andexanet alfa 200 mg powder for solution for infusion (Ondexxya®)

Portola Pharmaceuticals UK Ltd.

07 August 2020

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and, following review by the SMC executive, advises NHS Boards and Area Drug and Therapeutics Committees on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

andexanet alfa (Ondexxya®) is accepted for use within NHSScotland on an interim basis subject to ongoing evaluation and future reassessment.

Indication under review: 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.

In an open-label single-arm study andexanet alfa reduced anti-FXa activity and improved haemostatic efficacy in adults with major bleeds.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

Chairman
Scottish Medicines Consortium

Indication

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.[1]

Dosing Information

Patients who had apixaban ≤5mg or rivaroxaban ≤10mg, or who had apixaban >5mg or rivaroxaban >10mg more than 8 hours previously, should be given low dose andexanet alfa 400mg intravenous (IV) bolus (30mg/minute) then 480mg as an IV infusion over two hours (4mg/minute).

Patients who had apixaban >5mg or rivaroxaban >10mg within the preceding 8 hours or at an unknown time, should be given high dose andexanet alfa 800mg IV bolus (30mg/minute) then 960mg as an IV infusion over two hours (8mg/minute).

Andexanet alfa is restricted to hospital use only.[1]

Product availability date

July 2019

Andexanet alfa has a conditional marketing authorisation from the European Medicines Agency (EMA).

Summary of evidence on comparative efficacy

Andexanet alfa is a recombinant form of human FXa protein that has been modified to lack FXa enzymatic activity and anti-coagulant effects. It reverses the effects of FXa inhibitors mainly by binding and sequestration of them, thereby preventing their anticoagulant effects.[1]

An open-label ongoing phase III study (ANNEXA-4) recruited adults with acute major bleeding within 18 hours of receiving a FXa inhibitor (apixaban, rivaroxaban, edoxaban or ≥1mg/kg enoxaparin). Acute major bleeding was defined as potentially life-threatening; associated with haemoglobin (Hb) reduction of ≥2g/dL, Hb ≤8g/dL if no baseline available; or was in a critical area or organ. Initially all apixaban or rivaroxaban patients were given low-dose andexanet alfa 400mg IV bolus over 15 minutes followed by a 2-hour IV infusion of 480mg, except those who had rivaroxaban within the preceding 7 hours (or FXa inhibitor at an unknown time), as these patients received high-dose andexanet alfa 800mg IV bolus over 30 minutes then a 2-hour infusion of 960mg. After a protocol amendment the licensed andexanet alfa regimens specified in the summary of product characteristics (SPC) were used. The co-primary outcomes were percent change from baseline to nadir in anti-FXa activity and percentage of patients with excellent or good haemostatic efficacy at 12 hours after andexanet alfa, assessed by an independent adjudication committee using pre-specified criteria. These outcomes were assessed in the efficacy population, which comprised patients who retrospectively met both of these criteria: baseline

anti-FXa activity of at least 75ng/mL (or at least 0.25 IU/mL for patients receiving enoxaparin) and confirmed major bleeding at presentation, as determined by the adjudication committee.[2,3]

In the efficacy population, among the 134 patients who were receiving apixaban, median anti-factor Xa activity reduced from 149.7 ng/mL at baseline to 11.1 ng/mL at the end of the bolus administration, a 92% reduction (95% confidence interval [CI]: 91 to 93). Among the 100 patients who were receiving rivaroxaban, median anti-factor Xa activity fell from 211.8 ng/mL at baseline to 14.2 ng/mL at the end of the bolus administration, a 92% reduction (95% CI: 88 to 94). Of the 254 patients in the efficacy analysis, 249 were evaluable for haemostatic efficacy, and 82% (204) (95% CI: 77 to 87) had excellent or good haemostatic efficacy at 12 hours, with 69% having excellent haemostatic efficacy. In the subgroups of patients receiving apixaban and rivaroxaban, 83% (109/131) and 80% (79/99), respectively, achieved excellent or good haemostasis.[3]

The secondary objective of the study was to assess the relationship between the two primary endpoints. The EMA noted that this was challenging and concluded that a correlation of anti-FXa activity and haemostatic efficacy had not been established.[2]

Change in modified Rankin Scale (mRS) at 30 days follow-up in patients with intracranial haemorrhage (ICH) was an exploratory efficacy outcome in the ANNEXA-4 study and was used to calculate long-term mortality, quality of life and health state costs in the economic model. Results are marked as academic in confidence and cannot be reported here.

