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POSITION STATEMENT

Use of andexanet alfa: A British Society for Haematology position statement

Richard J. Buka[1,2] | **Deepa J. Arachchillage**[3,4] | **Catherine N. Bagot**[5] | **Gary Benson**[6] | **Charlotte A. Bradbury**[7] | **Nicola Curry**[8,9] | **Beverley J. Hunt**[10] | **David J. Sutton**[11] | **Mari R. Thomas**[12,13] | **John Paul Westwood**[14] | **Karen Breen**[12]

[1]Department of Cardiovascular Sciences, University of Birmingham, Birmingham, UK

[2]West Midlands Adult Comprehensive Care Haemophilia and Thrombosis Centre, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

[3]Department of Immunology and Inflammation, Centre for Haematology, Imperial College London, London, UK

[4]Department of Haematology, Imperial College Healthcare NHS Trust, London, UK

[5]Department of Haematology, Glasgow Royal Infirmary, Greater Glasgow and Clyde Health Board, Glasgow, UK

[6]Northern Ireland Haemophilia Comprehensive Care Centre and Thrombosis Unit, Belfast City Hospital, Belfast Health and Social Care Trust, Belfast, UK

[7]University Hospitals Bristol NHS Foundation Trust, Bristol, UK

[8]Oxford Haemophilia and Thrombosis Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

[9]Radcliffe Department of Medicine, Oxford University, Oxford, UK

[10]Thrombosis and Haemophilia Centre, Guys and St Thomas' NHS Foundation Trust, London, UK

[11]Department of Haematology, University Hospitals of North Midlands NHS Trust, Newcastle-under-Lyme, UK

[12]Department of Haematology, University College London Hospitals NHS Foundation Trust, London, UK

[13]Department of Haematology, National Institute for Health Research Cardiometabolic Programme, University College London Hospitals/University College London Biomedical Research Centre, London, UK

[14]Haemophilia Comprehensive Care Centre, Addenbrooke's Hospital, Cambridge, UK

Correspondence
Karen Breen, Centre for Haemostasis and Thrombosis, Guy's and St Thomas' NHS Foundation Trust, London, UK.
Email: karen.breen@nhs.net

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Andexanet alfa (Ondexxya) currently holds UK marketing authorisation (MA) for adult patients treated with a direct factor Xa (FXa) inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is indicated for life-threatening or uncontrolled bleeding.[1] In National Health Service (NHS) Scotland, andexanet alfa is reimbursed for bleeding at any site,[2] while in the rest of the United Kingdom, the National Institute of Health and Care Excellence (NICE) made recommendation in 2021 for its use in gastrointestinal bleeding only.[3] The summary of product characteristics states that serious arterial and venous thromboembolic events have been reported following treatment with andexanet alfa, including reports of early manifestation (within 72 h) after administration.[1]

The United States Food and Drug Administration (FDA) recently announced that, effective from 22 December 2025, AstraZeneca would withdraw andexanet alfa from manufacture and sale in the United Sates. This decision followed an unfavourable review of a supplemental Biologics Licensing Application to the FDA, which stated that:

> based on available data, the serious risks including the increase in thromboembolic events

> are such that the FDA considers the risks of the product to outweigh its benefits.[4]

In April 2025, the European Medicines Agency (EMA) reported that its Committee for Medicinal Products for Human Use (CHMP):

> … having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Ondexxya…[5]

Andexanet alfa received conditional MA from the UK Medicines and Healthcare products Regulatory Agency (MHRA) and the EMA and accelerated approval from the FDA based on data from Annexa-A4 trial (ANNEXA-4).[6,7] This was a prospective, single-arm trial that enrolled 479 patients, 331 with intracranial haemorrhage and 109 with gastrointestinal haemorrhage. The trial showed that andexanet alfa effectively reversed anti-factor Xa activity. Haemostatic efficacy was rated as excellent or good in 80.1% of patients but a lack of comparator means that it is impossible to discern neither the causal association with treatment nor the clinical relevance of these findings. Moreover, for patients with visible bleeding (e.g. gastrointestinal haemorrhage), outcomes were based on investigator assessment of time to cessation of bleeding rather than objective measures. Thrombosis occurred in 10.4% of patients with a 4.6% incidence of ischaemic stroke.[7]

The ANNEXA-I trial randomised patients with intracranial haemorrhage (>91.2% intracerebral haemorrhage) to either andexanet alfa or usual care. Although four-factor prothrombin complex concentrate (4F-PCC) was not mandated in the protocol for reversal of an oral factor Xa inhibitor, 85.5% of patients in the usual care group received it within 3 h of randomisation.[8] The use of 4F-PCC is an unlicensed indication and there are no prospective data reporting safety or efficacy that support its use.

