NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Andexanet alfa for reversing anticoagulation from apixaban or rivaroxaban

1 Recommendations

1.1 Andexanet alfa is recommended as an option for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled bleeding, only if:

- the bleed is in the gastrointestinal tract, and
- the company provides andexanet alfa according to the commercial arrangement (see section 2).

1.2 Andexanet alfa is recommended only in research for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled bleeding in the skull (intracranial haemorrhage), in the form of an ongoing randomised trial mandated by the regulator.

Why the committee made these recommendations

Apixaban and rivaroxaban are anticoagulants used for preventing and treating thromboembolism (blood clots). They can increase the risk of major bleeding, which may be life-threatening. If someone has a major bleed the anticoagulation effects need to be reversed. Andexanet alfa aims to reverse the effects of apixaban and rivaroxaban, in case of uncontrolled or life-threatening bleeding.

There is no clinical trial evidence directly comparing andexanet alfa with existing treatments, including prothrombin complex concentrate. An indirect comparison

suggests that andexanet alfa improves survival in people with gastrointestinal bleeding or intracranial haemorrhage (ICH), but lowers survival for people with bleeds in other parts of the body. However, there are differences between the populations in the 2 studies, so the results of the indirect comparison are uncertain. There is no robust evidence that andexanet alfa reduces long-term disability in ICH.

Because of the limitations of the clinical evidence, the cost-effectiveness estimates for andexanet alfa are uncertain. They are likely to be within what NICE considers a cost-effective use of NHS resources for gastrointestinal bleeding, but not for ICH or bleeds in other parts of the body. Therefore, andexanet alfa for reversing anticoagulation is recommended for routine use only in gastrointestinal bleeding. It is recommended only in research in ICH.

2 Information about andexanet alfa

Marketing authorisation indication

2.1 Andexanet alfa (Ondexxya, Alexion) 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 The dosage schedule is available in the summary of product characteristics.

Price

2.3 The list price for andexanet alfa is £11,100 per 4-vial pack of 200 mg of powder for solution for infusion (excluding VAT, BNF online accessed March 2021). The average cost of a course of treatment at list price is £15,000 per patient.

2.4 The company has a commercial arrangement (simple discount patient access scheme). This makes andexanet alfa available to the NHS with a

discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee (section 7) considered evidence submitted by Portola Pharmaceuticals, a review of this submission by the evidence review group (ERG), NICE's technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

In March 2020 the appraisal committee decided not to recommend andexanet alfa within its marketing authorisation. In June 2020 and February 2021 the committee discussed the following issues, some of which were new issues that were not included in the first appraisal consultation document.

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 preventing 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 and an increased risk of subsequent thrombotic events when anticoagulation is interrupted. The patient experts explained that thrombotic events can have a substantial physical and psychological effect on people's lives. Treatment for a thrombosis can affect employment, family planning, travel and social life. Also, many people fear having further blood clots. Anticoagulants therefore are of benefit to people, 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 experts explained that anticoagulation treatments are accepted by people because they are lifesaving, but there are concerns about safely managing anticoagulation if a major bleed happens. If bleeding is life-threatening then anticoagulation needs to be reversed. Treatment is challenging if there is no reversal agent and relies on treating symptoms until the effects of the anticoagulant stop, in line with the normal half-life of the drug. The clinical experts explained that established clinical management often includes prothrombin complex concentrate (PCC), which is used outside of its marketing authorisation to reverse a major bleed. However, there is limited clinical evidence to support its use. 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 people and healthcare professionals.

Clinical need is increasing because of changes in clinical practice

3.3 The patient experts explained that the recently published NICE guideline on venous thromboembolic diseases recommends offering apixaban or rivaroxaban as first choice for anticoagulation, including for people with cancer-associated thrombosis. Also, NHS England's clinical guide for managing anticoagulation services has been updated for the COVID-19 pandemic. This has resulted in more people starting or switching treatment to a direct oral anticoagulant. The patient experts explained that anxiety will be high because of COVID-19 and a reversal agent not being available would increase people's concerns. The committee concluded that because more people are having direct oral anticoagulants there is an increased need for a specific reversal agent.