Two similar double-blind, randomised phase III studies (ANNEXA-A and ANNEXA-R) recruited healthy older adults (50 to 75 years). Patients in ANNEXA-A were given apixaban 5mg orally twice daily for 3.5 days. Patients in ANNEXA-R were given rivaroxaban 20mg orally once daily for 4 days. At 4 hours after their last dose of FXa inhibitor patients were given randomly assigned andexanet alfa or placebo in a 3:1 ratio and a 2:1 ratio in the respective studies. The initial cohorts received a single IV bolus of andexanet alfa 400mg in ANNEXA-A (n=24) or placebo (n=9) and andexanet alfa 800mg (n=27) or placebo (n=14) in ANNEXA-R. The second cohorts received these initial bolus doses plus 2-hour IV infusions of 480mg (n=23) in ANNEXA-A and 960mg (n=26) in ANNEXA-R or placebo (n=8 and n=13) in the respective studies. The primary outcome in both studies was percent change in anti-FXa activity from baseline to nadir. This was assessed in the modified intention-to-treat population, which comprised randomised patients who received study drug and had baseline and at least one post-baseline measurement of anti-FXa activity. In the initial cohorts andexanet alfa, compared with placebo, significantly reduced anti-FXa activity within 2 to 5 minutes after the bolus injection by 94% versus 21% in ANNEXA-A and by 92% versus 18% in ANNEXA-R. These effects diminished over the following 2 hours. Similarly, in the second cohorts andexanet alfa, compared with placebo, significantly reduced anti-FXa activity by 92% versus 33% in ANNEXA-A and by 97% versus 45% in ANNEXA-R. These effects were maintained during the 2-hour infusions, then diminished over the following 2 hours.[4]

The submitting company presented an unanchored matching adjusted indirect comparison (MAIC) with propensity score matching comparing andexanet alfa (data from ANNEXA-4 study)[2,3] with prothrombin complex concentrate (PCC) (data from ORANGE study)[5] for 30-day mortality rate in all patients and subgroups with ICH, severe gastrointestinal (GI) bleeds and other bleeds. This suggested that andexanet alfa was associated with a lower 30-day mortality rate than PCC in the

whole study population and subgroups with ICH and severe GI. Published results are detailed in **Error! Reference source not found..** [18]

Table 1. Adjusted 30-day mortality rate [18]

Cohort	Adjusted 30-day mortality following NOAC related life-threatening bleed		
	andexanet alfa mortality (%)	PCC mortality (%)	Absolute % point reduction (95% CI)
Whole cohort (n= 408)	14.60	34.09	19.5 (8.7 to 30.3)
ICH (n=258)	15.31	48.94	33.6 (18.0 to 49.2)
Severe GI bleed (n=110)	12.20	25.00	12.8 (-5.6 to 31.2)
Other major bleeds (non-ICH/GI) (n=39)	16.13	12.50	3.6 (-34.7 to 27.4)
ICH = intracranial haemorrhage; GI = gastrointestinal; PCC = prothrombin complex concentrate; CI = confidence interval			

Other data were also assessed but remain confidential.*.

Summary of evidence on comparative safety

In the ANNEXA-A and ANNEXA-R studies in healthy subjects no serious or severe adverse reactions were reported. The most frequently observed adverse reactions were mild or moderate infusion-related reactions comprising symptoms such as flushing, feeling hot, cough, dysgeusia and dyspnoea occurring within a few minutes to a few hours of the infusion.[1]

Within the safety population of ANNEXA-4 84% (297/352) of patients received low dose andexanet alfa and 16% (55/352) received the high dose regimen.[3]

The proportion of patients who had a thromboembolic event within 30 days following administration of andexanet alfa was 10% (34/352), which included seven with myocardial infarction, 14 with ischaemic (or uncertain classification) stroke, one with transient ischaemic attack, 13 with deep vein thrombosis and five with pulmonary embolus. Anti-coagulant and anti-platelets were stopped at study enrolment. Within 30 days of andexanet alfa 220 patients (62% of the safety population) restarted anticoagulation (oral or parenteral), with 100 patients (28%) restarting oral anti-coagulation. Within the 220 patients who restarted anticoagulation eight patients had a thrombotic event after restarting anti-coagulation, with no thrombotic events in the subgroup who restarted oral anti-coagulation.[3]

