NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Andexanet alfa for reversing anticoagulation

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using andexanet alfa in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using andexanet alfa in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 13 May 2020

Second appraisal committee meeting: 9 June 2020

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Andexanet alfa is not recommended, within its marketing authorisation, for reversing anticoagulation with apixaban or rivaroxaban in adults with uncontrolled or life-threatening bleeding.

Why the committee made these recommendations

Apixaban and rivaroxaban are anticoagulants used for preventing and treating thromboembolism in conditions such as deep vein thrombosis and pulmonary embolism. They can increase the risk of major bleeding that cannot be controlled and may be life-threatening. Andexanet alfa aims to stop (reverse) their effects.

The clinical evidence is very limited. There is no direct evidence that andexanet alfa is better than an existing treatment, prothrombin complex concentrate, at helping people survive a major bleed. Also, there is not enough evidence to know whether andexanet alfa reduces long-term disability in people who have had an intracranial haemorrhage (bleeding inside the skull), paralysis in people who had an intraspinal bleed and monocular blindness in people who had an intraocular bleed.

The lack of evidence makes the cost-effectiveness estimates for andexanet alfa very uncertain. Therefore, it cannot be recommended.

2 Information about andexanet alfa

Marketing authorisation indication

2.1 Andexanet alfa (Ondexxya, Portola Pharmaceuticals) has a conditional marketing authorisation 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'.

Dosage in the marketing authorisation

2.2 There are 2 possible doses for andexanet alfa, depending on the timing of the last dose of apixaban or rivaroxaban:

- Low dose: 400 mg initial intravenous bolus at a target rate of 30 mg per minute, then 4 mg per minute by intravenous infusion for 120 minutes (480 mg)
- High dose: 800 mg initial intravenous bolus at a target rate of 30 mg per minute, then 8 mg per minute by intravenous infusion for 120 minutes (960 mg).

2.3 For full details of the dosage schedules, see the summary of product characteristics.

Price

2.4 £11,100 per 4-vial pack of 200 mg of powder for solution for infusion (excluding VAT, BNF online accessed March 2020). The average cost of a course of treatment at list price is £15,000 per patient.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Portola Pharmaceuticals, a review of this submission by the evidence review group (ERG), and the technical report developed through engagement with stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that several issues were discussed at the technical engagement stage and recognised that there were areas of uncertainty associated with the analyses presented (see technical report, table 1 page 35) and took these into account in its decision making. It discussed the following issues (issues 1 to 6), which were outstanding after the technical engagement stage.

Treatment pathway and clinical need

Direct anticoagulants are associated with a serious risk of major bleeding

3.1 Direct anticoagulants such as apixaban and rivaroxaban are used for preventing and treating thromboembolism in conditions such as deep vein thrombosis and pulmonary embolism, and for the prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation. Although

anticoagulants have a greater overall benefit than risk, major bleeding is a serious risk. People with a major bleed are at an increased risk of death, as well as an increased risk of subsequent thrombotic events when coagulation is interrupted. The patient experts explained that thrombotic events can have a substantial physical and psychological effect on patient's lives. Treatment for a thrombosis can affect employment, family planning, travel and social life. Also, many patients fear having further blood clots. Anticoagulants therefore are of benefit to patients, but they increase the risk of a major bleeding event. The committee concluded that direct anticoagulants are associated with a risk of major bleeding events.

There is a clinical need for effective anticoagulation reversal agents

3.2 The patient expert explained that anticoagulation treatments are accepted by patients because they are lifesaving, but there are concerns about safely managing anticoagulation should a major bleed occur. If bleeding is life-threatening then anticoagulation needs to be reversed. Treatment is challenging if there is no reversal agent and relies on treating symptomatically until the effects of the anticoagulant stop, in line with the normal half-life of the drug. The patient experts explained that there is an unmet need for a safe reversal agent for direct factor Xa anticoagulants such as apixaban and rivaroxaban. The committee concluded that the availability of an effective reversal agent would be greatly valued by patients and healthcare professionals.

Most relevant population

It is not appropriate to combine all bleed types for decision making

3.3 The clinical evidence came from ANNEXA-4, a single-arm trial of andexanet alfa in people taking a direct factor Xa inhibitor who had an acute major bleed. Initially, the company submitted results for 3 groups: the whole trial population, a cohort of people with intracranial haemorrhage (ICH) and severe gastrointestinal (GI) bleeds, and a cohort of people with ICH alone. After technical engagement, the company provided results for a cohort of people with severe GI bleeds alone. The

clinical experts explained that different types of bleeds should be considered separately because their treatment and outcomes vary. The committee noted that ICH may lead to mortality and long-term disability, whereas intraocular bleed may lead to blindness. The clinical experts explained that GI bleeds can be managed in most patients using measures such as endoscopy, embolisation or surgery. But treatment options are very limited for ICH, particularly if the bleed is into the brain tissue (an intracerebral bleed). The committee concluded that different types of bleeds should be considered separately for decision making.