Most relevant population

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

3.4 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 bleeds, and a cohort of people with ICH alone. After technical engagement, the company also provided results for a cohort of people with severe gastrointestinal bleeds alone. The clinical experts explained that different types of bleeds should be considered separately because the nature of the bleeds, their treatment and outcomes vary. The clinical experts explained that most gastrointestinal bleeds can be managed using measures such as endoscopy, embolisation or surgery. The committee noted that ICH may happen within the brain tissue (intracerebral) or outside the brain (subdural or subarachnoid) and can lead to mortality and long-term disability. They differ from gastrointestinal bleeds in that they happen into a closed rigid structure, the skull, rather than into an air-containing space like the gastrointestinal tract. Treatment options are very limited for ICH, particularly if the bleed is in the brain tissue where damage happens at the time of the bleed and surgery is not usually feasible. The clinical experts explained that outcomes and risk of further bleeding after initial treatment varies depending on the location and cause of an ICH. The effect of bleeding at sites of the body other than intracranial or the gastrointestinal tract would vary considerably, depending on where the bleed happened. For example, a bleed into the eye could lead to blindness in that eye. The committee concluded that different types of bleeds should be considered separately for decision making.

Clinical evidence

The evidence on clinical events is limited to 30-day mortality

3.5 The committee noted that the 2 primary outcomes in the trial were both haematological: change in 'anti-factor Xa activity' and haemostatic efficacy. The only outcome related to clinical events was the safety end point of 30-day mortality. However, the trial excluded all patients with an expected lifespan of less than 1 month. For ICH there were additional exclusions related to larger bleeds (volume over 60 ml) and reduced consciousness (a Glasgow Coma Score below 7). Therefore, the generalisability of the 30-day mortality data from ANNEXA-4 to routine NHS practice is questionable, particularly for ICH. In their response to technical engagement, the clinical experts also questioned the definitions of haemostatic efficacy in relation to intracerebral haemorrhage. A poor outcome was defined in ANNEXA-4 as more than 35% increase in haematoma volume. The experts considered that haemostatic efficacy as defined in the trial could not be considered directly predictive of clinical outcomes. The clinical expert explained that ICH types are heterogenous and have different management strategies and outcomes. They noted that outcomes after intracerebral haemorrhage are related to bleed volume. A large bleed volume at first presentation is a poor prognostic sign, and patients with large bleeds were excluded from ANNEXA-4. At the first committee meeting, the clinical experts stated that not all bleeds increase in size. However, at the third committee meeting, 1 expert stated that an increase in bleed size would be likely for people taking an anticoagulant. The committee noted that no data on intracranial haematoma growth was available for people on anticoagulants not treated with andexanet alfa. The clinical experts agreed that it is difficult to say that an increase of less than 35% for intracerebral haemorrhage can be considered a positive outcome or good haemostatic efficacy as defined in the trial. At the second consultation, the company submitted the results of a Delphi panel survey of clinical experts that supported the assumption that limiting

haematoma expansion would improve morbidity and quality of life outcomes. The company noted that this was in line with results from a meta-analysis from Davis et al. (2006). However, the committee agreed that the Delphi panel represented opinion rather than offering robust evidence on key areas of uncertainty, and that the results should be interpreted with caution. The committee concluded that the clinical evidence available for andexanet alfa was limited to only 30-day mortality in a trial that had several potentially relevant exclusion criteria.

There is no evidence directly comparing andexanet alfa with established clinical management and the indirect comparison has limitations

3.6 Because ANNEXA-4 is a single-arm trial there is no direct evidence for the efficacy of andexanet alfa compared with other treatments, which added to the uncertainty about its benefit in clinical practice. The company used the ORANGE study for the comparison with established clinical management. ORANGE was a UK observational study in people taking anticoagulants who were admitted to hospital with a major bleed. The company used a subgroup from the ORANGE study who had had PCC, which the company considered included people with severe enough bleeds to have andexanet alpha in clinical practice. These data were used in an indirect treatment comparison with andexanet alpha. ORANGE did not exclude patients with an expected survival less than 1 month, or those with the most severe intracranial bleeds, that is an intracerebral bleed volume of more than 60 ml or a Glasgow Coma Score lower than 7, which were exclusion criteria for ANNEXA-4. The committee noted that this could affect the comparability of results for 30-day mortality, particularly in the case of intracerebral bleeds for which there were added exclusion criteria. The company explained that the proportion of patients excluded based on the 30-day 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 or the intracerebral bleed was too severe. The clinical expert

