NICE National Institute for Health and Care Excellence

Andexanet alfa for reversing anticoagulation

Lead team presentation

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March 2020

Key clinical issues

1. Who would be considered for andexanet alfa in clinical practice, where factor X levels will not be available?
2. ANNEXA-4 had no direct clinical outcomes apart from the safety endpoint of 30-day mortality, although people expected to die within 30 days, or severely affected by ICH were excluded from the trial. How does this affect the interpretation of the potential benefits in clinical practice, and the comparison with the ORANGE observational study which had no restrictions?
3. The trial recruitment was adjusted to include more people with ICH. A primary outcome was efficacy of haemostasis, for example 'good' haemostasis was defined as an increase in volume of intracerebral bleed of less than 35%. Does this correlate with clinical experience and predictive of improved outcomes?
4. Is it appropriate to amalgamate different types of bleed into a single 'whole cohort' given that there are potentially different therapeutic approaches for different sites of bleeding?

[redacted]

Andexanet alfa

Conditional Marketing authorisation	Indicated for adults with a direct factor Xa (FXa) inhibitor (apixaban or rivaroxaban) when reversal is needed due to life-threatening or uncontrolled bleeding
Dosage and administration	2 possible doses based on type and timing of last dose of FXa inhibitor: Low dose: 400 mg initial IV bolus, then 4mg/min IV infusion -120 mins High dose: 800 mg initial IV bolus, then 8mg/min IV infusion -120 mins
Mechanism of action	Specific reversal agent for FXa inhibitors – Predominant action is binding and sequestration of the FXa inhibitor
Average list price per course of treatment	£15,081 based on the proportion receiving each low and high dose with wastage

Disease background

- **Anticoagulant therapy** is used for **preventing** and **treating thromboembolism** across various clinical indications including treatment and secondary prevention of deep vein thrombosis (**DVT**), pulmonary embolism (**PE**), after **orthopaedic surgery** as well as **prevention of stroke and systemic embolism** in people with non-valvular atrial fibrillation
- Direct oral anticoagulants (**DOACs**) specifically **inhibit** components of the coagulation cascade such as **factor Xa** (apixaban, rivaroxaban, edoxaban) or thrombin (dabigatran)
- **Major bleeding events** are a serious risk associated with anticoagulants and **antidotes** are needed to reverse anticoagulation in case of **life-threatening bleeding**
- Major bleeding can occur spontaneously or as a result of trauma, complications of invasive procedures or other conditions

Risk and burden of major bleeding events

- The International Society on Thrombosis and Haemostasis (ISTH) published a **definition of major bleeding** in non-surgical studies. Major bleed is defined as any of the following:
  - **Haemoglobin drop** more than 2g/dL
  - Bleeding is **expected to be fatal and/or symptomatic bleeding** that is intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular or retroperitoneal
  - **Transfusion**: More than 2 units of blood or packed red blood cells
- People who experience a major bleeding event are at an **increased risk of death** and increased risk of developing **subsequent thrombotic events** when anticoagulation interrupted
- The risk of death is especially high in people with **intracranial haemorrhage (ICH)** where 30-day mortality rates after major bleeding are reported to be **up to 45%**
- ICH may result in **disability**, which can be assessed by the modified Rankin scale (mRS)
- **Gastrointestinal (GI)** bleeding is also associated with increased mortality and morbidity

