**Medicine Guideline for the Safe Use of**

# Andexanet Alfa

Health
South Eastern Sydney
Local Health District

| ***Andexanet Alfa (Andexxa) IS A HIGH-RISK MEDICINE***<br>**USE WITH CAUTION AND ENSURE THE DIRECTIONS WITHIN THIS PROTOCOL ARE FOLLOWED CAREFULLY** | |
|---|---|
| **Areas where Protocol/Guideline applicable** | Emergency Department, Intensive Care Unit |
| **Authorised Approvers:** | Haematologist or Neurologist |
| **Indication for use** | Acute Intracranial haemorrhage (ICrH) and received a Factor Xa inhibitor (apixaban or rivaroxaban) within 18 hours. |
| **Important Safety Considerations** | **WARNING**<br>• Requires multiple 50 mL syringes or empty PVC or polyolefin IV bag(s), and a filter.<br>• If the loading dose and the 2-hour infusion are prepared in the same bag, make sure the rate is changed after the loading dose is given. |
| | **Xa assay use**<br>Commercial anti-FXa-activity assays are **unsuitable** for measuring anti-FXa activity following administration of ANDEXXA |
| | **Urgent surgery**<br>The efficacy and safety of ANDEXXA for reversal of anticoagulation before urgent surgery has **not been established.** |
| | **Thromboembolic and ischaemic risk**<br>Patients being treated with FXa inhibitors have underlying disease states that predispose them to thrombotic events. To reduce thromboembolic risk, **resume anticoagulant therapy as soon as medically appropriate** following treatment with ANDEXXA.<br><br>The safety of ANDEXXA has **not been evaluated** in patients who experienced thromboembolic events or disseminated intravascular coagulation within 2 weeks prior to the life-threatening bleeding event requiring treatment with ANDEXXA.<br><br>Safety of ANDEXXA has **not been evaluated** in patients who received prothrombin complex concentrates, recombinant factor VIIa, or whole blood products within 7 days prior to the bleeding event. |
| | **Use of heparin following administration of ANDEXXA**<br>Andexanet Alfa is a FXa analogue (decoy molecule) capable of binding heparin-bound anti-thrombin III (ATIII) and neutralising the anticoagulant effect of heparin. Use of heparin during surgeries requiring anticoagulation after administration of ANDEXXA for reversal of a direct FXa inhibitor **should be avoided**. In such cases, consideration should be given to the use of an alternative to heparin, such as a direct thrombin inhibitor. |

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| **Clinical condition** | **Inclusion criteria**<br>Acute Intracranial haemorrhage (ICrH) and had received a Factor Xa inhibitor (apixaban or rivaroxaban) within 18 hours. This includes intracerebral (with or without intraventricular extension), subdural, subarachnoid, and epidural haemorrhages.<br><br>**Key exclusion criteria**<br>- planned surgery within 12 hours (with the exception of minimally invasive operations or procedures)<br>- intracranial haemorrhage in a patient with a score of less than 7 on the Glasgow Coma Scale<br>- estimated haematoma volume of more than 60 mL<br>- expected survival of less than 1 month<br>- a thrombotic event within 2 weeks<br>- use of any of the following within the previous 7 days: vitamin K antagonist, prothrombin complex concentrate, recombinant factor VIIa, whole blood, or plasma. |
| **Proposed Place in Therapy** | First line when criteria for use are satisfied. |
| **Adjunctive Therapy** | • If concomitant coagulopathy due to massive transfusion, liver disease or Vitamin K deficiency, then **FFP** administration may be considered.<br>• If thrombocytopenia with platelets <80-100 **platelet transfusion** may be considered. |
| **Contra-indications** | Anaphylaxis to previously used Andexanet Alfa |
| **Precautions** | • **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**.<br>• **Hepatic impairment:** The effect of renal impairment on Andexanet Alfa exposure levels has **not been evaluated**.<br>• **Paediatric use:** The safety and efficacy of Andexanet Alfa in children and adolescents have **not been established**.<br><br>**Restarting antithrombotic therapy**<br>Patients being treated with FXa inhibitors have underlying disease states that predispose them to thromboembolic events. Reversing FXa inhibitor therapy exposes patients to the thrombotic risk of their underlying disease. To reduce this risk, **resumption of anticoagulant therapy should be considered as soon as medically appropriate**. |
| **Important Drug Interactions** | No interaction studies with andexanet alfa have been performed.<br><br>**Use of heparin following administration of ANDEXXA**<br>Andexanet Alfa is a FXa analogue (decoy molecule) capable of binding heparin-bound anti-thrombin III (ATIII) and neutralising the anticoagulant effect of heparin. Use of heparin during surgeries requiring anticoagulation after administration of ANDEXXA for reversal of a direct FXa inhibitor **should be avoided**. In such cases, consideration should be given to the use of an alternative to heparin, such as a direct thrombin inhibitor. |