pointed out that every patient with a life-threatening gastrointestinal bleed should have been screened for inclusion unless they were on a known end-of-life pathway. The committee concluded that the 30-day mortality evidence for andexanet alfa compared with established clinical management using PCC had limitations.

The indirect treatment comparison predicts a reduced 30-day mortality with andexanet alfa compared with established clinical management including PCC, but the results are uncertain

3.7 The company did a propensity score matching analysis to compare 30-day mortality rates from ANNEXA-4 and ORANGE. The results showed a reduced 30-day mortality with andexanet alfa compared with PCC for the gastrointestinal cohort and the ICH cohort but not for the 'other major bleeds' cohort (pericardial, retroperitoneal, intraspinal and intraocular bleeds), where the 30-day mortality was higher. 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. It 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 clinical experts explained that severity and volume of bleeds are 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 uncertain. The committee also noted that for gastrointestinal bleeds, no comparative data were available on what other treatments people had in the 2 studies, particularly endoscopic therapy. The clinical experts explained that in the absence of a randomised controlled trial it was very difficult to reach any conclusion about the clinical benefit of andexanet alfa compared with established

management, including PCC. The committee considered that the propensity score matching analysis predicted a reduced 30-day mortality for the gastrointestinal cohort and the ICH cohort, but the results were uncertain.

Andexanet alfa is likely to reduce 30-day mortality for people with gastrointestinal bleeds

3.8 The committee had concerns about the effect of andexanet alfa on 30-day mortality for gastrointestinal bleeds, because the ANNEXA-4 trial excluded patients with an expected survival of less than 1 month. In its response to the first appraisal consultation document, the company submitted an analysis of in-hospital mortality results from a US multicentre real-world study of patients who had andexanet alfa within its licensed indication. The study did not exclude patients with an expected survival of less than 1 month, unlike ANNEXA-4. However, the criteria for who had treatment in the study and what other treatments the patients had were not clear. The committee noted that in-hospital mortality in the real-world study was lower than in ANNEXA-4, even though an exclusion criterion based on expected survival was not applied. The committee considered that this potentially supported the generalisability of the trial outcomes to a broader population. The committee also considered the Rockall score submitted by the company for patients with gastrointestinal bleeds in ANNEXA-4. The clinical expert explained that the Rockall score is a validated predictor of mortality. In ANNEXA-4, patients had a lower mortality rate than predicted by the Rockall score, suggesting that andexanet alfa reduces mortality. The clinical expert noted that this data increased confidence about the benefit of andexanet alfa. The committee noted that the Rockall score was not developed in an anticoagulated population. However, it considered that the Rockall score submitted by the company was broadly supportive of andexanet alfa reducing 30-day mortality in patients with gastrointestinal bleeds. Nevertheless, in the absence of any direct evidence, there were still some uncertainties around

the efficacy of andexanet alfa in gastrointestinal bleeds. This is particularly because other treatments are available and andexanet alfa itself carries a risk of thrombosis. The clinical expert noted that andexanet alfa would be best used as part of a major gastrointestinal bleed protocol, in line with its use in ANNEXA-4. The committee concluded that andexanet alfa is likely to reduce 30-day mortality for people with life-threatening or uncontrolled gastrointestinal bleeds.