The SPC notes that reversal of FXa inhibitor therapy exposes patients to the thrombotic risk of their underlying disease. In addition, an independent pro-thrombotic effect of andexanet alfa cannot be ruled out.[1]

Other data were also assessed but remain confidential.*

Patients receiving direct FXa inhibitors who experience bleeding have their anticoagulant administration delayed or treatment discontinued as appropriate. They may be given activated charcoal to reduce absorption in the case of overdose. Management should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (for example, for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets. If bleeding cannot be controlled by these measures, a specific pro-coagulant reversal agent may be considered, such as PCC or recombinant factor VIIa (r-FVIIa).[2] Clinical experts consulted by SMC noted that PCC and other non-specific haemostatic agents are currently used, off-label, in the management of uncontrolled bleeding in patients on FXa inhibitors.

The key strengths and uncertainties of the clinical evidence are summarised below:

Key strengths
- Two double-blind phase III studies, ANNEXA-A and ANNEXA-R, demonstrated swift and significant reductions in anti-FXa activity with andexanet alfa compared with placebo in healthy older adults who had received a few days of apixaban or rivaroxaban, respectively. An open-label single-arm phase III study (ANNEXA-4) in adults with major bleeds also demonstrated swift reduction in anti-FXa activity with andexanet alfa and improvement in haemostatic efficacy.[2-4]

Key uncertainties
- The EMA noted that in the ANNEXA-4 study it was not possible to establish a relationship between the biomarker, anti-FXa activity, and haemostatic efficacy.[2]

- Another key issue noted by the EMA was the increased risk of thromboembolic events, with high-dose andexanet, previous anticoagulant and previous lower-dose of anticoagulant identified as potential risk factors. Safety evaluation pointed to significantly increased mortality and risk of thrombosis in patients >75 years of age. However, it is not clear if co-morbidities, risks of previous anti-coagulant treatment or andexanet alfa account for this finding.[2]

- Changes in the manufacturing process were made throughout the clinical development of andexanet alfa. The EMA highlighted lack of established comparability of Generation 1 and Generation 2 andexanet alfa, which was a concern as efficacy studies in healthy volunteers had used Generation 1.[2]

- The criteria for dosing changed during the ANNEXA-4 study, with only 40% of patients having the licensed regimen. This limits the evidence for the licensed dose. As the majority of patients, 70%, received low-dose andexanet alfa, there are limited data for high-dose andexanet alfa. The study excluded patients undergoing surgery.[2]

- ANNEXA-4 excluded some patients with a poorer prognosis, such as: ICH and a poor Glasgow Coma Score (GCS) score (<7); intracerebral haematoma with volume >60cc (or >30cc, prior to protocol amendment in first month of recruitment); life expectancy <1 month (or <2 months from causes other than bleeding prior to the protocol amendment in the first month of recruitment). This limits the application of study results to these patient groups.[2,3]

- There was no direct comparative evidence with current standard of care, creating uncertainty around the relative haemostatic efficacy and safety (in particular thrombotic events).

- There were weaknesses in the MAIC analysis limiting the validity of its conclusion. ANNEXA-4[2,3] was enriched with patients who had ICH, but it excluded some patients with a poorer prognosis. In contrast, ORANGE did not exclude any patients. Propensity score matching did not fully match all the differences between the study populations and did not include measures of bleeding severity of volume (due to lack of data collected). The analyses were unanchored and unobserved prognostic factors or effect modifiers may not have been included in the matching. The sample size of some cohorts was small. The MAIC only compared 30-day mortality. It did not include clinical outcomes, such as rate of thrombotic events or other adverse events, or measures of haemostatic efficacy.

