NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Andexanet alfa for reversing anticoagulation

Final scope

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.

In 2017 there were 6.5 million NHS prescriptions for factor Xa-inhibitors in primary care[1]. It is estimated that major bleeding with factor Xa inhibitors ranges from 1-3% and that intracranial haemorrhage rates range from 0.3-0.5%, based on clinical trial results[2,3].

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 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 (Ondexxya, 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, 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 need urgent reversal of anticoagulation due to an acute major bleed after receiving a factor Xa inhibitor.

Intervention	Andexanet alfa
Population	Adults requiring urgent reversal of anticoagulation in case of uncontrolled or life-threatening bleeding, after treatment with a factor Xa-inhibiting DOAC
Comparators	Established clinical management of uncontrolled or life-threatening bleeding without andexanet alfa (including prothrombin complex concentrate with or without 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 embolisation of bleeding vessel • Neurological outcomes (in people with intracranial bleeding) • 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	If the evidence allows consideration will be given to subgroups with intracranial bleeding. 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

References

1 NHS Digital Prescription Cost Analysis – England, 2017 [PAS]

2 Piccini JP et al. (2014) Management of major bleeding events in patients treated with rivaroxaban vs. warfarin: results from the ROCKET AF trial. European Heart Journal (2014) 35, 1873–1880.

3 Granger CB et al. (2011) Apixaban versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med 2011;365:981-92.