The extent that andexanet alfa reduces mortality in ICH is unclear

3.9 The indirect treatment comparison predicted that andexanet alfa reduces mortality in people with ICH. The committee considered this to be plausible, but recalled its concern that the 30-day mortality data for andexanet alfa came from a trial that excluded people with a predicted life expectancy of less than 30 days, and also excluded people with the largest bleed volumes. The Delphi panel reached consensus that for intracerebral bleeds, the population that would be offered treatment should be similar to the clinical trial population. This means that some people with major intracranial bleeds would not be treated in clinical practice, based on a projected life expectancy, bleed volume and clinical judgements about their prognosis, even though the marketing authorisation did not exclude these people. However, the clinical experts emphasised the difficulty in deciding when not to use andexanet alfa in clinical practice, because treatment should be given as soon as possible, and the decision may fall to relatively inexperienced doctors. For this reason, it is likely that all people would be treated in the NHS, rather than the selected group in ANNEXA-4 which excluded people with a life expectancy under 1 month, larger bleed volumes and a Glasgow Coma Score below 7. The committee noted that, by excluding these people, a lower 30-day mortality would have been expected in ANNEXA-4 compared with the population seen in clinical practice. Therefore, the generalisability of the ANNEXA-4 results, and the size of any mortality benefit for andexanet alfa when used in routine clinical practice is unclear.

The committee concluded that it is uncertain whether or to what extent andexanet alfa would reduce mortality in ICH.

The benefit of andexanet alfa on disability after an ICH is unproven

3.10 The company assumed that andexanet alfa would reduce the severity of long-term disability in people who had had an ICH, compared with conventional treatment including PCC. This assumption had a large effect on the incremental cost-effectiveness ratio (ICER). However, the committee was concerned by comments received at consultation from the British Association of Stroke Physicians, stating that it was unclear if andexanet alfa improves 'very disabled survival in people who would otherwise die, or is improving the number of people with excellent recovery'. This uncertainty would make treatment decisions difficult and might involve discussions with relatives about whether to use andexanet alfa for ICH. The British Association of Stroke Physicians commented at consultation that it was 'difficult to estimate any effect of this treatment on quality of life or recovery as the size of any beneficial treatment effect is unclear'. Disability after ICH is assessed using the modified Rankin scale (mRS) score, 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 established management with PCC it used data from Øie et al. (2018), a 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 potentially overestimated the severity of disability and mRS scores for established management, including PCC. The committee also recalled that ANNEXA-4 excluded people with the worst prognoses. The committee noted that there was no direct evidence that people would have better mRS scores and less disability after andexanet alfa than other treatments including PCC, and that the company's assumption was based on a naive comparison of data

from ANNEXA-4 and Øie et al. The clinical experts noted that without evidence from a study, it was impossible to predict a benefit in long-term disability. One clinical expert explained that around 80% of people who survive an ICH are on the dependent scale of mRS (scores of 3 or higher) and that evidence would need to show a clear shift in mRS scores to prove an improvement in disability. Another clinical expert stated that for an effective intervention that improves mortality, all people with an ICH would be expected to have an improved level of disability on their baseline. Consensus statements from the Delphi panel also supported an improvement in long-term morbidity after treatment with andexanet alfa. However the committee recalled its earlier conclusions that any mortality benefit with andexanet alfa was uncertain and that the Delphi panel results were based on clinical assumptions. The committee concluded that a benefit from andexanet alfa on long-term disability is unproven.

Additional data collection is needed on neurological outcomes compared with established clinical management

3.11 The committee noted that the marketing authorisation for andexanet alfa was on a conditional basis, with a need for a randomised controlled trial being completed in people with ICH to further explore the benefits and risks in this indication. The committee noted that the clinical outcome in this randomised controlled trial is neurological disability measured up to 24 hours from baseline, comparing andexanet alfa with standard care. The committee recognised that data from the randomised controlled trial will provide stronger evidence of haemostatic efficacy and short-term mortality and neurological outcomes, and it has been mandated by the regulator. It acknowledged that the trial will not resolve the uncertainty about long-term morbidity or mortality. However, it will address the key clinical question of whether having had the infusion people were more likely to be alive and in a better neurological state than if they had not had it. The committee concluded that additional data collection is needed on neurological outcomes compared with established clinical management.

The evidence in 'other major bleeds' is too unreliable for decision making

3.12 The committee noted that the indirect treatment comparison results for 'other major bleeds' showed that 30-day mortality was worse with andexanet alfa than established care in combination with PCC. The committee appreciated that the analysis was done with a very small sample size, however it considered it would be unreasonable to ignore these results. The company stated that it expected andexanet alfa treatment to be beneficial in this population. However, the committee concluded that andexanet alfa reducing mortality in 'other major bleeds' had not been shown or quantified.