Andexanet alfa has an EMA conditional marketing authorisation. To further confirm the efficacy, safety and posology of andexanet alfa, the company has a specific obligation to submit the full results of ANNEXA-4 and a pharmacokinetic study comparing Generation 1 and Generation 2 andexanet alfa. In addition, the company must submit the results of study 18-513, a global randomised controlled clinical study to investigate the use of andexanet alfa versus standard of care in patients with ICH taking apixaban, rivaroxaban, or edoxaban. Results are due June 2023[2] and are likely to address some of the key uncertainties in the clinical evidence.

SMC will consider an updated submission from the company after specific obligations and conditions of the licence have been removed. In the interim, as part of an approach to minimise delay in patient access as a result of the COVID-19 pandemic, andexanet alfa is accepted for use in NHSScotland subject to ongoing evaluation and future reassessment.

The introduction of andexanet alfa would provide the first medicine licensed for reversal of anticoagulation with the FXa inhibitors, apixaban and rivaroxaban, in adult patients who have life-threatening or uncontrolled bleeding. Clinical experts consulted by SMC consider that andexanet alfa is a therapeutic advance, appropriate for use in a small number of patients.

Summary of comparative health economic evidence

The submitting company presented a single de novo economic model to assess the cost-effectiveness of andexanet alfa compared with standard of care (PCC). The patient population considered by the submitting company for the cost-effectiveness analysis is based on the conditional marketing authorisation, which includes patients who received a direct FXa inhibitor

(apixaban or rivaroxaban) and are experiencing a life-threatening or uncontrolled bleeding event, which consequently requires anticoagulant reversal. The cost effectiveness of andexanet alfa was estimated in two cohorts including the whole cohort (all patients with either an ICH, GI bleed, or 'other major bleed') and the ICH plus GI cohort. In the whole cohort, the submitting company assumed 'other major bleeds' included intraocular bleeds, intraspinal bleeds, pericardial bleeds and retroperitoneal bleeds.

The economic analysis was based on a model comprising a short-term decision tree followed by a long-term Markov model. The decision tree estimates costs and QALYs for the first 30 days of the bleeding event; defined as either an ICH, severe GI bleed, intraocular bleed, intraspinal bleed, pericardial bleed or retroperitoneal bleed. Patients who survive transition to their respective survivor health states in the Markov model and remain in their respective health states until death. A cycle length of 1 month was implemented in the Markov model with a half cycle correction applied. The submitting company did not include treatment-related adverse events, or thrombotic events in the economic analysis.

The submitting company deemed the ANNEXA-4 study as the most representative population and based patient demographics at baseline in the model on the safety population in the ANNEXA-4 study. The submitting company also used the ANNEXA-4 study to inform the proportion of patients who suffer ICH and severe GI bleeding events in the decision-tree. No data were available from ANNEXA-4 detailing the breakdown of intraocular, intraspinal, pericardial and retroperitoneal bleeding events. Therefore, the ANNEXA-4 study and ORANGE study[5] (the key source used to inform the comparator) were used to estimate the distribution of patients across these 'other major bleeds'. For the ICH plus GI bleed cohort, the proportions were re-weighted to exclude 'other major bleeds'.

In the decision tree, the clinical efficacy of andexanet alfa and standard of care is given by the 30-day mortality rate following a life-threatening or uncontrolled bleeding event. In the absence of direct comparative evidence, an unanchored MAIC using propensity score matching was conducted to assess the comparative efficacy of andexanet alfa (using data from ANNEXA-4) and PCC (using data from ORANGE).[3,5] The proportions of patients in the decision tree who died due to ICH or GI bleeds were taken from the MAIC results. However, due to the paucity of data in ANNEXA-4 for 'other major bleeds', the submitting company replaced the MAIC results with assumptions, based on clinical expert opinion. Mortality for intraocular and intraspinal bleeds was set to 0% in both treatment arms based on UK clinical expert opinion. It was also assumed that there would a 25% reduction in the andexanet alfa 30-day mortality for pericardial bleeds and retroperitoneal bleeds compared to standard of care.

In the long-term Markov model, the benefits of andexanet alfa included a reduction in morbidity experienced by patients receiving andexanet alfa relative to standard of care. For patients surviving an intraocular bleed or intraspinal bleed, this is a reduction in complications (blindness and paralysis, respectively), based on clinical expert opinion. For patients surviving an ICH, this is a reduction in the modified Rankin Scale (mRS), taken from ANNEXA-4 for andexanet alfa patients and Øie et al. 2018[7] for standard of care patients (mRS distributions were not recorded in the

ORANGE study). In the economic model, mRS results feed into the long-term ICH mortality, quality of life and cost calculations.