Treatment pathway

Major bleeding in patients on DOACs

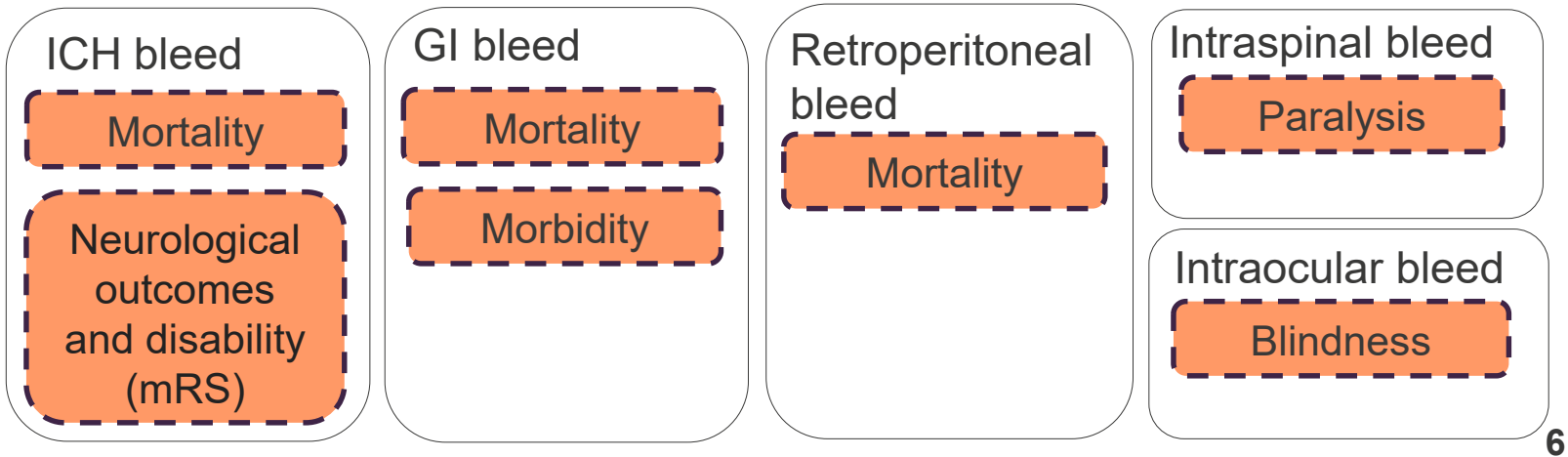
Major bleeding event, defined as any of the following:

- Haemoglobin drop more than 2g/dL
- Bleeding expected to be fatal and/or symptomatic bleeding that is intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular or retroperitoneal
- Transfusion: > 2 units of blood or packed red blood cells

Antagonisation of anticoagulation effects

- Oral activated charcoal
- specific reversal of anticoagulation effect if available
- non-specific reversal of anticoagulant activity if specific antidote is not available or sufficient (may include prothrombin complex concentrate or recombinant factor VIIa)

Outcomes according to bleed type (list non exhaustive)



Patient and carer perspectives

- Thrombotic events can have a **huge physical and psychological impact** on patient's lives
- Many are left with long-term, ongoing physical and/or psychological problems associated with the condition, particularly when the blood clots have caused a medical, life threatening emergency
- Treatment can impact on employment, future family planning, travel, work and social life
- Many patients speak about the **fear of further blood clots**, especially when their symptoms had initially been missed
- Current treatments are accepted by patients because they are life-saving but **concerns about safely managing anticoagulation** gives rise to many questions and for some, anxiety
- Patients diagnosed with a DVT or PE need both effective and **safe treatments that can be managed** should an emergency occur. Currently there is an **unmet need in provision**

Decision problem

	Final scope issued by NICE	Company submission
Population	Adults requiring urgent reversal of anticoagulation in case of uncontrolled or life-threatening bleeding, after treatment with a factor Xa-inhibiting direct oral anticoagulant (DOAC)	As per scope
Intervention	Andexanet alfa	As per scope
Comparators	Established clinical management of uncontrolled or life-threatening bleeding without andexanet alfa (including prothrombin complex concentrate with or without tranexamic acid)	Prothrombin complex concentrate (PCC)
Outcomes	The outcome measures to be considered include: • Requirement for blood products • Control of bleeding • Need for surgical control of bleeding or interventional radiology embolisation of bleeding vessel • Neurological outcomes (in people with ICH) • Hospital stay • Mortality • Adverse effects of treatment (including thrombotic events) • Health-related quality of life	The following outcome for ANNEXA-4 was not pre-specified and analyses are not yet available: • Need for surgical control of bleeding or interventional radiology embolisation of bleeding vessel The following pharmacodynamic outcomes are key in demonstrating the reversal of anticoagulation: • Anti-fXa activity, unbound anticoagulant plasma levels and thrombin generation

