CATAG
Council of Australian Therapeutic Advisory Groups

Facilitating the translation of evidence into best practice: andexanet alfa in life-threatening bleeds.

Key points

- Andexanet alfa is not routinely recommended for use in the management of patients treated with a factor-Xa inhibitor presenting with a severe and life-threatening bleed.
- Andexanet alfa is not recommended in the management of a factor-Xa inhibitor overdose
- Andexanet alfa is not recommended to reverse the effects of a factor-Xa inhibitor to facilitate surgical procedures.
- CATAG does not recommend andexanet alfa is listed on hospital or state-based medicine formularies.

Background

Andexanet alfa is a new reversal agent for direct-acting anticoagulants and has recently been provisionally approved by the Therapeutic Goods Administration (TGA) for the following therapeutic use:

> *Andexxa (andexanet alfa) has provisional approval in Australia 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.*

The TGA states that the decision to approve this indication has been made on the basis of haemostatic efficacy and reduction in anti-FXa activity. Continued approval of this indication depends on verification and description of benefit in a confirmatory trial.

Andexanet alfa is a recombinant form of human Factor Xa (FXa) protein that has been modified to lack FXa enzymatic activity and is a specific reversal agent for FXa inhibitors. The predominant mechanism of action is the binding and sequestration of the FXa inhibitor. In addition, andexanet alfa has been observed to bind to, and inhibit tissue factor pathway inhibitor (TFPI). Inhibition of TFPI activity can increase tissue factor-initiated thrombin generation inducing a pro-coagulant effect.

Whilst this appears to represent an important step forward in improving the safety of anticoagulation for patients, there are significant limitations to the available outcome data and a need to define the patient group most likely to receive benefit from receiving this high-cost medicine.

Purpose

CATAG, with the assistance of an Expert Advisory Group (EAG), has developed this document to facilitate and support the translation of best available evidence into practice for the use of andexanet alfa for adult patients receiving a direct factor Xa (FXa) inhibitor (apixaban or rivaroxaban) presenting with severe and life-threatening bleeds.

This document provides consensus statements based on the current available evidence (as at September 2023) on the use of andexanet alfa. This will assist good governance and decision-making for health service organisations, medicines governance committees and health professionals in their evaluation, approval and use of this medicine. It can be used in conjunction with formulary decisions and recommendations.

These recommendations will be reviewed and updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

RECOMMENDATIONS

Do not routinely use andexanet alfa in the management of patients treated with a factor-Xa inhibitor presenting with a severe and life-threatening bleed.

There is a lack of high-quality evidence demonstrating meaningful patient outcomes to support the use of andexanet alfa to reverse the effects of a factor-Xa inhibitor, in a patient presenting with a severe, or life-threatening bleed. Current quality evidence is limited to demonstrating haemostatic efficacy, which may not translate directly to clinically relevant outcomes such as mortality, functional status, length of stay or hospital resource utilisation.

Available evidence comparing andexanet alfa to the standard of care is limited to indirect comparators and observational studies with a high risk of bias. Whilst the Expert Advisory Group (EAG) considered it plausible that andexanet alfa may offer benefit in measures such as mortality, there remains a high degree of uncertainty. The benefits of using any drug must be weighed against the potential risks, and the EAG noted significant increases in adverse events, particularly thrombosis rates compared with historical cohorts.

Based upon currently available evidence, it is not possible to identify those patient populations most likely to receive benefit, and those most likely to suffer harm. The EAG considered that there was a high and likely risk of leakage into a wide range of haemorrhage scenarios, with insufficient evidence to support safe use. Without improved data to guide practice, a *first do no harm* approach must apply.

Andexanet alfa has not been independently evaluated for cost-effectiveness in the Australian health care setting. Given the available evidence, any estimate of cost-effectiveness would be associated with a high degree of uncertainty. Based on international HTA evaluations, there is high probability that andexanet alfa would not be cost-effective at the current list price.

Despite being marketed internationally for several years, andexanet alfa is not routinely considered the standard of care in managing life threatening bleeds for patients using a factor-Xa inhibitor product. The EAG consider it is appropriate to await further evidence regarding patient outcomes in defined patient populations to understand how, and where, this drug may be safely and effectively implemented in the future.

