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. ANNEXA-I has been recently published and is yet to be reviewed by the TGA.

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 the introduction of this treatment in Australia 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

The Council of Australian Therapeutic Advisory Groups (CATAG), with the assistance of an Expert Advisory Group (EAG), undertook a review of the quality of evidence, safety, efficacy, cost-effectiveness, and place in therapy of andexanet alfa. Consensus statements on the use of andexanet alfa based on the current available evidence (as of May 2024) have been developed.

These statements facilitate and support the translation of best available evidence into practice for the use of andexanet alfa for adult patients receiving a direct FXa inhibitor (apixaban or rivaroxaban) presenting with severe and life-threatening bleeds. These will assist good governance and decision-making for health service

organisations, Medicines and Therapeutics Advisory Committees[1] (also known as Drug and Therapeutics Committees) and health professionals in their evaluation, approval and use of this medicine.

Medicines and Therapeutics Advisory Committees make formulary decisions based on the highest quality of evidence available. These decisions require consideration of the efficacy, safety, cost-effectiveness, place in therapy and affordability of a medicine. These decisions are essential to ensure equity and sustainability of healthcare is maintained.

Where a medicine is not listed on formulary, case-by-case approval through an individual patient use (IPU) / individual patient approval (IPA) process is available within most Australian health care facilities.

Health Service Organisations additionally decide whether to stock or hold a medicine depending on predicted frequency and urgency of use, as well as financial factors.

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

RECOMMENDATIONS

1. 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.

For many bleeding presentations, the available evidence comparing andexanet alfa to the current recommended usual care[2,3] is limited to indirect comparators and observational studies with a risk of bias. ANNEXA-I represents the first higher quality RCT comparing andexanet alfa to usual care in patients with intracerebral haemorrhage. ANNEXA-I demonstrates that andexanet alfa, in a selected cohort of patients, provides better haemostatic efficacy than usual care (adjusted difference, 13.4 percentage points; 95% confidence interval [CI], 4.6 to 22.2; P=0.003) in patients with intracerebral haemorrhages (Connolly, Sharma et al. 2024). In this study, 'haemostatic efficacy' was a composite marker (including computed tomography (CT) changes, clinical assessment and rescue therapy use), which were used as indicators for improved patient outcomes.

ANNEXA-I confirmed earlier safety signals of increased thrombotic risk. The rate of thrombotic events was greater with andexanet alfa versus usual care, 10.3% versus 5.6% (95% CI: 0.1, 9.2; p=0.048), including an increase in ischaemic strokes at a rate of 6.5% for andexanet alfa and 1.5 % for usual care (95% CI: 1.5, 8.8;Connolly, Sharma et al. 2024).

[1] Examples of medicines and therapeutics advisory committees include drug and therapeutics committees, medicines advisory committees or equivalent, medication safety committees.
[2] Product AusPAR XARELTO rivaroxaban Bayer Australia Pty Ltd PM-2017-04819-1-3 FINAL 22 October 2019 https://www.tga.gov.au/sites/default/files/auspar-rivaroxaban-191022-pi.pdf.
[3] Product information for AusPAR Eliquis Apixaban Bristol-Myers Squibb Australia Pty Ltd PM-2011-03165-3-3 Date of Finalisation 21 June 2013 https://www.tga.gov.au/sites/default/files/auspar-apixaban-130621-pi.pdf.

ANNEXA-I did not demonstrate differences at 30 days in mortality (27.8% andexanet alfa versus 25.5% usual care, p=0.51) or functional outcome (modified Rankin score 0-3, 28% andexanet alfa versus 31% usual care), or other clinically meaningful measures (Connolly, Sharma et al. 2024). The study was not designed or powered to show a difference in these measures.

The EAG considered it plausible that while treatment with andexanet alfa may offer a favourable benefit:harm profile in a highly selected patient group, there remains a high degree of uncertainty. The EAG noted the ANNEXA-I trial itself had already selected a smaller subset of intracranial haemorrhage patients (only patients with intracerebral haemorrhage were eligible) where the benefit of haemostatic reversal may be expected to be more favourable.

Despite recent evidence, it is not possible to broadly identify those patient populations most likely to receive benefit, and those most likely to suffer harm. The EAG noted any post hoc exploratory subgroup analyses of ANNEXA-I should be interpreted with caution and should not be considered as high-level evidence for the purposes of formulary decisions. If andexanet alfa is available within a facility, it may be appropriate to consider exceptional use, taking into consideration a patient's clinical condition, medical history and other relevant factors on a case-by-case basis.

The EAG considered that there was a likely risk of leakage into a wide range of haemorrhage scenarios, with insufficient evidence to support safe use.