Clinical evidence for andexanet alfa – ANNEXA - 4

Study design	Single-arm, open-label, prospective, multicentre Phase IIIb/IV trial (ongoing)
Population (N=352)	People receiving apixaban, rivaroxaban, edoxaban, or enoxaparin with acute major bleeding and baseline anti-fXa activity≥75ng/mL – most received apixaban or rivaroxaban (n=322)
Exclusion criteria (not exhaustive)	• Expected survival < 30 days • People with ICH with any of the following: Glasgow coma score <7 or estimated intracerebral haematoma volume > 60cc as assessed on imaging
Intervention	Andexanet alfa - 2 possible regimens Low dose: 400 mg IV bolus then 4mg/min IV High dose: 800 mg IV bolus then 8mg/min
Outcomes	• Primary endpoints: • % change in anti-FXa activity • rate of excellent/good haemostatic efficacy 12 hours after andexanet alfa infusion • Secondary endpoint: Relationship between anti-FXa activity and haemostatic efficacy, (is anti-FXa activity predictor of haemostatic efficacy) • Safety endpoint: 30-day all-cause mortality and overall safety
Protocol amendment	Amendment 4: 1) Threshold time and dose criteria to determine a low vs high dose 2) Population enriched with ICH people. 139 people enrolled under Amendment 4 of the protocol
[redacted]	2 additional RCT vs placebo in healthy volunteers (ANNEXA-A and ANNEXA-R) supported application for marketing authorisation but not used in model

Clinical evidence for comparator PCC – ORANGE study

Study design	Prospective cohort study across multiple hospitals in UK on patients admitted for major bleeding event while on oral anticoagulant (2013-2016)
Population (N=2,192)	Adults on oral anticoagulation therapy at the time when they developed major bleeding were eligible → 372 people developed a bleed on apixaban or rivaroxaban. Of these 372 people, **149 received PCC**
Exclusion criteria	None related to expected survival, haematoma volume or GCS score
Intervention	Normal course of treatment (included PCC, tranexamic acid, vitamin K and FEIBA [Anti-inhibitor coagulant complex]) Only people who received PCC are included in the analysis
Outcomes	• Clinical outcomes at 30 days, death or discharge • Comorbidities, bleeding sites, haematological laboratory results, management of bleeding and first outcome up to 30 days

Major bleeding event definition in ANNEXA-4 and ORANGE studies

ANNEXA-4 – Acute major bleeding	ORANGE – Major bleeding event
Acute major bleeding event requiring urgent reversal of coagulation, defined by at least one the following: 1. Potentially life-threatening, e.g. with signs/symptoms of haemodynamic compromise such as severe hypotension, poor skin perfusion, mental confusion, low urine output that cannot be explained otherwise 2. Fall in haemoglobin by ≥20g/L OR haemoglobin ≤80g/L if baseline not available 3. Acute overt bleeding in a critical area or organ such as retroperitoneal, intraarticular, pericardial, epidural or intracranial bleeding or intramuscular bleeding with compartment syndrome	Augmented version of the ISTH criteria; defined as bleeding requiring hospitalisation and at least one of the following: 1. Resulting in death 2. Transfusion of ≥2 units of red blood cells or drop in haemoglobin of ≥20g/L 3. Symptomatic bleeding in a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, intramuscular with compartment syndrome 4. Transfusion of fresh-frozen plasma 5. PCC or recombinant activated factor VII or factor VIII inhibitor or fibrinogen concentrate administration *The rationale for appending 4. and 5. was to ensure that the routes for case identification were as comprehensive as possible*

Clinical evidence- 30-day mortality rates in ANNEXA-4 trial

- Bleeds included in submission: ICH, severe GI, pericardial, retroperitoneal, intraocular and intraspinal – last four classified as ‘other major bleeds

Patients with apixaban or rivaroxaban in the ANNEXA-4 trial	
	Deaths within 30 days (95% CI)
Whole cohort ([redacted])	[redacted]
Patients with ICH ([redacted])	[redacted]
Patients with GI ([redacted])	[redacted]
Patients with other major bleeds ([redacted])	[redacted]

