NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Andexanet alfa for reversing anticoagulation

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of andexanet alfa within its marketing authorisation for reversing anticoagulation.

Background

Anticoagulant therapy is used for preventing and treating thromboembolism across various clinical indications, including the treatment and secondary prevention of deep vein thrombosis (DVT), pulmonary embolism (PE) and after orthopaedic surgery for the prevention of venous thromboembolism as well as to prevent stroke and systemic embolism in patients with non-valvular atrial fibrillation. Direct oral anticoagulants (DOACs) act by inhibiting specific components of the coagulation cascade, such as factor Xa (apixaban, edoxaban, rivaroxaban) or thrombin (dabigatran). Major bleeding events are potential adverse effects of anticoagulants and specific antidotes are not available for DOACs that inhibit factor Xa. Antidotes are needed to reverse anticoagulation in case of life-threatening bleeding or emergency surgery.

The number of people estimated to be having treatment with DOACs in England ranges from 200,000 to 350,000, of whom 90% are having a factor Xa-inhibitor. It is estimated that major bleeding involving the gastrointestinal tract, urinary tract or soft tissue occurs in up to 6.5% of patients on anticoagulant therapy[1]. The incidence of mayor bleeding, such as intracranial haemorrhage, is approximately 1% annually in people on anticoagulant therapy[2].

There is no specific agent available for reversal of anticoagulation effect of factor Xa inhibitors. A position statement from the European Society of Cardiology provides guidelines on the management of the reversal of DOACs. In the case of life threatening bleeding, or emergency surgery it recommends oral charcoal intake followed by antagonisation of antiplatelet therapy with specific antidote if available. If no antidote is available for the specific DOAC, consider prothrombin complex concentrate or recombinant factor VIIa. NICE Guideline 39 on major trauma: assessment and initial management recommends to consult a haematologist for advice on adults (16 or over) who have active bleeding and need reversal of any anticoagulant agent other than a vitamin K antagonist. A NICE evidence summary on the reversal of the anticoagulant effect of dabigatran: idarucizumab (ESNM73) concludes that idarucizumab effectively reverses the anticoagulant effect of dabigatran etexilate, a thrombin inhibiting DOAC.

The technology

Andexanet alfa (brand name unknown, Portola Pharmaceuticals) is a recombinant modified version of human factor Xa clotting protein that lacks factor Xa enzymatic activity. It binds to direct factor Xa inhibitors with high affinity and also binds to indirect factor Xa inhibitors complexed with antithrombin III, making them unavailable to exert their anticoagulant effects. Andexanet alfa is administered as an intravenous infusion.

Andexanet alfa does not currently have a marketing authorisation in the UK for reversing anticoagulation. It has been studied in a single arm trial in adults who had acute major bleeding episode within 18 hours after administration of an anticoagulant.

Intervention	Andexanet alfa
Population	Adults requiring urgent reversal of anticoagulation in case of severe or life-threatening bleeding, after treatment with a factor Xa-inhibiting DOAC
Comparators	Established clinical management without andexanet alfa (including prothrombin complex concentrate with tranexamic acid)
Outcomes	The outcome measures to be considered include: • Requirement for blood products • Control of bleeding • Need for surgical control of bleeding or interventional radiology embolization of bleeding vessel • Effects of intracranial haemorrhage • Hospital stay • Mortality • Adverse effects of treatment (including thrombotic events) • Health-related quality of life.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Guidelines: 'Major trauma: assessment and initial management' (2016). NICE guideline 39. Related NICE Advice: 'Reversal of the anticoagulant effect of dabigatran: idarucizumab' (2016) Evidence summary 73 'Non-vitamin K antagonist oral anticoagulants (NOACs)' (2016) Key therapeutic topic 16 Related NICE Pathways: Trauma (2016) NICE pathway http://pathways.nice.org.uk/
Related National Policy	Department of Health, NHS Outcomes Framework 2015-2016, Dec 2014. Domains 1, 3 and 4. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385749/NHS_Outcomes_Framework.pdf

Questions for consultation

Would andexanet alfa be used only in case of severe or life-threatening bleeding? If so, how should severe or life-threatening bleeding be defined?

What is established clinical management without andexanet alfa likely to include?
Are the outcomes listed appropriate? Do any other outcomes need to be included?

Are there any subgroups of people in whom andexanet alfa is expected to be more clinically effective and cost effective or other groups that should be examined separately? Should people with intracranial bleeding be considered separately?

Where do you consider andexanet alfa will fit into the existing NICE pathway, Trauma?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which andexanet alfa will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider andexanet alfa to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of andexanet alfa can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction)

References

1 Zareh M, Davis A, Henderson S. (2011) Reversal of Warfarin-Induced Hemorrhage in the Emergency Department. West J Emerg Med. 2011 Nov; 12(4): 386–392. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3236169/

2 Enrique A, Lip G and Baranchuk A. (2015) Anticoagulation reversal in the era of the non-vitamin K oral anticoagulants. Europace 27 March 2015. http://europace.oxfordjournals.org/content/early/2015/03/26/europace.euv030