Do not use andexanet alfa in the management of adults presenting with a factor-Xa inhibitor overdose.

Currently, there is no evidence evaluating the safety, or effectiveness, of andexanet alfa in reversing the effects of a factor-Xa inhibitor overdose. In most instances, patients with a factor-Xa inhibitor overdose will not experience a concomitant bleed, and as such, there may be no benefit to provide a reversal agent. The EAG expressed concerns regarding identifying an appropriate dosing regimen in this setting. Should a patient present with an overdose and a concomitant bleed, urgent advice should be sought through toxicology services (which can be accessed via the Poisons Information Hotline for any services without 24/7 toxicology coverage).

Do not use andexanet alfa to reverse the effects of a factor-Xa inhibitor to facilitate surgical procedures.

Currently, there is no evidence evaluating the safety or effectiveness of andexanet alfa in reversing the effects of a factor-Xa inhibitor prior to surgery. Until further evidence is available, do not use andexanet alfa in this setting.

Health Service Organisations and Medicines Governance Committees[1] should consider not listing andexanet alfa on hospital or state-based formularies.

Since the evidence does not suggest the routine use of andexanet alfa for any indication, CATAG does not support the listing of andexanet alfa on formulary.

Any Individual Patient Use (IPU) or Individual Patient Approval (IPA) approvals to use andexanet alfa should be made on a case-by-case basis, considering the Product Information and available evidence. Efficacy and safety information should be considered. This is summarized in Use of andexanet alfa in NSW health facilities under Considerations for the use of andexanet alfa. If andexanet alfa is approved on an Individual Patient Use (IPU) or Individual Patient Approval (IPA) basis, then the Medicines Governance Committee should specify outcome evaluation, monitoring and review processes at the time of approval.[2] Medicines Governance Committees should consider auditing its use.

If andexanet alfa is to be used for a non-licensed indication, then CATAG suggests referring to CATAG's *Rethinking medicines decision-making in Australian Hospitals. Guiding principles for the quality use of off-label medicines.*

LATEST EVIDENCE

Evidence Summary – Severe and life-threatening bleeding

Numerous studies demonstrate andexanet alfa's efficacy in terms of haemostatic efficacy. However comparative mortality outcomes are a more clinically relevant measure. Evidence demonstrating mortality benefit is limited to matched observational data, with significant limitations. It is considered possible that andexanet alfa improves mortality outcomes in patients on a factor-Xa inhibitor presenting with a severe and life-threatening bleed, however this is highly uncertain and may vary by bleeding site. Evidence exploring other relevant outcomes such as functional outcomes, length of stay and hospital resource utilisation remains significantly limited.

What evidence is informing this recommendation?

Annexa-4 is the pivotal trial underpinning the TGA registration for andexanet alfa. Annexa-4 sub-study (Demchuk et al.) considers safety markers as a secondary outcome. One such safety marker is 30-day mortality. However, this is a single arm study with no comparator. The authors compare the 30-day mortality rate from subjects enrolled in Annexa-4 trial who suffered an intracranial haemorrhage and received andexanet alfa, to 30-day mortality rates following intracranial haemorrhage in pivotal stroke prevention studies found elsewhere in literature.

The EAG considered several indirect comparative studies:

- Dobesh, et al. (2023) was a retrospective observational study including 2122 patients receiving andexanet alfa and 2273 patients receiving standard care (4 factor-PCC), with a primary outcome of in-hospital mortality.

[1] Examples of medicines governance committees include drug and therapeutics committees, medicines advisory committees or equivalent, medication safety committees

[2] Achieving effective medicines governance. Guiding principles for the roles and responsibilities of Drug and Therapeutics Committees in Australian public hospitals. Council of Australian Therapeutic Advisory Groups; 2013

- Cohen et al. (2022) retrospectively compared datasets from 2 unrelated studies (322 patients included from Annexa-4 and 88 patients included from the ORANGE study).
- Sutton et al. (2023) was an observational database analysis among US veterans, including 85 who received andexanet alfa and 170 who received PCC over a 6-year period.
- Several meta-analyses have also attempted to provide guidance.
  - Luo, C et al. (2021), Nederpelt et al. (2021), Shrestha et al.(2021) and Chaudhary et al (2022) with the latter 2 focusing on the intracranial haemorrhage cohort.