Patients were only included if their presenting haematoma volume was between 0.5 and 60 mL, and if they had taken their most recent dose of anticoagulant within 15 h before randomisation. The trial was stopped early as it met its primary end-point of 'haemostatic efficacy', which was a composite of three surrogate outcomes including haematoma volume expansion at 12 h after baseline scan. It was not powered to detect differences in survival or disability at 30 days and as such the effect of treatment with andexanet alfa on these end-points is unknown.[8,9] 67.0% of andexanet alfa-treated patients met the primary end-point versus 53.1% in the usual care group ($p = 0.003$). In andexanet alfa-treated patients, there was a 10.3% incidence of thrombosis compared with 5.6% in the usual care group ($p = 0.048$). Independent review of data by the FDA amended this thrombosis rate to 14.6% versus 6.9%.[9] The difference in thrombosis rates was driven by an excess incidence of stroke (6.5% vs. 1.5% [ANNEXA-I manuscript] and 8.7% vs. 1.7% [FDA data]). The excess thrombosis rate seen with andexanet alfa is thought to be due to sequestration by the drug of tissue factor pathway inhibitor, an endogenous anticoagulant.[10,11]

There have been no randomised controlled trials of andexanet alfa in patients with bleeding at sites other than intracranial. However, several retrospective, observational studies have been published. A large study presented a propensity score-matched analysis reporting a significant reduction in in-hospital mortality (4.3%–2.5%, $p = 0.01$).[12] This included a substantial in-hospital mortality benefit in patients with intracranial haemorrhage but no data on thrombotic events were reported. A study comparing outcomes in 59 patients with gastrointestinal (GI) haemorrhage treated with andexanet alfa after an institutional switch compared to 67 treated with PCC prior to the switch found no significant difference in deterioration-free discharge.[13] Reversal Agents in Patients antIcoagulated with Direct Oral anticoagulants (RAPIDO), a recently published UK-wide study of patients treated with reversal agents, presented a propensity score-matched (PSM) analysis of 494 patients with gastrointestinal haemorrhage.[14] This showed no difference in efficacy outcomes between andexanet alfa and 4F-PCC but corroborated the increased rate of thrombosis and stroke with andexanet alfa.

In view of the increased risk of thromboembolic events with andexanet alfa, we consider that the risks of andexanet alfa appear to outweigh the benefits for patients presenting with an oral factor Xa inhibitor-associated bleed. Nevertheless, we acknowledge that andexanet alfa remains available in the United Kingdom and is the only licensed reversal agent for apixaban and rivaroxaban. However, andexanet alfa is not licensed for the reversal of edoxaban or heparin-based anticoagulants nor for reversal prior to urgent surgery. Previous British Society for Haematology recommendations for the management of bleeding in patients on antithrombotic agents[15] remain unchanged and a full, updated guideline is currently in preparation.

RECOMMENDATIONS

- Clinicians should be aware that administration of andexanet alfa is associated with a significantly increased risk of thromboembolic events, particularly ischaemic stroke. (1A)
- If administration of andexanet alfa is being considered, clinicians should be aware that thromboembolic risk may outweigh benefit. (2A)
- If andexanet alfa is to be given, clinicians should ensure that it is only administered within its licensed indication. (1A)

AUTHOR CONTRIBUTIONS

R.J.B. drafted the manuscript, and K.B. chaired the writing group. All other members contributed to writing and revising of the manuscript.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

No original data were produced in the writing of this manuscript and all data cited are freely available.

ETHICS STATEMENT

As this is not original research, no ethical approval was sought or required for this work.

PATIENT CONSENT STATEMENT

No individual patient data were used in the writing of this manuscript.

ORCID

Richard J. Buka https://orcid.org/0000-0002-2738-6236
Deepa J. Arachchillage https://orcid.org/0000-0001-5993-4850
Nicola Curry https://orcid.org/0000-0002-3849-0688
Beverley J. Hunt https://orcid.org/0000-0002-4709-0774
Mari R. Thomas https://orcid.org/0000-0001-9288-7259

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