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 Health Technology Assessment (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 medicine. Specialist guidelines are mixed and andexanet alfa is not universally recommended in guidelines (where present, these recommendations tend to be conditional and supported by very low-quality evidence).

The EAG consider it is appropriate to await further evidence regarding patient outcomes in defined patient populations to understand how, and when, this drug may be safely and effectively implemented in the future.

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

Andexanet alfa is not registered for the management of a factor-Xa inhibitor overdose and is considered off-label for this indication. 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).

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

Andexanet alfa is not registered to reverse the effects of a factor-Xa inhibitor to facilitate surgical procedures and is considered off-label for this indication.

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.

4. Health Service Organisations and Medicines and Therapeutics Advisory Committees should consider not listing andexanet alfa on hospital or state-based formularies.

Since the available evidence does not suggest the routine use of andexanet alfa for any indication, CATAG does not support the listing of andexanet alfa on hospital or statewide formularies.

Given the exceptional circumstances in which andexanet alfa could be used, it may be appropriate for some hospitals (depending on the case mix and specialty of the hospital) to hold stock. These hospitals may include those that routinely treat large numbers of trauma patients. Andexanet alfa in these circumstances could be used via an established IPU/IPA pathway, approved by the Medicines and Therapeutics Advisory Committee under an approved mechanism and pre-determined procedure, for example by an on-call haematologist, or senior anaesthetist (as is presently the case for factor VIIa use in many facilities).

Any IPU or IPA requests to use andexanet alfa should be assessed and approved on an individual basis, considering the Product Information and available evidence of efficacy and safety. The EAG were unable to reach a consensus with regards to defining IPU/IPA patient groups as current evidence does not support the identification of an appropriate subgroup that may receive benefit.

Given the uncertainty surrounding the benefit or risk of harm associated with andexanet alfa, CATAG suggests that, where possible, obtaining patient consent (or consent from their substitute decision maker) prior to administration be considered, acknowledging the challenges of obtaining consent in emergency settings. If andexanet alfa is approved on an IPU/IPA basis, to ensure time critical approval, an institutional protocol should be approved by the Medicines and Therapeutics Advisory Committee, with appropriate gatekeeper delegation (for example by a haematologist, or senior anaesthetist) to provide time critical approval. The Medicines and Therapeutics Advisory Committee should have endorsed a local procedure which specifies outcome evaluation, monitoring and review processes.[4] Medicines and Therapeutics Advisory Committees should consider auditing the use of andexanet alfa.

Further evidence is required to determine the effectiveness of this treatment in terms of meaningful patient outcomes. CATAG welcomes future robust evidence and supports and encourages opportunities for Australian randomised clinical trials in the use of andexanet alfa.

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

[4] 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 https://catag.org.au/resource/achieving-effective-medicines-governance/

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.

ANNEXA-I was published in May 2024, this was an open-label randomized, multicentre clinical trial including 530 participants with acute intracerebral haemorrhage who received either andexanet alfa or usual care. The primary outcome in ANNEXA-I was the rate of effective haemostasis, and the secondary outcome was change in anti-Xa activity. The safety analysis reported on thrombosis and death at 30 days (Connolly, Sharma et al. 2024).

The EAG had previously considered several indirect comparative studies:

- Dobesh, et al. (2023) was a retrospective observational study including 2122 patients receiving andexanet alfa and 2273 patients receiving usual care (4 factor-PCC), with a primary outcome of in-hospital mortality.
- Cohen et al. (2022) retrospectively compared datasets from 2 unrelated studies (322 patients included from ANNEXA-4 and 88 patients (who received PCC) included from the ORANGE study (a prospective, observational study of anticoagulated patients in UK hospitals).
- 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 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.

Table 1. Safety outcomes of reviewed studies

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

	Sutton et al.	Adjusted HR 0.31, 95% CI: 0.14–0.71	Low	uncertainty with respect to this outcome.
	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	
	Connolly et al.(ANNEXA-I)	27.8% AA versus 25.5% usual care, 95% CI: -5.0, 10.0; p=0.51	High	It is possible that andexanet alfa increases 30-day mortality but there is a high degree of uncertainty with respect to this outcome
All-cause mortality	Luo et al.	24% AA vs 19% aPCC/4F-PCC	Low	It is possible that andexanet alfa increases 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	

AA- Andexanet alfa, PCC – Prothrombin complex concentrate, 4F-PCC- 4 factor prothrombin complex concentrate

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 haemorrhage cohort as they had the greatest enrolment, and this cohort was 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 from 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.

Subsequently, ANNEXA-I directly compared a select cohort of patients with intracerebral haemorrhage who either received andexanet alfa or usual care. This study was ceased early because it met its prespecified efficacy endpoint at the interim analysis. Effective haemostasis (a composite outcome measure) was achieved in 67% of patients receiving andexanet alfa versus 53.1% receiving usual care (95% CI, 4.6-22.2, p=0.003).