Furthermore, the submitting company assumed that patients who survive an uncontrolled or life-threatening bleed will have a decreased life expectancy compared to the general population. Long-term mortality for ICH survivors is based on the mRS distribution of patients from ANNEXA-4 for andexanet alfa patients and Øie et al. 2018[7] for standard care patients. The submitting company fitted parametric distributions to the Kaplan Meier (KM) overall survival data reported in Huybrechts et al. 2008[8] for each mRS category and produced a weighted survival curve for each treatment arm. As for non-ICH survivors, the submitting company adjusted all-cause general population mortality using evidence in patients with atrial fibrillation (Friberg et al. 2007)[9].

No quality of life data were collected in either the ANNEXA-4 or ORANGE studies. Utility values implemented in the model are based on EQ-5D data or time trade off (TTO) data identified in the literature. Values for acute events in the decision tree part of the model (1 month) were estimated to quantify the short-term impact of a life-threatening or uncontrolled bleeding event. In the long-term model, the submitting company assumed that survivors of GI, retroperitoneal and pericardial bleeds will not suffer long-term morbidity and as such utility values will return to baseline levels (0.73). For survivors of intraspinal bleeds, the submitting company assumed that 50% will suffer from paralysis and incur a utility decrement, and 25% of intraocular bleed survivors will have monocular blindness and incur a utility decrement. The submitting company also assumed a 25% reduction in paralysis and monocular blindness for intraspinal and intraocular bleed survivors who received andexanet alfa, aligned with the assumption on mortality benefit. Long-term HRQoL for ICH survivors is based on the mRS distribution of patients from ANNEXA-4 for andexanet alfa patients and Øie et al. 2018[7] for standard care patients. The submitting company obtained utility values by mRS from Fletcher et al. 2015[10] and calculated weighted utilities for andexanet alfa (0.53) and standard care (0.42). The submitting company then applied the difference in utility (0.11) to the TA341[11] baseline assumed for standard of care (0.61) to obtain the utility value for andexanet alfa. Thus, the health state utility values used in the economic model for ICH survivors in the standard of care arm and andexanet alfa arm are 0.61 and 0.72, respectively.

The costs considered in the economic model consist of: intervention and comparator acquisition and administration costs; acute bleed management costs; long-term bleed management costs; and, re-initiation of FXa inhibitor costs. Long-term bleed management costs were incurred by ICH survivors and the proportion of patients affected by paralysis and blindness in the intraspinal bleed survivor and intraocular bleed survivor states, respectively. In line with the assumptions regarding quality of life for intraocular and intraspinal bleeds, the proportion of patients experiencing paralysis and blindness was reduced by 25% for patients receiving andexanet alfa. Long-term costs for ICH survivors were based on the mRS distribution of patients from ANNEXA-4 for andexanet alfa patients and Øie et al. 2018[7] for standard of care patients mapped to the disability categories reported in Luengo-Fernandez et al. 2013[12] to calculate weighted hospital costs and in Persson et al. 2017[13] to calculate weighted rehabilitation costs.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price of andexanet alfa.

SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS figures can be presented.

The deterministic base case results presented by the submitting company, at list prices are presented in table 2. The key scenario analysis on relative reductions carried out by the submitting company for the whole cohort are presented in 3.

Table 2. Base case results at list price

Therapy	Incremental costs at list prices	ICER at list prices
Whole cohort		
Andexanet alfa versus SoC	£12,077	£11,196
ICH and severe GI cohort		
Andexanet alfa versus SoC	£19,522	£17,356
GI, gastrointestinal; ICER, incremental cost-effectiveness ratio; ICH, intracranial haemorrhage; QALY, quality-adjusted life year; SoC, standard of care		

From the submitting company's one-way sensitivity analysis, results for the whole cohort were most sensitive to the relative reductions in paralysis and blindness for andexanet alfa compared to standard care, and the long-term bleed management cost for intraspinal survivors in the standard care arm. The ICERs increased to a maximum of £20,298 at list prices in the one way analyses. In the ICH plus GI cohort, the main drivers of the model include the long-term cost of ICH care and utility of ICH survivors. The ICERs increased to a maximum of £22,117 at list prices in the ICH plus GI cohort.