Clinical evidence

There is no primary clinical outcome or direct comparative evidence for andexanet alfa

3.4 ANNEXA-4 had no primary clinical outcomes. The only clinical outcome was the safety endpoint of 30-day mortality. However, the trial excluded all patients with an expected lifespan of less than 1 month. The clinical experts explained that in clinical practice all patients would be offered treatment, rather than only a selected group based on anticipated survival. Therefore, the generalisability of the 30-day mortality data from ANNEXA-4 is questionable. Also, because ANNEXA-4 was a single-arm trial there was no comparison with existing treatments such as prothrombin complex concentrate (PCC), further adding to the uncertainty about the clinical benefit of andexanet alfa in clinical practice. The committee noted that the 2 primary outcomes in the trial were both haematological: change in 'anti-factor Xa activity' and haemostatic efficacy. In their response to technical engagement, the clinical experts questioned the definitions of haemostatic efficacy in relation to intracerebral haemorrhage. They considered that haemostatic efficacy as defined in the trial could not be considered predictive of clinical outcomes. The committee concluded that the evidence available for andexanet alfa was limited.

The comparability of ANNEXA-4 and the ORANGE study is uncertain

3.5 Because ANNEXA-4 is a single-arm trial, there is no direct evidence for the efficacy of andexanet alfa compared with other treatments. The company therefore used data for PCC from the ORANGE study to do an indirect comparison. ORANGE was a UK observational study in people taking anticoagulants who were admitted to hospital with a major bleed. In ANNEXA-4, people were excluded if survival was expected to be less than 1 month, they had a Glasgow Coma Score lower than 7 or an intracerebral bleed volume of more than 60 ml. However, these criteria were not used in ORANGE. The committee noted that this could affect the comparability of results for 30-day mortality. The company explained that the proportion of patients excluded based on the survival criterion was extremely low. However, the committee noted that some patients may not have been screened for inclusion if the clinicians considered that they were too ill to meet the criteria. The clinical experts pointed out that every patient with a life-threatening bleed should have been screened for inclusion unless they were on a known end-of-life pathway. The committee concluded that the comparability of the 2 studies and of their 30-day mortality rates are subject to great uncertainty.

The indirect treatment comparison for 30-day mortality is too unreliable for decision making

3.6 The company conducted a propensity score matching analysis to compare 30-day mortality rates from ANNEXA-4 and ORANGE. The committee understood that important prognostic factors such as severity and volume of the bleed could not be included as covariates, because these were not collected in ORANGE. The committee also noted that 30-day mortality was a key driver of the economic model. The company explained that only patients from ORANGE who had PCC were matched to patients in ANNEXA-4. The company assumed that patients who had PCC in ORANGE were a good proxy for those with more severe bleeds, because PCC is used off-label and would be reserved for more severely affected patients. The committee noted that this assumption was not

supported by evidence. The clinical experts explained that severity and volume of bleeds were the primary prognostic factors for bleed-related mortality. The committee considered that without key prognostic factors accounted for, the results of the propensity score matching analysis were very uncertain. In addition, the committee noted that for GI bleed, no comparative data was available on what other treatment people had received in the two studies, particularly embolisation of a bleeding vessel. The clinical experts explained that in the absence of a randomised controlled trial it was very difficult to reach any conclusion on the clinical benefit of andexanet alfa compared with PCC. The committee considered that the results of the propensity score matching analysis were too uncertain and unreliable to be used for decision making. The committee concluded that the potential benefit of andexanet alfa on mortality has not been adequately demonstrated or quantified.

A benefit from andexanet alfa on long-term disability after an ICH is not supported by evidence

3.7 The company assumed that andexanet alfa would reduce the severity of long-term disability in people who had had an ICH, compared with PCC. This assumption had a large effect on the incremental cost-effectiveness ratio (ICER). Long-term disability after an ICH is reflected by modified Rankin scale (mRS) scores, and in the economic model these affected mortality risk, costs and utilities. The company used 2 different sources for mRS scores. For andexanet alfa, it used data from ANNEXA-4. For PCC it used data from Øie et al. (2018) study that included patients with intracerebral haemorrhage only and excluded those with other intracranial bleeds. The ERG and the clinical experts explained that intracerebral haemorrhage is the most severe type of ICH and therefore the company's comparison overestimated the severity of disability and mRS scores for PCC. The committee noted that there was no direct evidence that people would have better mRS scores and less disability after andexanet alfa than PCC, and that the comparison was based on a naive comparison of data from ANNEXA-4 and Øie et al. The committee concluded that a

benefit from andexanet alfa on long-term disability was not demonstrated by the evidence.