Other measures were considered as secondary or exploratory endpoints. These included 30-day mortality, health related quality of life, effect on neurological function and assessment of Modified Rankin Score.

In the ANNEXA-I safety analysis, thrombotic events by 30 days occurred in almost twice as many patients receiving andexanet alfa (10.3%) than those receiving usual care (5.6%). Of these, ischemic stroke was the most common and occurred in 6.5% versus 1.5% and myocardial infarction in 4.2% vs 1.5%, respectively. At 30 days numerically more deaths occurred in the AA arm (27.8% vs 25.5%), but this outcome was not statistically significant. The study was not powered to determine superiority of the effect of treatment on mortality. In the conclusion, the authors stated that in a trial involving patients with intracerebral haemorrhage who had taken a factor Xa inhibitor within the previous 15 hours, andexanet alfa rapidly reduced anti-factor Xa activity and resulted in better control of haematoma expansion on a composite measure than usual care, but was associated with thrombotic events.

For the indirect studies:

- Dobesh et al (2023) found in-hospital mortality occurred in 6% of the treatment group and 10.6% of the usual 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 usual 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, it 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.

Confidence in the results

ANNEXA-I was the first higher quality randomized-controlled trial comparing andexanet alfa to usual care (Connolly, Sharma et al. 2024). Of note, a number of post-commencement amendments were made to the study protocol excluding patients with certain bleed types such as subdural and subarachnoid haemorrhages. Despite narrowing the inclusion criteria to intracerebral haemorrhages, it remains difficult to determine which patients will benefit the most from treatment and which patients are likely to be harmed.

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
CT	Computed tomography
EAG	Expert Advisory Group
4F-PCC	4 factor-PCC
FXa	Factor Xa
HR	Hazard Ratio
HTA	Health Technology Assessment
Medicines and Therapeutics Advisory Committee	A multidisciplinary committee with a commitment to the overall governance of the medicines management system in their health service organisation to ensure the judicious, appropriate, safe, effective and cost-effective use of medicines. Examples of medicines and therapeutics advisory committees include drug and therapeutics committees, medicines advisory committees or equivalent, medication safety committees.
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 and Therapeutics Advisory 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.

The position statement was further updated between June and October 2024 following the release in May of the ANNEXA-I study.

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 and medicines governance issues was convened. Members of the advisory group reviewed the evidence, agreed on consensus statements, reviewed feedback and drafts of the document and approved the final position statement.

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

- ACT Health
- Clinical Excellence Commission, NSW 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)

Valuable contributions from the following individuals are gratefully acknowledged.

- Dr Joel Iedema, Clinical Pharmacologist and Endocrinologist, Redland Hospital, QLD (Chair)
- Dr Josephine Adattini, Pharmacist and Improvement Lead, Clinical Excellence Commission, NSW
- Grace Clapp, Senior Pharmacist, Department of Health, WA
- Dr Kate Hill, Haematologist, Princess Alexandra Hospital, QLD
- Dr Sam Hitchins, Staff Specialist (Pathology/Haematology), Royal Hobart Hospital, TAS
- A/Prof Katherine Isoardi, Senior Staff Specialist Emergency Physician & Clinical Toxicologist, Princess Alexandra Hospital, QLD
- Professor Jennifer H. Martin, Physician, Clinical Pharmacologist, Hunter Medical Research Institute and Clinical Excellence Commission, NSW
- Dr Christopher Morris, Clinical Pharmacologist, Princess Alexandra Hospital, QLD
- Clin A/Prof Kavitha Subramaniam, Senior Staff Specialist Gastroenterology, Canberra Hospital, ACT
- Sarah Reeve, Senior Specialist Pharmacist, Medication Governance and Access, TAS
- Anita Shutt, Director, Medication Governance and Access, TAS

These individuals were also consulted but do not endorse this document

- Professor Bruce Campbell, Head of Neurology and Stroke, Royal Melbourne Hospital, Chair of Stroke Living Guidelines Committee, VIC
- Professor Timothy Kleinig, Head of Stroke, Royal Adelaide Hospital, President of Australian and New Zealand Stroke Organisation, SA

Version number
Version 3: October 2024

Recommended Citation:
Council of Australian Therapeutic Advisory Groups. Facilitating the translation of evidence into best practice: andexanet alfa in life-threatening bleeds. CATAG, October 2024.