[redacted]

Indirect treatment comparison results on mortality

- In absence of direct comparative evidence, an indirect treatment comparison was conducted to assess the comparative efficacy of andexanet alfa (ANNEXA-4 trial) and PCC (ORANGE study)
- Studies compared using a **propensity score matching analysis**, to produce adjusted estimates of treatment effect and replicate randomisation by identifying and **comparing patients** who had **similar characteristics:** age, site of bleed, history of coronary artery disease, history of stroke, transient ischaemic attack, atrial fibrillation, hypertension, diabetes, renal dysfunction, cancer
- Prognostic factors such as volume and severity of bleed were not reported in ORANGE and could not be included as covariates
- 30-day mortality rates are key drivers of the model

Population	Number of matches	Adjusted 30-day mortality (%) (95% CI)	
		PCC	Andexanet alfa
Whole population	[redacted]	[redacted]	[redacted]
ICH subgroup	[redacted]	[redacted]	[redacted]
GI subgroup	[redacted]	[redacted]	[redacted]
Other major bleeds (non-ICH/GI)	[redacted]	[redacted]	[redacted]

[redacted]

Source: ERG report, table 45

Haemostasis (co-primary trial outcome): definition used in the trial for ICH bleeds

Excellent (effective)	**≤ 20% increase:** • Intracerebral haematoma: **haematoma volume** compared to baseline on repeat imaging at both the 1- and 12-hour post infusion time points • Subarachnoid bleed: **maximum thickness** on the follow-up vs baseline at both the 1- and 12-hour post infusion time points • Subdural haematoma: **maximum thickness** at both the 1- and 12-hour post infusion assessments compared to baseline.
Good (effective)	**> 20% but ≤ 35% increase:** • in haematoma volume compared to baseline on a repeat imaging at +12-hour time point for **intracerebral haematoma** • in maximum thickness using the most dense area on the follow-up at +12 hours vs baseline for **subarachnoid bleeding**. • in maximum thickness at +12 hours compared to baseline for **subdural haematoma**.
Poor (not effective)	**> 35% increase:** • in haematoma volume on a CT or MRI compared to baseline on a repeat CT or MRI scan at +12-hour time point in **intracerebral haematoma**. • in maximum thickness using the most dense area on the +12 hours vs at baseline for **subarachnoid bleeding**. • in maximum thickness at +12 hours compared to baseline for **subdural haematoma**.

Haemostasis results in the trial

- In the whole cohort of ANNEXA-4, 69% patients were adjudicated as excellent haemostatic efficacy and 33 (13%) as good
- In the ICH bleed cohort, the rate of excellent or good haemostatic efficacy was 80%
- In the GI bleed cohort, the rate of excellent or good haemostatic efficacy was 85%

Clinical experts comments

- These criteria are not used routinely
- Most of the criteria used in the trial for haemostasis are not in line with clinical practice. There are no such data from ORANGE study

Issue 1: Who would be eligible for andexanet alfa in clinical practice?

Background

- ICERs calculated for **3 cohorts**: **whole cohort**, **ICH and severe GI**, **ICH only-** at engagement, company provided ICER for **severe GI bleeds cohort**.
- Bleed types proportions based on ANNEXA-4 trial ([redacted]% ICH, [redacted]% GI and [redacted]% other major bleeds) which was **enriched** with people **with ICH –** at engagement, company provided scenario with **proportions based on ORANGE.**
- ERG highlighted that **other major bleeds** in the **trial included 12 different bleeds – high uncertainty around 'other major bleeds' assumptions and results.**
- To amalgamate all types of bleeds may not be appropriate – very **different bleeds** lead to **different morbidity and outcomes.**

Stakeholder comments

- **Clinical experts**: any patient with major bleed could benefit from andexanet alfa, but ICH group seem to benefit the most.
- In clinical practice, **GI** bleeds **may be more frequent than ICH.**
- ICH, GI and other bleeds have different behaviour and outcomes – **should be considered as separate groups.**
- **Company**: ICH and GI were combined as they represent the 2 largest groups of indication but recognise importance of the **results of a severe GI bleed only cohort.**
- Company recognises that bleed proportions from ORANGE may be a better representation of clinical practice in the UK.
- **ERG** considers ORANGE data **not sufficient** to inform bleed types proportions – **ANNEXA-4 data more appropriate.**