Table 3. Results of key scenario analyses for the whole cohort

Parameter	Base case	Scenario	ICER at list prices
Base case			£11,196
Threshold benefit for intraspinal and intraocular bleeds	25%	0%	£17,864
		12.5%	£11,234
		37.5%	£7,896
		50%	£4,616

The submitting company provided three additional subgroup analyses on request. A subgroup for 'other major bleeds' was requested because the impact of alternative modelling assumptions for 'other major bleeds' in the whole cohort is minimised by the large proportion of ICH and GI bleeds which may lead to inappropriate conclusions for 'other major bleeds'. To determine if the combined ICH plus GI cohort is driven by benefits in the ICH cohort or GI cohort, these were

subgroups were also requested. The results obtained from these additional subgroups are given in table 4.

Table 4. Results of additional cohorts provided by the submitting company

Cohort	Treatment	Incremental costs (£) at list prices	ICER (£/ QALY) at list prices
ICH only cohort	Andexanet alfa	20,950	17,102
GI only cohort	Andexanet alfa	14,960	19,427
Other bleeds cohort	Andexanet alfa	-94,282	Dominant
GI, gastrointestinal; ICER, incremental cost-effectiveness ratio; ICH, intracranial haemorrhage; ; QALY, quality-adjusted life year; SoC, standard of care			

One key scenario provided by the company assumed equal efficacy in neurological outcomes for each treatment i.e. mRS distributions from ANNEXA-4 were used to inform both treatment arms (table 5).

Table 5. Additional scenario provided by the submitting company – ANNEXA-4 mRS distributions applied to both treatment arms

Cohort	Treatment	ICER at list prices
Whole cohort	Andexanet alfa	16,446
ICH + GI cohort	Andexanet alfa	25,736
ICH only cohort	Andexanet alfa	28,098
GI, gastrointestinal; ICER, incremental cost-effectiveness ratio; ICH, intracranial haemorrhage; QALY, quality-adjusted life year; SoC, standard of care		

Table 6 provides the results from a combined scenario that removes treatment benefits in 'other major bleeds' and treatment benefits from mRS distributions in ICH survivors. This showed that the cost-effectiveness results for the other bleeds group was particularly volatile as it became dominated by standard of care.

Table 6. Additional scenario provided by the submitting company – combined scenario

Cohort	Treatment	ICER (£/QALY) at list prices
Whole cohort [a,b,c]	Andexanet alfa	26,654
Other bleeds only [a,b]	Andexanet alfa	Dominated

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

[a] 0% relative reduction in 30-day mortality following pericardial and retroperitoneal bleeds between andexanet alfa and SoC

[b] 0% relative reduction in paralysis and monocular blindness following intraspinal and intraocular bleeds between andexanet alfa and SoC

[c] mRS values from ANNEXA-4 applied to both treatment arms

Limitations

The economic analysis was associated with a number of weaknesses and uncertainties:

- Very limited evidence exists for the efficacy of andexanet alfa in the treatment of patients with intraspinal, intraocular, pericardial and retroperitoneal bleeding. Hence, the clinical effectiveness of andexanet alfa in these patient groups is largely based on assumptions and consultation with UK clinicians. The submitting company assumed that treatment with andexanet alfa would reduce the risk of 30-day mortality by 25% for pericardial and retroperitoneal bleeds compared with standard of care, and reduce the instances of paralysis in intraspinal survivors and monocular blindness in intraocular survivors by 25% compared with standard of care. In the absence of any evidence to substantiate the 25% reductions associated with andexanet alfa, a scenario of no relative reduction is a more appropriate, if, conservative scenario.

- The submitting company included the most severe other life-threatening or uncontrolled bleeds in the economic analysis (intraocular, intraspinal, pericardial and retroperitoneal bleeds). However, a wider range of 'other major bleeds' was seen in ANNEXA-4. Therefore, if other less severe life-threatening or uncontrolled bleeds were to receive andexanet alfa treatment in UK clinical practice, the cost effectiveness of andexanet alfa compared to standard of care is likely to be overestimated.