References

- Andexanet alfa 200 mg powder for solution for infusion (Ondexxya®). Detailed advice SMC2273. (2020) Scottish Medicines Consortium. NHS Scotland. www.scottishmedicines.org.uk.
- Andexanet alfa for reversing anticoagulation from apixaban or rivaroxaban. (2021) NICE technology appraisal guidance 697. www.nice.org.uk/guidance/ta697.
- CADTH reimbursement recommendation. Andexanet alfa (Ondexxya®). (2023) Canada's Drug and Health Technology Agency. https://www.cadth.ca.
- Chaudhary R, Singh A, Chaudhary R, Bashline M, et al. Evaluation of direct oral anticoagulant reversal agents in intracranial hemorrhage: A systematic review and meta-analysis. JAMA Netw Open. 2022 Nov 1;5(11):e2240145.
- Chuck C, Kim D, Kalagara R, et al. Modeling the clinical implications of andexanet alfa in factor xa inhibitor-associated intracerebral hemorrhage. Stroke, 2021, 52(Suppl 1).
- Cohen AT, Lewis M, Connor A, et al. Thirty-day mortality with andexanet alfa compared with prothrombin complex concentrate therapy for life-threatening direct oral anticoagulant-related bleeding. J Am Coll Emerg Physicians Open. 2022 Mar 5;3(2):e12655.
- Coleman CI, Dobesh PP, Danese S, et al. Real-world management of oral factor Xa inhibitor-related bleeds with reversal or replacement agents including andexanet alfa and four-factor prothrombin complex concentrate: a multicenter study. Future Cardiol. 2021 Jan;17(1):127-135.
- Connolly SJ, Crowther M, Eikelboom JW, et al. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. N Engl J Med 2019; 380:1326-1335.
- Connolly SJ, Sharma M, et al. Andexanet for Factor Xa Inhibitor-Associated Acute Intracerebral Hemorrhage. N Engl J Med 2024; 390: 1745-1755.
- Demchuk AM, Yue P, Zotova E, et al. Hemostatic efficacy and anti-FXa (Factor Xa) reversal with andexanet alfa in intracranial hemorrhage: ANNEXA-4 substudy. Stroke. 2021 Jun;52(6):2096-2105. Erratum in: Stroke. 2021 Aug;52(8):e525.
- Dobesh PP, Fermann GJ, Christoph MJ, et al. Lower mortality with andexanet alfa vs 4-factor prothrombin complex concentrate for factor Xa inhibitor-related major bleeding in a U.S. hospital-based observational study. Res Pract Thromb Haemost. 2023 Aug 30;7(6):102192.
- Fanikos J, Goldstein JN, Lovelace B, et al. Cost-effectiveness of andexanet alfa versus four-factor prothrombin complex concentrate for the treatment of oral factor Xa inhibitor-related intracranial hemorrhage in the US. J Med Econ. 2022 Jan-Dec;25(1):309-320.
- Gómez-Outes A, Alcubilla P, Calvo-Rojas G, et al. Meta-analysis of reversal agents for severe bleeding associated with direct oral anticoagulants. J Am Coll Cardiol. 2021 Jun 22;77(24):2987-3001.
- Jaspers T, Shudofsky K, Huisman MV, et al. A meta-analysis of andexanet alfa and prothrombin complex concentrate in the treatment of factor Xa inhibitor-related major bleeding. Res Pract Thromb Haemost. 2021 May 24;5(4):e12518.
- Kanjee Z, McCann ML, Freed JA. Availability of specific direct oral anticoagulant reversal agents in US hospitals. JAMA Netw Open. 2021 May 3;4(5):e2110079.
- Luo C, Chen F, Chen YH, et al. Prothrombin complex concentrates and andexanet for management of direct factor Xa inhibitor related bleeding: a meta-analysis. Eur Rev Med Pharmacol Sci. 2021 Mar;25(6):2637-2653.
- Nederpelt CJ, Naar L, Krijnen P, et al. Andexanet alfa or prothrombin complex concentrate for factor Xa inhibitor reversal in acute major bleeding: A systematic review and meta-analysis. Critical care medicine 49(10):p e1025-e1036, October 2021.
- Product information for AusPAR Eliquis Apixaban Bristol-Myers Squibb Australia Pty Ltd PM-2011-03165-3-3 Date of Finalisation 21 June 2013 https://www.tga.gov.au/sites/default/files/auspar-apixaban-130621-pi.pdf.
- Product AusPAR XARELTO rivaroxaban Bayer Australia Pty Ltd PM-2017-04819-1-3 FINAL 22 October 2019 https://www.tga.gov.au/sites/default/files/auspar-rivaroxaban-191022-pi.pdf.
- Shrestha DB, Budhathoki P, Adhikari A, et al. Efficacy and safety of andexanet alfa for bleeding caused by factor Xa inhibitors: A systematic review and meta-analysis. Cureus. 2021 Dec 23;13(12):e20632.
- 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. J Thromb Thrombolysis. 2023 Jul;56(1):137-146. Erratum in: J Thromb Thrombolysis. 2023 Jun.