Cost-effectiveness of andexanet alfa (Ondexxya®) for adult patients treated with a direct factor Xa inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding

The NCPE has issued a recommendation regarding the cost-effectiveness of andexanet alfa (Ondexxya®). Following assessment of the submission, the NCPE recommends that andexanet alfa (Ondexxya®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the Applicant's (Alexion Pharmaceuticals UK Ltd) health technology assessment dossier on andexanet alfa (Ondexxya®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified. Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **May 2022**

Summary

In July 2021, Alexion Pharmaceuticals UK Ltd submitted a dossier which investigated the clinical effectiveness, cost effectiveness and potential budget impact of andexanet alfa for adult patients who are treated with a direct factor Xa (FXa) inhibitor (apixaban or rivaroxaban) and where reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. Andexanet alfa received a conditional Marketing Authorisation for this indication from the European Medicines Agency (EMA). It is the only licensed treatment for this indication. Reimbursement in the hospital setting is sought.

Andexanet alfa is a recombinant form of human FXa protein that has been modified to lack FXa enzymatic activity. Andexanet alfa is a specific reversal agent for FXa inhibitors. The predominant mechanism of action is the binding and sequestration of the FXa inhibitor.

Andexanet alfa is administered as either a low or high-dose regimen. The low-dose regimen is given as a bolus intravenous (IV) injection of 400mg (at a target rate of 30mg/min) followed by a 4mg/min IV infusion for 120 minutes (i.e. 480mg infusion). The low dose regimen is recommended for patients who have received 5mg or less of apixaban or 10mg or less of rivaroxaban less than 8 hours previously or at an unknown time, or patients who have received any dose of apixaban or rivaroxaban 8 hours or more ago. The high dose regimen is given as a bolus IV injection of 800mg (at a target rate of 30mg/min) followed by an 8mg/min IV infusion for 120 minutes (i.e. 960mg infusion). The high dose regimen is recommended for patients who have received more than 5mg apixaban or more than 10mg rivaroxaban less than 8 hours previously or at an unknown time, or patients who have received an unknown dose of apixaban or rivaroxaban less than 8 hours previously.

The comparator, in the Irish setting, is Octaplex® which is a prothrombin complex concentrate (PCC). Octaplex® is not licensed for this indication.

1. Comparative effectiveness of andexanet alfa

The efficacy and safety of andexanet alfa was supported by a number of trials including a phase IIIb/IV multinational, prospective, single arm study in the target population (ANNEXA-4). Patients hospitalised with acute major bleeding, were enrolled from 15 June 2015

through 31 May 2018. Between July 2016 to August 2017, only patients with intracranial haemorrhage (ICH) were enrolled in order to enrich the study with patients with ICH. Key exclusion criteria included expected survival of less than one month, and, for patients with ICH, a score of less than 7 on the Glasgow Coma Scale or an estimated hematoma volume of more than 60 cc.

The safety population included all patients who enrolled and received andexanet alfa. This comprised 352 patients, of whom 322 were taking apixaban (n=194) or rivaroxaban (n=128). Approximately half of the patients were male, 87% were white and the mean age was 77.4 years. Most had experienced either an ICH (65.3%) or a GI bleed (26.7%). The majority of patients (84.4%) received the low-dose regimen of andexanet alfa; the remaining received the high-dose regimen. The efficacy population included patients who met both criteria: (i) baseline anti-FXa activity of 75ng/ml or more and (ii) confirmed major bleeding at presentation. There were 254 patients in the efficacy population, of whom 234 were taking apixaban (n=134) or rivaroxaban (n=100). Baseline characteristics were similar to those of the safety population.

A key clinical endpoint outcome was 30-day all-cause mortality which was measured in the safety population. The two co-primary endpoints measured in the efficacy population were (i) the percent change in anti-FXa activity from baseline to the nadir between five minutes after the end of the bolus until the end of the infusion and (ii) the rate of excellent or good haemostatic efficacy in the 12 hours after andexanet alfa infusion with haemostatic efficacy assessed by an independent adjudication committee on the basis of prespecified criteria.

Of the patients in the safety population who completed the 30-day follow up (n=351), 54 (15.4%) died; 49 had died by day 30 and 5 died after day 30. In the efficacy population the median anti-FXa activity at baseline was 149.7 ng/mL for patients taking apixaban and 211.8 ng/mL for patients taking rivaroxaban. Median change from baseline to nadir in anti-FXa activity was -93.4% (95% CI -93.4 to -92.4%) for apixaban, and -92.5% (95% CI -92.4 to -90.3%) for rivaroxaban. Haemostatic efficacy, at 12 hours post-andexanet alfa infusion, was good or excellent in 204 of 249 patients (82%, 95% CI 77 to 87%). Of these, 171 were adjudicated as excellent and 33 as good. Sensitivity analysis indicated that the haemostatic

efficacy in the safety population was comparable to that in the efficacy population. The most recent analysis demonstrated that the change in anti-FXa activity (a surrogate endpoint) was not predictive for achievement of haemostatic efficacy. A specific obligation of the conditional Marketing Authorisation is that correlation of the anti-FXa activity with haemostatic efficacy be substantiated.

