">Size and timing of last dose of apixaban or rivaroxaban taken determines whether high or low dose regimen is used.</td></tr>
<tr><td rowspan="2">FXa inhibitor</td><td rowspan="2">Last dose</td><td colspan="2">Timing of last dose before andexanet administration</td></tr>
<tr><td>< 8 hours or unknown</td><td>≥ 8 hours*</td></tr>
<tr><td rowspan="2">Apixaban</td><td>≤5mg</td><td>Low dose</td><td rowspan="2">Low dose</td></tr>
<tr><td>>5mg or unknown</td><td>High dose</td></tr>
<tr><td rowspan="2">Rivaroxaban</td><td>≤10 mg</td><td>Low dose</td><td rowspan="2">Low dose</td></tr>
<tr><td>>10 mg or unknown</td><td>High dose</td></tr>
<tr><td colspan="4">*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.</td></tr>
</table>

Andexanet alfa is not suitable for pre-treatment of urgent surgery
Interaction with heparin: Use of andexanet prior to heparinization e.g. during surgery should be avoided as andexanet causes unresponsiveness to heparin
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.
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.
Manufacturer advises to consider re-starting anticoagulant therapy as soon as medically appropriate to reduce the risk of thrombosis.

</td></tr>
</table>

Information provided relates to Ondexxya® manufactured by or Astra Zeneca.