# CLOT

## Andexanet Alfa (Ondexxya®) – For Front Line Clinicians

### What is it and how does it work? [1]

- Andexanet alfa is a recombinant-modified human factor Xa protein that lacks procoagulant activity. It binds to factor Xa inhibitors with high affinity, and frees endogenous factor Xa to resume its normal function.
- Andexanet alfa is indicated as an antidote for apixaban and rivaroxaban. Although most of the data is with apixaban and rivaroxaban, it will bind to all factor Xa inhibitors[2-4]
- Most patients have a rapid decrease in anti-Xa activity (by greater than 90%) within 2 minutes of bolus administration. This decrease is maintained throughout the duration of continuous infusion
- Andexanet alfa also binds to tissue factor pathway inhibitor (TFPI). This action may lead to increased thrombin generation

### Who should get it? [1]

- Adult patients treated with factor Xa inhibitors (rivaroxaban or apixaban) when rapid reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding

### Who should NOT get it? [1]

- Andexanet alfa is not intended for factor Xa inhibitor reversal for elective procedures (cost is significantly higher than Prothrombin Complex Concentrate or idarucizumab (Praxbind))
- The risk in patients with known hypersensitivity (e.g. anaphylactoid reaction) to andexanet alfa or to any of the excipients needs to be weighed cautiously against the potential benefit of such an emergency treatment

### If a patient receives it, what do I need to know? [1]

- Thromboembolic Risk – reversing an anticoagulant exposes patients to the thrombotic risk of their underlying disease. Clinical judgment should dictate when anticoagulation should resume. Also, due to inhibition of TFPI, andexanet alfa may increase thrombin generation, which can result in an increased risk of thrombosis (note: there was a higher incidence of ischemic stroke with andexanet alfa versus usual care (6.5% vs 1.5%) at 30 days in the ANNEXA-I trial[4])
- Recurrence or Continuation of Bleeding – Andexanet alfa binds to factor Xa inhibitors (rivaroxaban and apixaban). It does not repair other causes of bleeding (e.g. damaged vessels) which may require urgent repair. Monitor for signs/symptoms of bleeding and seek assistance accordingly
- Adverse Effects: Frequency similar to placebo in trials with healthy volunteers and included: infusion related hypersensitivity reaction (9.1%), infusion related reaction (2.6%), URTI (3.1%), headache (6.5%), presyncope (2.2%), arthralgia (1.2%), fatigue (1.7%), and muscle spasm (1.7%)

### Where and how should it be stored? [1]

- Andexanet alfa is stored in a refrigerator in its original box (2 to 8°C). It is temperature sensitive. It does not need to be brought to room temperature before reconstitution
- Reconstituted solution still in the vial can be stored for 16 hours at 2 to 8°C (ie. in the fridge). If necessary, after being transferred to the IV bag, the reconstituted solution can be stored at room temperature for an additional 8 hours
- Chemical and physical in-use stability has only been demonstrated over a 24 hour period

### Where and how should it be given? [1]

- Administration should be in facilities such as an emergency department equipped to clinically assess the patient and subsequently administer IV therapies
- Administration of andexanet alfa includes both an initial IV bolus and a subsequent continuous IV infusion
- Andexanet alfa is used at either a high or a low dose. This is dependent on anticoagulant dose and time since last dose of the anticoagulant to be reversed. See reverse for dosing and administration instruction

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## Andexanet Alfa Specifics[1]