Outcome	Study	Study results and measures	Certainty of Evidence	Plain language summary
In-hospital mortality	Dobesh et al	6% AA vs 10.6% 4F-PCC (OR, 0.50; 95% CI, 0.39-0.65)	Low	It is possible that andexanet alfa improves in-hospital mortality, but there is a high degree of uncertainty with respect to this outcome.
	Sutton et al.	Adjusted HR 0.31, 95% CI: 0.14–0.71	Low	
	Shrestha et al.	OR 0.37 95% CI, 0.20-0.71 Intracranial haemorrhage population	Low	
	Nederpelt et al.	No significant differences between andexanet alfa and PCC	Low	
30-day mortality	Cohen et al.	14.6% AA vs 34.1% PCC (RR 0.43, 95% CI, 0.29-0.63)	Low	It is possible that andexanet alfa improves 30-day mortality, but there is a high degree of uncertainty with respect to this outcome.
	Sutton et al.	Adjusted HR 0.54, 95% CI: 0.30–0.98	Low	
All-cause mortality	Luo et al.	24% AA vs 19% aPCC/4F-PCC	Low	It is possible that andexanet alfa worsens overall mortality, but there is a high degree of uncertainty with respect to this outcome.
	Chaudhary et al.	No significant differences between andexanet alfa and PCC	Low	

What are the main results?

In Annexa-4, 10% developed a thrombotic event and death occurred in 14% of overall patients within 30 days.

The Annexa-4 sub-study specifically investigated the intracranial haemorhage cohort as they had the greatest enrollment and this cohort were considered to have the most severe manifestation of acute major bleeding. In the Annexa-4 sub-study, thromboembolic events occurred in 9.3% and death in 15% across all patients. For patients with spontaneous bleeds, 30-day mortality occurred in 18.8% whereas patients with a traumatic ICH,

30-day mortality rates were 10.1%. The Annexa-4 sub-study suggests that some sub-populations of patients suffering intracranial haemorrhage receive no benefit in 30-day mortality, and that other subgroups may receive benefit. Importantly, this study concludes that a properly controlled evaluation is necessary to yield a meaningful understanding of mortality outcomes.

For the indirect studies:

- Dobesh et al (2023) found in-hospital mortality occurred in 6% of the treatment group and 10.6% of the standard care group (p<0.1). This translates into a 50% lower likelihood of death (OR 0.50, 95%CI, 0.39-0.65).
- Cohen et al (2022) found that adjusted 30-day mortality in the treatment group was 14.6% and 34.1% in the standard care group (4 factor-PCC) (RR 0.43, 95%CI, 0.29-0.63). When bleed type was considered, 30-day mortality was significantly lower for the intracerebral haemorrhage (ICH) cohort (RR, 0.31; 95% CI, 0.20–0.48), but was not statistically significant for gastrointestinal bleeds and for other major bleeds. However, Annexa-4 excluded subjects with poor prognostic features, especially for the ICH cohort, including GCS less than 7 and larger haematoma volumes, or those with an expected survival of less than one month, where ORANGE did not.
- Sutton et al. (2023) reported a 69% lower hazard for in hospital mortality (aHR 0.31, 95% CI: 0.14–0.71) and 45.6% lower hazard for 30 day mortality rate (aHR 0.54, 95% CI: 0.30–0.98) for andexanet alfa over PCC but other secondary outcomes such as hospital and ICU length of stay were not significantly different.
- Luo et al. (2021) included 22 single arm, non-comparative studies. The pooled, all-cause mortality rate within 30 days was higher in patients administered andexanet alfa at 24% (95% CI; 12% to 35%) compared with aPCC/4F-PCC at 19% (95% CI; 14% to 25%). As was the pooled rate for thrombotic complications for andexanet alfa at 13% (95% CI; 5% to 20%) compared to aPCC/4F-PCC 4% (95% CI; 3% to 5%).
- Nederpelt et al. (2021) indicated a higher 30-day symptomatic VTE rate of 5% for andexanet alfa vs 1.9% for PCC and higher in-hospital mortality of 23.3% vs 15.8%, respectively. However, when adjusted for confounding factors, concluded that there were no significant differences between andexanet alfa and PCC for effectiveness, occurrence rate of thromboembolic complications and mortality.
- Shrestha et al. (2021) included 3 studies in the quantitative analysis and reported on in-hospital mortality for patients with ICH. Andexanet alfa resulted in lower odds of mortality compared to 4F- PCC (OR 0.37, 95% CI, 0.20-0.71). There were no differences in thrombotic events, or ICU length of stay in this study.
- Chaudhary et al (2022) was a systematic review and meta-analysis of 36 retrospective studies and case series. This analysis showed no differences between andexanet alfa and 4F-PCC in anticoagulation reversal, proportional mortality or thromboembolic events.