- ICH bleeds, GI bleeds and 'other major bleeds' (including intraocular bleeds, intraspinal bleeds, pericardial bleeds and retroperitoneal bleeds) are easily identifiable as clinically distinct subgroups and should be considered separately because their treatment and outcomes vary. Additionally, the impact of alternative modelling assumptions for other major bleeds in the whole cohort is minimised by the large proportion of ICH and GI bleeds which may lead to inappropriate recommendations for treating patients with 'other major bleeds'. As shown by the figures in table 6 the cost-effectiveness results for the 'other major bleeds' group is particularly volatile.

- The use of the mRS for estimating the impact of andexanet alfa on ICH survivors has been a central issue for the cost-effectiveness analysis as it affects the estimation of costs, quality of life and mortality. The study used to inform the severity of ICH survivors in the standard care arm (Øie *et al*. 2018)[7] represents patients with a severe subtype of ICH (intracerebral

haemorrhage) and therefore overestimates the severity of the mRS in the standard care arm.

- An additional and related area of concern with ICH survivors is the submitting company's estimation of long-term utility values. The submitting company initially performed calculations using published utility and mRS data to calculate weighted utilities for andexanet alfa and standard of care, which only serve the purpose of estimating the potential utility increment associated with andexanet alfa. The utility increment is applied to another utility value (0.61) obtained from TA341[11], which is used to represent standard of care. The final calculated utility for andexanet alfa, applying the utility increment to the NICE TA341 utility value is 0.72, which is 0.01 less than the UK general population norms for people aged 75 years and above. The weighted utility values for standard of care and andexanet alfa (0.42 and 0.53, respectively) are more appropriate to use in the model as the source utilities are based on a population closer in age to the ANNEXA-4 population (mean age of 77 years) and it eliminates the introduction of another utility from a different source, resulting in an unnecessary calculation step. The submitting company provided additional analysis using these values from Fletcher et al in ICH survivors and this resulted in ICERs of £ £13,710, £21,326 and £22,010 respectively at list prices.

The above uncertainties should be viewed in the context of a medicine with a conditional marketing authorisation accepted on an interim basis (as noted in the clinical effectiveness section above) and will be subject to future reassessment by SMC in due course.

Other data were also assessed but remain confidential.

Summary of patient and carer involvement

Patient Group Submissions were not required as this submission was assessed through an amended process used during the COVID-19 pandemic.

Additional information: guidelines and protocols

In 2016 the British Committee for Standards in Haematology (BCSH) published a guideline on peri-operative management of anticoagulant and antiplatelet therapy. This notes that there are few data on the management of emergency surgery in patients receiving direct oral anti-coagulants. When possible, surgery should be delayed to allow the plasma concentration of the drug to fall. The guideline recommends that PCC should not be routinely used in patients on direct oral anti-coagulants prior to emergency surgery. Tranexamic acid is likely to reduce bleeding in patients who have a residual anticoagulant effect. Drugs and colloids that impair the haemostatic mechanism should be avoided in the peri-surgical management of patients receiving direct oral anti-coagulants. Andexanet alfa, when available, should be used to reverse apixaban or rivaroxaban prior to emergency invasive procedures and surgery where the bleeding risk is considered significant.[14]

In 2012 the British Committee for Standards in Haematology (BCSH) published a guideline on the management of bleeding in patients on antithrombotic agents. This notes that there is no specific antidote for rivaroxaban. Management of bleeding should be through cessation of treatment and general haemostatic measures. In situations with ongoing life-threatening bleeding, PCC, APCC and r-FVIIa should be considered.[15]

In 2013 the Scottish Intercollegiate Guidelines Network (SIGN) updated publication number 129: Antithrombotics, indications and management. This notes that in healthy subjects dosed with rivaroxaban, 4-factor PCC effectively reversed the anticoagulant effect and it could be considered in emergency situations in patients.[16]

In 2019 the British Society for Gastroenterology published a guideline on diagnosis and management of acute lower gastrointestinal bleeding. This recommends interrupting direct oral anticoagulant therapy at presentation and considering treatment with inhibitors such as idarucizumab or andexanet alfa for life-threatening haemorrhage on direct oral anticoagulants. It suggests restarting direct oral anticoagulant drug treatment at a maximum of 7 days after haemorrhage.[17]