<table>
<tr><td>Product Supplied</td><td>Single-use 20 mL vial containing andexanet alfa 200 mg as white powder to be reconstituted</td></tr>
<tr><td>Dose & Administration</td><td>
<table>
<tr><th rowspan="2">Drug Used</th><th rowspan="2">Strength of last dose</th><th colspan="2">Time since last dose was taken</th></tr>
<tr><th>Less than 8 hours or unknown</th><th>8 hours or more</th></tr>
<tr><td rowspan="2">Rivaroxaban</td><td>10 mg or less</td><td>Low Dose</td><td rowspan="2">Low dose</td></tr>
<tr><td>greater than 10 mg or unknown</td><td>High Dose</td></tr>
<tr><td rowspan="2">Apixaban</td><td>5 mg or less</td><td>Low Dose</td><td rowspan="2">Low dose</td></tr>
<tr><td>Greater than 5 mg or unknown</td><td>High Dose</td></tr>
</table>
<table>
<tr><th>Dose</th><th>Initial IV Bolus</th><th>Follow-on IV infusion*</th><th>Total vials</th></tr>
<tr><td>Low Dose</td><td>400 mg at 30 mg/min</td><td>480 mg at 4 mg/min</td><td>2 for bolus & 3 for infusion</td></tr>
<tr><td>High Dose</td><td>800 mg at 30 mg/min</td><td>960 mg at 8 mg/min</td><td>4 for bolus & 5 for infusion</td></tr>
</table>
* IV infusion duration is 120 minutes. Safety and efficacy of more than one dose has not been evaluated.<br><br>
Each vial of andexanet alfa needs to be reconstituted with 20 mL of sterile water<br>
• Vial should then be gently swirled (not shaken as that can lead to foaming). Dissolution will take approximately 5 minutes. Inspect product for particulate matter or discoloration<br>
• Reconstituted drug should be withdrawn and transferred to empty IV bags (1 for bolus and 1 for infusion)<br>
• Administer andexanet alfa using a 0.2 or 0.22 micron in-line polyethersulfone or equivalent low protein-binding filter. Continuous IV infusion should be started within 2 minutes following the bolus dose
</td></tr>
<tr><td>Half Life</td><td>3.78 hours (low dose) and 4.24 hours (high dose)</td></tr>
<tr><td>Metabolism</td><td>Based on native factor Xa, andexanet alfa is likely rapidly broken down in plasma by endogenous proteases</td></tr>
<tr><td>Excretion</td><td>Little to no renal clearance.<br>No dosage adjustment in renal impairment or geriatrics (65 years of age or older).<br>No data in patients with hepatic impairment, pregnancy, nursing women, pediatrics.</td></tr>
<tr><td>Volume of distribution</td><td>9.47 L (low dose) and 8.94 L (high dose)</td></tr>
<tr><td>Drug Interactions</td><td>No drug-drug interactions studies have been performed.<br>In vitro data suggests use of andexanet alfa before heparin could cause unresponsiveness to heparin.</td></tr>
<tr><td>Contraindications</td><td>Hypersensitivity to andexanet alfa or any ingredient in the formulation or component of the container</td></tr>
<tr><td>Monitoring</td><td>Signs / symptoms of bleeding, thromboembolic events, ischemic events and cardiac arrest.<br>For moderate infusion reactions, brief interruption or slowing of infusion can be considered.<br>Commercial anti-Xa assays are unsuitable for measuring anti-Xa activity following administration of andexanet alfa.</td></tr>
<tr><td>Duration of Reversal[2]</td><td>Anti-Xa activity returns to placebo levels approximately 2 hours after completion of infusion</td></tr>
<tr><td>Clinical Trial Program Experience to Date[2-4]</td><td>Two randomized, double-blind, placebo controlled trials in healthy volunteers (ANNEXA-A and ANNEXA-R); n=145[2]<br><br>
ANNEXA-4 – multicenter, prospective phase-3b/4, single group cohort study designed to assess andexanet alfa in patients with factor Xa inhibitor associated major bleeding; n=479[3]<br>
• Included patients taking apixaban (51%), rivaroxaban (37%), edoxaban (8%) & enoxaparin (5%)<br><br>
ANNEXA-I – randomized, multicenter, clinical trial designed to assess andexanet alfa versus usual care in adult patients with factor Xa inhibitor associated intracranial hemorrhage. n=530[4]<br>
• Included patients taking apixaban (62%), rivaroxaban (29%), and edoxaban (9%)</td></tr>
</table>


**References**

1) Ondexxya® Product Monograph. AstraZeneca Canada Inc. Mississauga, Ontario. June 16, 2023
2) Siegal DM et al. NEJM 2015; 373:2413-2424
3) Milling TJ Jr. et al. Circulation 2023; 147:1026-1038
4) Connolly SJ et al. NEJM 2024; 390:1745-1755