Cost effectiveness

The company's economic model is suitable for decision making

3.13 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 was suitable for decision making.

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

3.14 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). The analysis results for these bleeds did not favour andexanet alfa compared with established clinical management with PCC, so the company considered it was counterintuitive 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 0 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 reduced the long-term management costs and improved the long-term utilities. These assumptions were based on clinical opinion only. 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. At consultation, the company agreed that its assumptions were uncertain because of the limited evidence available. The committee concluded that the company's assumptions were not supported by evidence.

The long-term outcomes and utilities after ICH are highly uncertain

3.15 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 (see section 3.10). Differences in mRS scores affected the long-term mortality risk, costs and utilities in the model. The long-term utility value for people who had an ICH in the established clinical management arm (using PCC as a proxy) in the company's model was 0.61. This was obtained from a 3-month post-acute care utility value for people who had an 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. (2018). 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 over. 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). In its updated base case, the ERG's preferred scenario was to assume no benefit in morbidity and use the same mRS scores from the

trial. At the second consultation, the company provided scenarios with varying utility benefits for andexanet alfa compared with PCC. It presented results using baseline utility values mapped from ANNEXA-4 and results using baseline utility values from NICE's guidance on apixaban. The committee recalled that the Delphi panel consensus supported an improvement in morbidity after treatment with andexanet alfa. However, it was concerned that any increase in benefit was uncertain, as was the size of the benefit. It noted the company had included a utility benefit in its base case that was higher than any predicted by individual experts or in the consensus statement from the Delphi panel. One clinical expert advised that a specific recommendation should be made for people having surgery, in which there is an unmet need. The committee recognised that theoretically a specific reversal agent would be useful. But it agreed there was as yet no evidence that in the situation of surgery andexanet alfa would be better than established clinical management including PCC, so it could not justify a specific recommendation for this situation. 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 is likely to be cost effective compared with established clinical management including PCC in gastrointestinal bleeds

3.16 The committee considered the company's and the ERG's ICERs for the gastrointestinal cohort, which were very similar. Although associated with some uncertainty, the ICERs from the company and ERG were at a level that included a margin to accommodate uncertainty about mortality benefit. The committee concluded that the ICERs for the gastrointestinal cohort are likely to be within what NICE considers a cost-effective use of NHS resources.

Andexanet alfa has not been shown to be cost effective compared with established clinical management including PCC in ICH

3.17 The committee noted that the extent of the clinical benefit for ICH was uncertain. Therefore, the most plausible ICER for ICH was uncertain. One company scenario included the mortality benefit from the indirect comparison and the modal utility benefit predicted by the Delphi panel in their individual responses. This was within the range NICE normally considers a cost-effective use of NHS resources. However, the committee was concerned that the 30-day mortality benefit from andexanet alpha in this population is highly uncertain because ANNEXA-4 excluded both those with a life expectancy of less than 30 days, and those with the most severe intracranial bleeds, and clinical experts explained that these people would not be excluded from treatment in an emergency situation in clinical practice. The committee also had concerns about the assumption of a benefit from andexanet alfa on long-term disability. The committee further considered the ERG's updated base case and scenarios modelling different utility benefits for andexanet alfa for the ICH cohort, all of which used baseline utility values mapped from ANNEXA-4, which the committee considered was appropriate, because it came directly from the trial in question. The ICERs which all included the 30-day mortality benefit from the indirect comparison, either with no utility benefit, as preferred by the ERG, or the modal benefit as suggested by the Delphi panel, were above what NICE normally considers a cost-effective use of NHS resources. The committee recalled that the extent to which andexanet alfa reduces mortality is uncertain and that reducing the 30-day mortality benefit for andexanet alfa compared with established clinical management including PCC would further increase the ICER. Therefore, the committee was not confident that any of the ICERs for ICH were robust, and those presented may well be underestimates. It 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 ICH. However, it concluded that andexanet alfa had not been shown to be a

cost-effective use of NHS resources for ICH. Therefore it could not recommend it for routine use in the NHS, pending further research as mandated by the regulator.