We note that the comparative effectiveness of andexanet alfa, on reduction in morbidity or mortality, relative to current standard-of-care, is unknown. Furthermore, patients with poor prognosis were excluded from ANNEXA-4 so it is unclear if the results could be generalised to routine clinical practice. Uncertainties around the approved posology remain as dosage recommendations are based upon data-modelling in healthy volunteers and validation has not been successful. Confirmation of approved posology is a specific obligation of the conditional Marketing Authorisation. Furthermore, changes in eligibility criteria for the low and high dose regimens during ANNEXA-4 resulted in only 40% of patients receiving the dose now licensed for their indication.

There is no direct comparative evidence with PCC. The Applicant carried out an indirect treatment comparison (ITC) of andexanet alfa and PCC by combining data from ANNEXA-4 with the ORANGE study using propensity score matching. The ORANGE study was a multicentre, 3-year prospective, observational study of patients 18 years and over, on oral anticoagulants who were admitted to hospitals in the UK for a major bleeding episode. Data on major bleeding events were collected from patient case notes between October 2013 and August 2016. Patients were followed for 30 days or until discharge or death, whichever occurred first. The Applicant considered the subgroup of patients, in ORANGE, who received either apixaban or rivaroxaban and who were treated with PCC (n=145) to be suitable for matching; these were matched to patients in the safety population of ANNEXA-4 also taking apixaban or rivaroxaban (n=322).

The outcome compared was 30-day mortality; this is the main driver of the cost-effectiveness results. The propensity score matching analyses in the full licensed population (i.e. all patients with any life-threatening or uncontrolled bleeding) suggest that andexanet alfa reduces 30-day mortality relative to PCC (RR of 0.45, 95% CI 0.30 to 0.69), with a

statistically significant reduction seen in the subgroup with ICH (RR of 0.31, 95% CI 0.20 to 0.47) but not in the subgroups with GI bleed (RR of 0.49, 95% CI 0.21 to 1.16). The Review Group had a number of concerns with the ITC, including differences in study inclusion criteria and imbalances in unmeasured prognostic factors across studies. The Review Group explored adjustments for potential confounding bias in key sensitivity analyses. A 30-day mortality benefit, vs PCC, in patients with ICH remained in all cases. The Review Group concluded that there is likely to be some reduction in ICH mortality with andexanet alfa, but that the magnitude of this reduction is uncertain. It is plausible, but not certain, that andexanet alfa reduces 30-day mortality, vs PCC, in patients with GI bleed. No conclusions could be drawn for other bleed types.

2. Safety of andexanet alfa

Safety of andexanet alfa was evaluated in a number of clinical trials (comprising 247 healthy subjects administered an FXa inhibitor) and in 352 patients in ANNEXA-4. In healthy subjects administered an FXa inhibitor, and who then received andexanet alfa, no serious or severe adverse reactions were reported. The most frequently observed adverse reactions were mild or moderate infusion-related reactions. In ANNEXA-4, one patient experienced a serious or severe infusion-related reaction.

In ANNEXA-4, 36 of 352 patients (10.3%) with 30-day safety follow-up data had thrombotic events. Ten of the 36 patients had restarted antithrombotic therapy at the time of the event, and all 36 patients had been anticoagulated for a prior history of venous thromboembolism and/or atrial fibrillation at the time of receiving andexanet alfa. The risk of thromboses and thromboembolic events will be subject to further evaluation in the post-authorisation phase.

3. Cost effectiveness of andexanet alfa

A cohort level, state-transition model was used in the submission, which consisted of a decision tree component and a Markov component. Survivors of the 30-day decision tree model entered the long-term Markov model. The model consisted of health states for survivors of each bleed type, as well as an absorbing state for death. The model had a lifetime horizon, defined as 22.3 years. Patient characteristics were generally based on the

subgroup of patients in ANNEXA-4 who were treated with apixaban or rivaroxaban (safety population, n=322). The mean age of patients entering the model was 77.7 years. The modelled population comprised patients with ICH (64.9% of population), patients with GI bleeds (25.5% of population) and patients with 'other bleeds' (9.2% of population). 'Other bleeds' were modelled as a mixture of intraocular bleeds, intraspinal bleeds, pericardial bleeds and retroperitoneal bleeds. The Review Group considered the model population to be broadly representative of the full licensed population. Cost effectiveness was also evaluated in the subgroup of patients with ICH and in the subgroup of patients with GI bleed. The main clinical outcome captured was overall survival.