Cost effectiveness

The company's economic model is suitable for decision making

3.8 The company submitted a decision tree followed by a Markov model to estimate the cost effectiveness of andexanet alfa compared with PCC. The committee considered that the model is suitable for decision making.

The company's assumptions about 'other major bleeds' are not sufficiently justified

3.9 The propensity score-matching analysis was based on a small number of patients for bleeds classified as 'other major bleeds' (pericardial, retroperitoneal, intraspinal and intraocular bleeds). Also, the analysis results for these bleeds did not favour andexanet alfa compared with PCC so the company considered it was counter intuitive and several assumptions were made to model these bleeds. The company assumed that andexanet alfa would lead to a 25% relative reduction in mortality for pericardial and retroperitoneal bleeds, and it set the mortality to zero for intraspinal and intraocular bleeds. The company also assumed that andexanet alfa would reduce paralysis and blindness by 25% after intraspinal and intraocular bleeds, which reduces the long-term management costs and improves long-term utilities. These assumptions were based on clinical opinion. The clinical experts explained that the evidence was too scarce to make assumptions of 25% relative reduction in mortality, paralysis and blindness and that the ERG's assumption of 0% relative reduction was more reasonable in the absence of robust evidence. The committee concluded that the company's assumptions were not supported by evidence.

The long-term outcomes and utilities for people who had an ICH are highly uncertain

3.10 The committee noted that there was no direct evidence that people who had an ICH had better long-term outcomes with andexanet alfa than if they had PCC (section 3.7). Differences in mRS scores affect the long-term mortality risk, costs and utilities in the model. The long-term utility value for people who had an ICH in the PCC arm in the company's model was 0.61. This was obtained from a 3-month post-acute care utility value in people with ICH, which was used in NICE's guidance on apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism. The company calculated that andexanet alfa increased the long-term utility of people who had an ICH by 0.11 compared with PCC, based on the difference in mRS scores between ANNEXA-4 and Øie et al. This resulted in a long-term utility of 0.72 after an ICH for people who had andexanet alfa. The ERG was concerned that a utility of 0.72 is not plausible because it is only 0.01 lower than the UK general population aged 75 and above. Also, the differences in long-term outcomes were driven by the naive comparison of mRS scores from ANNEXA-4 and Øie et al. The ERG's preferred scenario was to use the mRS scores from Øie et al. only in people who had an intracerebral haemorrhage in ANNEXA-4, or alternatively to use the ANNEXA-4 mRS scores for both treatments (assuming no benefit in mRS scores). The committee concluded that differences in the long-term outcomes and utilities for people after an ICH, depending on the treatment they had, are highly uncertain.

Cost-effectiveness estimates

Andexanet alfa has not been shown to be cost effective compared with PCC

3.11 The committee noted that the magnitude of clinical benefit was very uncertain; therefore, the most plausible ICERs were very uncertain. The company's ICERs were within the range normally considered a cost-effective use of NHS resources. However, the committee had concerns

about the methods and assumptions used in the model. These included the differences in 30-day mortality from trials with different inclusion criteria, major uncertainty in a propensity score matching analysis that omitted key prognostic factors, and the assumption of a benefit from andexanet alfa on long-term disability after an ICH that had not been adequately justified or evidenced. The committee considered a scenario that assumed there was no benefit in 30-day mortality for all bleed types, and no benefit in long-term disability for people who had an ICH. For the ICH plus GI cohort, the ICH cohort and the GI cohort, this scenario resulted in andexanet alfa being dominated by PCC (that is, andexanet alfa was less effective and cost more than PCC). Therefore, the committee was not confident that the results were robust. The committee recognised the need for an effective reversal agent for direct factor Xa inhibitors, such as apixaban and rivaroxaban, in people with uncontrolled or life-threatening bleeding. However, it was not convinced that andexanet alfa had been shown to be a cost-effective use of NHS resources. Therefore, it concluded that andexanet alfa could not be recommended for use in the NHS.

Conclusion

Andexanet alfa is not recommended for reversing anticoagulation in life-threatening or uncontrolled bleeding

3.12 There is a high unmet need for an effective reversal agent of direct factor Xa anticoagulants such as apixaban and rivaroxaban. However, there are major limitations in the clinical evidence and substantial uncertainty in the modelling. The committee was not persuaded that andexanet alfa has been shown to be cost effective. Therefore, andexanet alfa is not recommended for reversing anticoagulation in adults with life-threatening or uncontrolled bleeding.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive when the results of the randomised controlled trial of andexanet alfa compared with prothrombin complex concentrate in intracranial haemorrhage are available. The results are anticipated in 2023. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Jane Adam
Chair, appraisal committee
March 2020

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Caroline Bregman

Technical lead

Rufaro Kausi

Technical adviser

Thomas Feist

Project manager

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