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**Dosage**

There are two doses ('**low dose**' and '**high dose**') of andexanet alfa. The appropriate dose is based on the specific FXa inhibitor and dose being taken by the patient at the time of the bleed.

**Dose Selection**

| FXa Inhibitor | Last FXa Inhibitor Dose | Last FXa Inhibitor Dose < 8 Hours Prior/Unknown | Last FXa Inhibitor Dose ≥ 8 Hours Prior |
|---|---|---|---|
| Rivaroxaban | ≤ 10 mg | low dose | low dose |
| Rivaroxaban | > 10 mg / unknown | high dose | low dose |
| Apixaban | ≤ 5 mg | low dose | low dose |
| Apixaban | > 5 mg / unknown | high dose | low dose |

**Low Dose Protocol**

**Bolus**: 400 mg (40 mL) via IV infusion over 15 minutes.
**Infusion**: 480 mg (48 mL) via IV infusion over 120 minutes.

**High Dose Protocol**

**Bolus**: 800 mg (80 mL) via IV infusion over 30 minutes.
**Infusion**: 960 mg (96 mL) via IV infusion over 120 minutes.

**Duration of therapy**

**STAT dose**

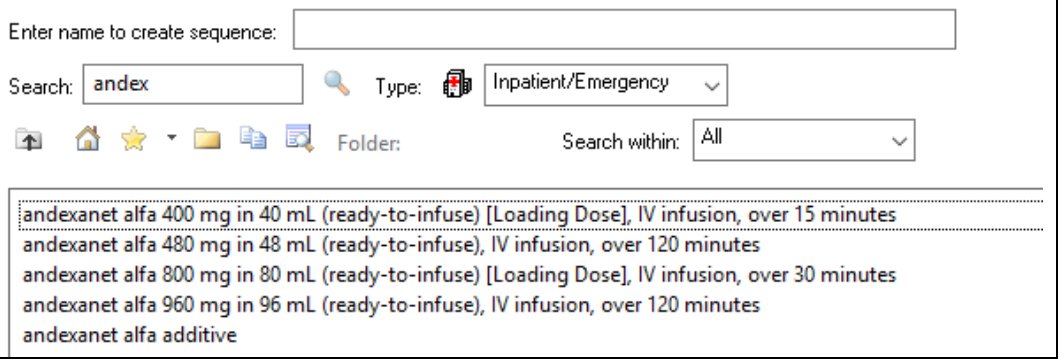
**Location**

Andexanet Alfa will be located in the After Hours Drug Cupboard at SGH, POW and TSH.

**Prescribing Instructions**

Prescribe in eFluids.

Select the appropriate **Low Dose** or **High Dose** protocol order sentences from the pre-built options (see below for details).



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**Preparation Instructions**

Vial contains 200 mg of andexanet alfa.

| Protocol | Loading dose | | 2-hour infusion | | Total number of vials |
|---|---|---|---|---|---|
| | Dose | Vials | Dose | Vials | |
| Low dose | 400 mg (40 mL) | 2 | 480 mg (48 mL) | 3 | 5 |
| High dose | 800 mg (80 mL) | 4 | 960 mg (96 mL) | 5 | 9 |

Use aseptic technique

- Reconstitute each vial with 20 mL of water for injections.
- Inject the diluent down the wall of the vial to minimise foaming. Swirl gently until dissolved, it may take up to 5 minutes. **Do not shake**.
- The solution is clear and colourless to slightly yellow.
- The concentration is 10 mg/mL.