Our confidence in the results

Dobesh et al. included observational data and had a high risk of bias.

Cohen et al had significant limitations, and broad exclusion criteria, removing the most at risk patient groups. Of note, only a small proportion of ORANGE study subjects were considered eligible for inclusion, and it is difficult to determine if that sample remained representative. Dobesh et al. and Cohen et al. demonstrate contradictory outcomes when considering mortality rates related to gastrointestinal bleeding. For mortality outcomes in the

meta-analysis, Shrestha et al (2021) did favour andexanet alfa, however Nederpelt et al. and Chaudhary et al (2022) reported no significant differences. All-cause mortality was higher for andexanet alfa in Luo et al. A lack of consistent, or favourable outcomes, further contributes to the high uncertainty in the study results.

Appendices

Appendix 1: Glossary

Term	Definition
AA	Andexanet alfa
aPCC	Activated prothrombin complex concentrate
CATAG	Council of Australian Therapeutic Advisory Groups
EAG	Expert Advisory Group
4F-PCC	4 factor-PCC
FXa	Factor Xa
HR	Hazard Ratio
Medicine Governance Committee	Committee providing governance for medicines access, also known as drug and therapeutics committee
OR	Odds ratio
PCC	Prothrombin Complex Concentrates
RR	Relative risk
TFPI	Tissue factor pathway inhibitor
TGA	Therapeutic Goods Administration
VTE	Venous thromboembolism

Appendix 2: How this guidance was developed

This document is intended to provide short summarised best practice recommendations to hospital Drug and Therapeutics Committees using a consensus development model. This will assist good governance and decision-making for health service organisations, medicines governance committees and health professionals.

CATAG has developed this document, based on the review of current literature. International cost-effectiveness reviews from Canada, UK and Scotland were reviewed. The pivotal Annexa trials were reviewed and a literature review was undertaken to find studies with indirect comparisons. Free full text clinical trials, meta-analysis, RCT, reviews and systemic reviews were searched within PubMed between 2021 and 2023 using the search term andexanet alfa. 67 results were found and 9 included. Reviews with <50 patients or if the study had no comparator, were excluded.

An expert advisory group (EAG) comprised of individuals with recognised expertise in a range of relevant areas including therapeutics/QUM, evidence-based medicine, clinical medicine; clinical pharmacy; health economics, medicines governance and consumer issues was convened. Members of the advisory group reviewed the evidence, agreed on consensus statements, reviewed drafts of the document and approved the final document

This guidance was developed in consultation with the CATAG member organisations listed below:

- ACT Health
- NSW Therapeutic Advisory Group (NSW TAG)
- Northern Territory Drug and Therapeutics Committee
- Queensland Health Medicines Advisory Committee (QHMAC)
- South Australian Medicines Advisory Committee (SAMAC)
- Tasmanian Medicines Access and Advisory Committee (TMACC)
- Victorian Therapeutics Advisory Group (Vic TAG)
- Western Australian Therapeutics Advisory Group (WATAG)

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