Additional information: comparators

PCC and other non-specific haemostatic agents.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost course (£)
Andexanet alfa	**400mg IV bolus then 480mg IV infusion or 800mg IV bolus then 960mg IV infusion**	**13,875 to 24,975**

Costs from BNF online on 30 March 2020. Costs calculated using the full cost of vials assuming wastage. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated that the population eligible for treatment would be 572 patients in year 1, rising to 1,788 patients in year 5 to which confidential estimates of treatment uptake were applied.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

References

1. Portola Pharmaceuticals. Andexanet alfa 200 mg powder for solution for infusion (Ondexxya®) summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk/emc/. Last updated 21 February 2020.

2. European Medicines Agency. European public assessment report: andexanet alfa (Ondexxya®), Committee for Medicinal Products for Human Use (CHMP) Assessment report, EMA/347546/2019, 28 February 2019.

3. Connolly SJ, Crowther M, Eikelboom JW, et al. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. N Engl J Med 2019; 380: 1326–1335.

4. Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity. N Engl J Med 2015; 373: 2413–2424.

5. Green L, Tan J, Morris JK, et al. A three-year prospective study of the presentation and clinical outcomes of major bleeding episodes associated with oral anticoagulant use in the UK (Orange study). Haematologica Haematologica 2018; 103(4): 738-45.

6. Portola Pharmaceuticals. Clinical study report for Study Number 14-505, 17 June 2019.

7. Øie LR, Madsbu MA, Solheim O et al. Functional outcome and survival following spontaneous intracerebral hemorrhage: A retrospective population-based study. Brain Behav 2018; 8: e01113.

8. Huybrechts KF, Caro JJ, Xenakis JJ, Vemmos KN. The prognostic value of the modified Rankin Scale score for long-term survival after first-ever stroke. Results from the Athens Stroke Registry. Cerebrovasc Dis 2008; 26: 381-7.

9. Friberg L, Hammar N, Pettersson H, Rosenqvist M. Increased mortality in paroxysmal atrial fibrillation: report from the Stockholm Cohort-Study of Atrial Fibrillation (SCAF). Eur Heart J 2007; 28: 2346-53.

10. Fletcher JJ, Kotagal V, Mammoser A, et al. Cost-effectiveness of transfers to centers with neurological intensive care units after intracerebral hemorrhage. Stroke 2015; 46: 58-64

11. National Institute for Health and Care Excellence (NICE). Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism: technology appraisal guidance [TA341], 2015. Available from: https://www.nice.org.uk/guidance/ta341. Date accessed: April 2020.

12. Luengo-Fernandez R, Yiin GS, Gray AM, Rothwell PM. Population-based study of acute- and long-term care costs after stroke in patients with AF. Int J Stroke 2013; 8: 308-14.

13. Persson J, Aronsson M, Holmegaard L, Redfors P, Stenlöf K, Jood K, et al. Long-term QALY-weights among spouses of dependent and independent midlife stroke survivors. Qual Life Res. 262017. p. 3059-68.

14. British Committee for Standards in Haematology (BCSH). Guideline on peri-operative management of anticoagulant and antiplatelet therapy. Br J Haematol 2016; 175: 602–613.

15. British Committee for Standards in Haematology (BCSH). Guideline on the management of bleeding in patients on antithrombotic agents. Br J Haematol 2012; 160: 35–46.

16. Scottish Intercollegiate Guidelines Network (SIGN). Publication number 129: Antithrombotics, indications and management, updated June 2013.

17. Oakland K, Chadwick G, East JE et al. Diagnosis and management of acute lower gastrointestinal bleeding: guidelines from the British Society of Gastroenterology. Gut 2019: 68: 776–789.

18. Cohen A, Lewis M, Connor A et al. 30-day mortality following andexanet alfa in ANNEXA-4 compared with prothrombin complex concentrate (PCC) therapy in the ORANGE study for life threatening non-vitamin K oral anticoagulant (NOAC) related bleeding. Journal of American College of Cardiology 2020; 75:11 [presentation number: 1213-209]

This assessment is based on data submitted by the applicant company up to and including 16 July 2020.

Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.