Reconstituted Andexxa in vials is stable at room temperature (≤ 25°C) for up to 8 hours, or may be stored for up to 24 hours at 2°C to 8°C.

**For infusion by syringe pump**

Transfer the volumes required for the loading dose and the 2-hour infusion into separate 50 mL syringes.

**The high dose protocol requires 2 syringes for the loading dose and 2 syringes for the infusion (4 syringes in total).**

**For infusion from an IV bag**

Transfer the volumes required for the loading dose and the 2-hour infusion ideally into separate empty PVC or polyolefin IV bags.

**If the loading dose and the 2-hour infusion are combined into a single bag, make sure the rate is changed after the loading dose has been given.**

Reconstituted Andexxa in IV bags is stable at room temperature (≤ 25°C) for up to 8 hours.

**Administration Instructions**

Use a low protein-binding 0.2 or 0.22 PES filter.
Flush the line with sodium chloride 0.9%.

**Low Dose Protocol**

**IV infusion:**
Infuse a loading dose of 400 mg over 15 minutes.
**The rate is 160 mL/hour (approximately 30 mg/minute) for 15 minutes.**
Follow immediately (within 2 minutes), with an infusion.
**The rate is 4 mg/minute (24 mL/hour) for 2 hours.**

**High Dose Protocol**

**IV infusion:**
Infuse a loading dose of 800 mg over 30 minutes.
**The rate is 160 mL/hour (approximately 30 mg/minute) for 30 minutes.**
Follow immediately (within 2 minutes), with an infusion.
**The rate is 8 mg/minute (48 mL/hour) for 2 hours.**

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| **Adverse effects** | Andexanet Alfa is subject to additional monitoring in Australia. Healthcare professionals should report any suspected adverse events.<br><br>Patients being treated with FXa inhibitors have underlying disease states that predispose them to thrombotic events.<br><br>Infusion reactions including rigors, chills, hypertension, oxygen desaturation, agitation and confusion may be mild to moderate, and transient. |
| **Monitoring requirements** | Critical care / procedural / neuro – observations to be determined by the authorised prescriber (Haematologist or Neurologist).<br><br>Monitor patients treated with Andexanet Alfa for signs and symptoms of arterial and venous thromboembolic events, ischaemic events, and cardiac arrest. |
| **Management of Complications** | There is no clinical experience with overdose of Andexanet Alfa.<br><br>Adverse effects should be managed in accordance with local guidelines (e.g., anaphylaxis). |
| **Storage requirements** | • Unopened vials should be stored refrigerated at 2°C to 8°C.<br>• Do not freeze.<br>• Protect from light.<br>• Reconstituted medicinal product should be used as soon as practicable after reconstitution/preparation.<br>• If storage is necessary, hold at 2°C to 8°C for not more than 24 hours or intermittent storage at room temperature (≤25°C) for not more than 8 hours. |
| **Basis of Protocol/Guideline:** (including sources of evidence, references) | 1. MIMS Online. ANDEXXA® (Andexanet Alfa) powder for solution for infusion. Product Information. 01 March 2024<br>2. Australian Injectable Drugs Handbook. Andexanet Alfa. 9th Edition. 13 February 2024.<br>3. Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet Alfa for the reversal of factor Xa inhibitor activity. N Engl J Med. 2015;373(25):2413-2424.<br>4. Milling Jr TJ, Middeldorp S, Xu L, et al. Final Study Report of Andexanet Alfa for major bleeding with factor Xa inhibitors. Circulation 2023; 147:1026-1038<br>5. Sutton SS, Magagnoli J, Cummings TH, et al. Real-world clinical outcomes among US Veterans with oral factor Xa inhibitor-related major bleeding treated with andexanet alfa or 4-factor prothrombin complex concentrate [published online ahead of print May 23, 2023]. J Thromb Thrombolysis. 2023. |
| **Groups consulted in development of this guideline** | Haematology<br>Neurology |

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