Andexanet alfa has not been shown to be cost effective compared with established clinical management for 'other major bleeds'

3.18 The committee noted that the indirect treatment comparison for 'other major bleeds' showed that mortality was worse with andexanet alfa than PCC. Also, the company's assumptions on a potential morbidity benefit were not supported by evidence. Therefore, the committee considered that the ICERs for 'other major bleeds' were very uncertain and that andexanet alfa had not been shown to be a cost-effective use of NHS resources for 'other major bleeds'.

Other considerations

Equalities

3.19 The committee noted an equality concern. Some people do not accept blood products, so would be unable to have PCC as part of their standard care. The committee noted that PCC is not an established treatment for reversing anticoagulation with apixaban or rivaroxaban and is used outside of its marketing authorisation. The committee was aware that people who would not be able to have PCC would have alternative clinical management. In the ORANGE study, 39% of patients had PCC, 41% had a blood transfusion and 28% had tranexamic acid. It noted that no data had been presented that compared established clinical management outcomes with and without blood products. The committee noted that data from the ongoing randomised controlled trial might reduce this uncertainty in ICH, because it compares andexanet alfa with standard care, which is not limited to PCC. However, the committee concluded that the effectiveness of andexanet alfa in ICH and other bleeds was still highly uncertain for people who could and could not have blood products. Therefore, there was no need to alter its recommendation. During the

second consultation, stakeholders and clinical experts noted a further equality concern that there would be national variation in access to andexanet alfa if recommended only in research. However, the committee understood that any variation in access is governed by entry to a randomised controlled trial which had been mandated by the regulator. It concluded that the ability to take part in this research was not an issue that needed its recommendation to be altered.

Conclusion

Andexanet alfa is recommended for reversing anticoagulation in life-threatening or uncontrolled bleeding in gastrointestinal bleeds

3.20 Andexanet alfa is likely to reduce 30-day mortality for people with gastrointestinal bleeds. Despite the uncertainty, the committee concluded that the ICER for the gastrointestinal cohort is likely to be within what NICE considers a cost-effective use of NHS resources. Therefore, it concluded that andexanet alfa is recommended in gastrointestinal bleeds as defined in the ANNEXA-4 trial and used as part of a major gastrointestinal bleed protocol.

Andexanet alfa is recommended only in research for reversing anticoagulation in life-threatening or uncontrolled bleeding in ICH bleeds

3.21 The extent of benefits in terms of mortality and long-term disability from andexanet alfa in ICH are unclear and the committee was not confident that the cost-effectiveness results for ICH were robust. There is a need for an effective reversal agent for direct factor Xa inhibitors, such as apixaban and rivaroxaban, in people with uncontrolled or life-threatening bleeding in ICH. However, the committee was not convinced that andexanet alfa had been shown to be a cost-effective use of NHS resources in ICH. Therefore, andexanet alfa should be used only in research in ICH as part of the trial mandated by the regulator.

Andexanet alfa is not recommended for reversing anticoagulation in life-threatening or uncontrolled bleeding in 'other major bleeds'

3.22 The potential benefits of andexanet alfa in the 'other major bleeds' cohort were not supported by evidence and the cost-effectiveness estimates were very uncertain. Therefore, andexanet alfa is not recommended for reversing anticoagulation in life-threatening or uncontrolled bleeding in 'other major bleeds'.

4 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has a life-threatening or uncontrolled gastrointestinal bleed and the doctor responsible for their care thinks that andexanet alfa is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Recommendations for research

5.1 The committee noted an ongoing randomised controlled trial of the effectiveness of andexanet alfa compared with standard care in people with ICH. The main outcomes of interest are haemostatic efficacy and short-term mortality and neurological outcomes.

6 Review of guidance

6.1 The guidance on this technology will be considered for review by the guidance executive when the results are available from the randomised controlled trial of andexanet alfa compared with standard care in intracranial haemorrhage. The results are anticipated in 2025. 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
June 2020

7 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, Emma Douch
Technical leads

Rufaro Kausi, Lorna Dunning
Technical advisers

Thomas Feist
Project manager

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