NSW Medicines Formulary Information 03/23

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Use of andexanet alfa in NSW health facilities

Summary

Andexanet alfa has been provisionally approved by the Therapeutic Goods Administration (TGA) 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.[1]

Andexanet alfa is not listed on the NSW Medicines Formulary. Andexanet alfa will be reconsidered if the TGA transitions andexanet alfa to full registration OR when clinical trial data with comparative clinical endpoints becomes available. Use of andexanet alfa in NSW Health facilities requires Individual Patient Use (IPU) approval.

What is TGA provisional registration?

The TGA provisional registration process allows certain medicines to be provisionally registered in the Australian Register of Therapeutic Goods for a limited duration (2 years unless extended or revoked). These medicines are registered based on preliminary clinical data, where the benefit of early availability of the medicine outweighs the risk inherent in the fact that additional data are still required.

The TGA decision to provisionally approve andexanet alfa was made on the basis of haemostatic efficacy and a reduction in anti-FXa activity. Continued approval of this indication depends on verification and description of benefit in a confirmatory trial.[1]

Formulary review

The NSW Medicines Formulary Committee reviewed the available evidence for the use of andexanet alfa in September 2023.

There are currently no published head-to-head trials comparing the current standard of care to andexanet alfa. Randomised controlled trials comparing andexanet alfa to the current standard of care are underway and expected to strengthen the evidence base and understanding of the comparative clinical benefits and risks. The extent of benefit for patients treated with andexanet alfa in terms of mortality and functional outcomes (level of disability, quality of life) is uncertain.

As a high-cost medicine, state-wide governance and formulary decisions should be based on high quality evidence that support effectiveness, safety as well as comparative effectiveness and safety of the medicine (CATAG guiding principles for the governance of high-cost medicines in Australia).[2]

Considering the limited availability of robust evidence comparing andexanet alfa with existing standards of care, and therefore uncertainty regarding its effectiveness and safety, andexanet alfa does not currently meet the threshold for inclusion on the NSW Medicines

Formulary. This decision will be reviewed if the TGA transitions andexanet alfa to full registration OR when clinical trial data with comparative clinical endpoints becomes available.

Considerations for the use of andexanet alfa in NSW public hospitals

Use of andexanet alfa in NSW Health facilities requires IPU approval from the local Drug and Therapeutics Committee (or nominated delegate) as per NSW Health Policy Directive Approval Process for Medicines and Their Use (PD 2022_056). Facilities are to have appropriate mechanisms in place to facilitate rapid assessment and approval for urgent IPU applications.

IPU approvals to use andexanet alfa should be made on a case-by-case basis, considering the Product Information and available evidence. The following efficacy and safety information should be considered:

- Andexanet alfa has not been shown to be effective for the treatment of bleeding related to other FXa inhibitors (for example, enoxaparin or fondaparinux).[3]
- The efficacy benefit for the reversal of direct FXa inhibitors compared to the current standard of care (for example, prothrombin complex concentrate) is uncertain due to indirect comparisons, limitations in study design and bias.
- The extent of benefit in terms of mortality and functional outcomes (level of disability, quality of life) for patients treated with andexanet alfa is uncertain. For patients that achieved haemostatic efficacy, as defined in the pivotal clinical trials, there is uncertainty of the patient's clinical outcome in patients with intracranial haemorrhage.
- Thrombotic events have been reported following treatment with andexanet alfa (10.5% of patients had a thrombotic event within 30 days in the ANNEXA-4 study[4]).
    - Patients being treated with FXa inhibitors have underlying disease states that predispose them to thrombotic events.[3] The Product Information recommends resumption of anticoagulant therapy should be considered as soon as medically appropriate after completion of treatment.[3]The optimal time for resumption of anticoagulant therapy is unknown.
- There is no evidence to support the efficacy or safety of andexanet alfa in perioperative settings[3]:
    - The risk of bleeding in patients without anticoagulant reversal compared to the risk of thrombosis with anticoagulant reversal is uncertain. Patients with planned surgery within 12 hours of andexanet alfa administration were excluded from clinical trials.[4]
    - Andexanet alfa is capable of binding heparin-bound anti-thrombin III (ATIII) and neutralising the anticoagulant effect of heparin.[3] Use of heparin during surgeries

requiring anticoagulation after administration of andexanet alfa should be avoided[3], due to the potential significant risk of acute, severe thrombosis.

- The safety and efficacy of andexanet alfa has not been established for repeated dosing. A single dose only has been approved in the provisional registration.[3]
- The safety and efficacy of andexanet alfa has not been established in patients with a recent thrombosis (within the last 2 weeks), or in patients treated with prothrombin complex concentrates, recombinant factor VIIa or whole blood products within the last 7 days prior to the bleeding event.[4]
- The dose and dosing regimen of andexanet alfa are based on dose ranging studies in healthy volunteers on therapeutic doses of apixaban or rivaroxaban.[3] There are no efficacy studies for andexanet alfa use in patients with supratherapeutic doses of apixaban or rivaroxaban (i.e., in an overdose setting).
- There is no role for the monitoring of anti-Xa activity after andexanet alfa therapy. Commercial anti-FXa-activity assays are unsuitable for measuring anti-FXa activity following andexanet alfa administration.[3] Assays may show falsely elevated levels of anti-Xa activity, causing a substantial underestimation of the reversal activity of andexanet alfa.[3] In clinical trials, there was no correlation with anti-FXa activity levels and haemostasis achieved.[4]

Prescribing and administration information

For information about prescribing and administration refer to the Product Information and CEC Direct Oral Anticoagulant Guidelines.

References:

1. Therapeutic Goods Administration, *Andexxa*. 2023 [5 Oct 2023]; Available from: https://www.tga.gov.au/resources/auspmd/andexxa.
2. Council of Australian Therapeutic Advisory Groups. Navigating high-cost medicines - Guiding principles for the governance of high-cost medicines in Australian hospitals. CATAG; 2022.
3. 'Australian Product Information - Andexxa® (andexanet alfa) powder for solution for infusion'. Australian Register of Therapeutic Goods: 2023.
4. Connolly SJ, Crowther M, et al., 'Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors', *N Engl J Med*, 2019,380(14):1326-35.

Clinical Excellence Commission
Tel: 02 9269 5500 **Email:** CEC-MedicineFormulary@health.nsw.gov.au
Website: www.cec.health.nsw.gov.au

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