In the decision tree, the 30-day mortality in the subgroup with ICH bleeds and the subgroup with GI bleeds were informed by the propensity score matching analyses. Due to the paucity of data for patients with 'other bleeds', the effects on 30-day mortality rates here were informed by assumptions, the literature and clinical opinion. The Review Group consider these model inputs to be uncertain; however, model outputs were not sensitive to these inputs.

For survivors of ICH, post-bleed modified Rankin Scale (mRS) scores predicted long-term survival and utility values in the Markov model. The Review Group note that mRS scores for individual patients may change over time, however, the model structure did not allow for this. Long-term morality for survivors of non-ICH bleeds and utility values for the different bleed types were informed by the literature. The Applicant assumed survivors of ICH in the andexanet alfa arm had more favourable mRS scores than those in the PCC arm. This assumption was removed from the NCPE adjusted base case, with one-month mRS scores from ANNEXA-4 applied in both arms. The Applicant's assumptions on additional treatment benefits in the 'other bleed' cohort were also removed owing to lack of robust evidence to support such assumptions. However, concerns with the ITC remain and the Review Group concluded that the results were too uncertain to provide a meaningful estimate of treatment effect.

Deterministic incremental cost-effectiveness ratios (ICERs) generated under the NCPE adjusted base case and the Applicant's base case assumptions are shown in Table 1 and Table 2, respectively.

Table 1 NCPE adjusted base case incremental cost-effectiveness results*

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Full licensed population					
Andexanet alfa	85,989	2.62	-	-	-
PCC	64,013	2.14	21,977	0.48	46,117
Intracranial haemorrhage subgroup					
Andexanet alfa	84,705	1.62			
PCC	57,231	1.07	27,474	0.55	50,209
Gastrointestinal bleed subgroup					
Andexanet alfa	26,610	3.91			
PCC	11,423	3.43	15,187	0.49	31,016

ICER: incremental cost-effectiveness ratio; PCC: prothrombin complex concentrate; QALY: quality-adjusted life year; SoC: standard of care

* A discount rate of 4% on costs and outcomes is applied. Figures in the table are rounded, and so calculations may not be directly replicable.

Table 2 Applicant base case incremental cost-effectiveness results*

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Full licensed population					
Andexanet alfa	90,028	2.51	-	-	-
PCC	65,842	1.56	24,186	0.95	25,378
Intracranial haemorrhage subgroup					
Andexanet alfa	84,705	1.78			
PCC	56,736	0.68	27,968	1.10	25,373
Gastrointestinal bleed subgroup					
Andexanet alfa	26,610	3.89			
PCC	11,270	3.26	15,340	0.63	24,572

ICER: incremental cost-effectiveness ratio; PCC: prothrombin complex concentrate; QALY: quality-adjusted life year;

* A discount rate of 4% on costs and outcomes is applied. Figures in the table are rounded, and so calculations may not be directly replicable.

In both the NCPE-adjusted and Applicant's base case, the probabilistic ICERs were similar to the deterministic ICERs. The probability of cost effectiveness in the full licensed population, at a willingness-to-pay threshold of €45,000 per QALY, was 48% in the NCPE adjusted base case and 92% in the Applicant base case. At a willingness-to-pay threshold of €20,000 per QALY the probability of cost effectiveness, in the full licensed population, was 6% in the NCPE adjusted base case and 34% in the Applicant base case. The probabilistic sensitivity analyses highlighted the uncertainty in relative effectiveness.

4. Budget impact of andexanet alfa

The price to wholesaler of andexanet alfa is €12,800 per pack of 4x200mg vials. The Applicant assumed that 80% of patients receive the low-dose regimen and 20% receive the high dose regimen. Applying a Framework Agreement rebate of 5.5%, the weighted cost per treatment with andexanet alfa is €21,808 per patient (€17,539 excluding VAT).

The five-year cumulative gross drug budget impact is an estimated €17.54 million (€14.1 million excluding VAT) and the five-year cumulative net budget impact is an estimated €14.65 million (€11.78 million excluding VAT). The Review Group consider that the Applicant's assumptions of eligible population numbers and market share are likely to be conservative; the budget impact estimates may be underestimated.

5. Patient organisation submissions.

No patient organisation submissions were received during the course of this assessment.

6. Conclusion

This is the only licensed treatment for the reversal of the anticoagulation effects of apixaban and rivaroxaban. The current evidence is insufficient to provide a meaningful estimate of treatment benefit over the unlicensed PCC. Following assessment of the Applicant's submission, the NCPE recommends that andexanet alfa (Ondexxya®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

** This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.*