# Northern (NHS) Treatment Advisory Group

## Treatment Appraisal: Decision Summary

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| **Date** | 3rd September 2019 |
| **Appraisal & Details** | The Northern (NHS) Treatment Advisory Group considered an appraisal of<br>**Andexanet alfa (Ondexxya®), Factor Xa inhibitor antidote** |
| **Recommendation** | **The Northern (NHS) Treatment Advisory Group <u>does not</u> currently recommend the use of andexanet alfa (Ondexxya®) for use in 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**<br>The group was concerned about the following:<br>• The lack of randomisation or comparison with a control group other than placebo in the ANNEXA-4 trial. There is therefore no clear evidence whether it is more effective in achieving haemostasis than conventional care alone.<br>• Overall, the evidence is limited and no comparative studies are available to determine whether 4-PCC or aPCC would still constitute a comparable effective alternative to andexanet alfa in the management of direct FXa-related major bleeding.<br>• Unlike idarucizumab (Praxbind®▼), it is not licensed when rapid reversal of anticoagulant effects is required for emergency surgery/urgent procedures<br>• Poor or no efficacy was observed in 18% of patients treated despite a reduction in anti-FXa activity<br>• Further information on potential patient numbers who may require andexanet alfa is required so that cost-effectiveness versus current treatment options can be accurately assessed.<br>• Concerns around cost-effectiveness versus current treatment options based on the current evidence, and the current NHS List price. It is not yet known whether any commercial arrangements will be offered.<br>The group noted that NICE is due to issue a technology appraisal for andexanet alfa in March 2020. |
| **Clinical evidence summary** | ANNEXA-4 trial has evaluated 352 adult patients with acute major bleeding taking apixaban (n=194, 54%), rivaroxaban (n=128, 36%), edoxaban (n=10, 3%) and enoxaparin (n=20, 6%). A 92% reduction of anti-FXa activity was observed in patients that had been treated with apixaban or rivaroxaban. Excellent or good haemostasis occurred in 204 of 249 patients (82% of efficacy population) over a 12-hour period following infusion.<br><br>Edoxaban-treated patients will be additionally analysed in the extension phase of the ANNEXA-4 study, the currently ongoing prospective phase IIIb/IV trial open-label study to evaluate haemostatic efficacy of andexanet alfa in patients receiving a FXa inhibitor with an acute major bleeding episode requiring urgent reversal of FXa anticoagulation. |

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| | The reversal activity of andexanet alfa is not permanent, unlike idaricizumab, but the effect returns to placebo levels within 2–3 h after stopping infusion. Therefore, continued clinical and laboratory monitoring might need to be considered since DOAC concentrations may recover and contribute to recurrent or continued bleeding. |
| **Safety** | From a safety population of 352 patients in ANNEXA-4, death occurred in 49 patients (14%) and a thrombotic event in 34 (10 %) within 30 days. Deaths mostly occurred of cardiovascular causes (71%). Thrombotic events reported included myocardial infarction in 7 patients, ischemic stroke in 14, DVT in 13, and pulmonary embolism in 5.<br>No serious or severe adverse drug reactions were reported in the clinical trials with healthy subjects (ANNEXA-A and –R). The most frequently observed adverse drug reactions in healthy subjects were mild or moderate infusion-related reactions (e.g. flushing, feeling hot, cough, dysgeusia, and dyspnoea) occurring within a few minutes to a few hours of the infusion. |
| **Patient Perspective** | Around 1-2% of patients treated with DOACs might experience significant or life-threatening bleeding that would require rapid reversal of anticoagulation.<br><br>Andexanet alfa is a first-in class FXa inhibitor antidote licensed in the EU for use in adult patients treated with a direct FXa inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.<br><br>Patients taking FXa inhibitors who need immediate reversal due to severe or life-threatening bleeding are currently managed using prothrombin complex concentrates (unlicensed indication), fresh frozen plasma and anti-fibrinolytic agents. |
| **Cost analysis summary** | Two dose regimens of andexanet alfa are approved: a low and a high dose regimen, requiring 5 or 9 vials respectively. The listed NHS price for 4 vials of Ondexxya® 200 mg powder for solution for infusion is £11,100, exclusive of VAT. Prices for low and high dose will therefore be £13,875 and £24,975 per patient per dose, respectively. It is not yet known whether any commercial arrangements will be offered. |
| **Financial impact**<br><br>**PbR: tariff excluded CCG commissioned drug** | The financial impact of this recommendation is expected to be nil. |