[redacted]

Issue 2 : Generalisability and comparability of ANNEXA-4 trial and ORANGE study

Background

- ANNEXA-4 is a **single-arm trial** and ORANGE is an **observational study.**
- In ANNEXA-4, people were **excluded** if **survival** was expected to be **less than 1 month** or if they had **low GCS score (<7).**
- These criteria were **not used** in the **ORANGE study.**
- The generalisability of the trial population to UK population and comparability of the studies results for mortality are therefore questionable.

Stakeholder comments

- **Clinical experts:** Exclusion criteria used in trial introduce **bias** and **uncertainty** in comparison with PCC .
- Acute GI bleeding has high mortality (about 10%), proportion of people expected to have a survival <1 month is high.
- Uncertainty as to how these exclusion criteria were objectively assessed in a population with already high expected mortality.
- **Company**: The criterion on survival was specifically requested by FDA - Proportion of patients in trial who failed pre-screening due to exclusion criteria was extremely low ([redacted]).
- **ERG** consider the use of **pre-screening failure data** from ANNEXA-4 to account for bias due to people excluded based on survival **not sufficient** – people are less likely to enter pre-screening if clinicians did not consider them likely to meet inclusion criteria.
- ERG considers that 30-day mortality from the 2 studies are **not comparable.**

[redacted]

Issue 3: Uncertainty in the relative treatment effect of andexanet alfa vs PCC

Background

- In propensity score matching analysis for 30-day mortality, known prognostic factors such as **severity and volume of bleed could not be included** as not collected in ORANGE – **Key limitation** of the analysis.
- ERG noted differences remaining between treatment arms after matching – analysis is subject to inherent bias.
- ERG concerned that 60% of patients in PCC group were matched multiple times.
- **30-day mortality** is the **model's main driver.**
- Scenario with 30-day mortality equal for both treatments was tested – this **increased the ICER**

Stakeholder comments

- **Clinical experts:** Lack of detail on volume of bleed is a **major limitation as** haematoma volume is a **critical predictor** of mortality for ICH bleeds - results are therefore uncertain.
- The **suitability** of 30-day mortality results for decision making is **limited.**
- Results obtained for PCC seem in line with what is observed in clinical practice.
- **Company**: results for 30-day mortality aligned with literature findings for life-threatening or uncontrolled bleeding (ranging 33-45% and 10-20% for ICH and severe GI respectively).
- Company believe the exclusion of severity and volume of bleed in the analysis is likely to result in milder patients being included from ORANGE study, resulting in an underestimation of mortality with PCC.
- **ERG** consider data from literature used to compare results are **not appropriate.**
- ERG considers the **validity of the results** of the analysis to be **highly uncertain.**

[redacted]

Key clinical issues

1. Who would be considered for andexanet alfa in clinical practice where factor X levels will not be available?
2. ANNEXA-4 had no direct clinical outcomes apart from the safety endpoint of 30-day mortality, although people expected to die within 30 days, or severely affected by ICH were excluded from the trial. How does this affect the interpretation of the potential benefits in clinical practice, and the comparison with the ORANGE observational study which had no restrictions?
3. The trial recruitment was adjusted to include more people with ICH. A primary outcome was efficacy of haemostasis, for example ‘good’ haemostasis was defined as an increase in volume of intracerebral bleed of less than 35%. Does this correlate with clinical experience and predictive of improved outcomes?
4. Is it appropriate to amalgamate different types of bleed into a single ‘whole cohort’ given that there are potentially different therapeutic approaches for different sites of bleeding?

[redacted]

Key cost-effectiveness issues

1. For ICH and GI bleeds, the model uses the 30-day mortality rates from the propensity score matching analysis. What is the impact of the uncertainty in this analysis on the robustness of the cost-effectiveness results?
2. Is it reasonable to assume that, for pericardial and retroperitoneal bleeds, that andexanet alfa reduces 30-day mortality by 25%?
3. Is it reasonable to assume that, for intraspinal and intraocular bleeds, andexanet alfa reduces paralysis and monocular blindness by 25%?
4. Whether and how should the model consider that andexanet alfa affects the severity of disability in ICH survivors?
5. How valid are the utility estimates for ICH survivors with and without andexanet alfa?

[redacted]

Cost-effectiveness model

Model type	Decision tree followed by Markov model
Population	Patients from the ANNEXA-4 trial - People receiving apixaban or rivaroxaban and presenting with acute major bleeding Bleed types included were ICH, severe GI, other major bleeds (pericardial, retroperitoneal, intraocular and intraspinal)
Intervention	Andexanet alfa
Comparator	PCC
Mortality modelling	• Decision tree: Propensity score matching analysis between ANNEXA-4 and ORANGE study • Markov model: All-cause mortality adjusted with data from literature
Time horizon	Lifetime
Model cycle	1 month
Discount rates	3.5% for both costs and outcomes
Utility values	Utility values based on literature – Clinical trial did not collect HRQoL data
Perspective	NHS and PSS

Effect of andexanet alfa in the model

Effect in the model	Source
Reduces 30-day mortality due to ICH and GI bleeds.	Propensity score matching ANNEXA-4 vs ORANGE.
Reduces 30-day mortality due to retroperitoneal bleeds and pericardial bleeds.	Assumption based on clinical expert input.
Reduces severity of ICH as measured by mRS scores ↳ Reduces long-term mortality risk. ↳ Reduces long-term NHS costs. ↳ Improves long-term utilities.	Naïve comparison of ANNEXA-4 vs Øie et al.
Reduces paralysis and monocular blindness for intraspinal and intraocular bleeds. ↳ Reduces long-term management costs. ↳ Improves long-term utilities.	Assumption based on clinical expert input.

Issue 3: 30-day mortality rates due to ICH and GI bleeds

Population	Adjusted 30-day mortality for PCC (%)	Adjusted 30-day mortality for andexanet alfa (%)
Model inputs based on propensity score matching analysis (95% CI)		
ICH subgroup	[redacted]	[redacted]
GI subgroup	[redacted]	[redacted]

Source: adapted from ERG report, table 45

Stakeholder comments

- **Clinical experts:** Results are uncertain - lack of detail on volume of bleed is major limitation (haematoma volume is a critical predictor of mortality for ICH).
- Results obtained for PCC seem in line with what is observed in clinical practice.
- **Company**: results for 30-day mortality aligned with literature findings for life-threatening or uncontrolled bleeding (ranging 33-45% and 10-20% for ICH and severe GI respectively).
- Company believe the exclusion of severity and volume of bleed in the analysis is likely to result in milder patients being included from ORANGE study, resulting in an underestimation of mortality with PCC.
- **ERG** consider data from literature used to compare results are **not appropriate.**
- ERG considers the **validity of the results** of the analysis to be **highly uncertain.**

[redacted]

Issue 4: 30-day mortality rates for pericardial and retroperitoneal bleeds within 'other major bleeds'

Background

- **Company:** propensity score matching analysis results **counter intuitive** for 'other major bleeds' (adjusted 30-day mortality rate of [redacted]% for PCC vs [redacted]% for andexanet alfa) and based on small number of patients ([redacted] for PCC).
- Company assumed andexanet alfa would lead to **25% relative reduction in mortality** for **pericardial** and **retroperitoneal** bleeds and set the mortality **to zero** for **intraspinal** and **intraocular** bleeds.
- **ERG: no clear clinical rationale** or evidence for these assumptions, **scenario of 0% relative reduction in mortality** more appropriate and conservative.
- **ICER increased** by £1,000 when assuming 0% relative reduction in mortality.

Stakeholder comments

- **Clinical experts:** Evidence too scarce to make assumptions of 25% relative reduction in mortality.
- It is reasonable to assume a 0% relative reduction in absence of robust evidence.
- It is reasonable to set mortality to zero for intraspinal and intraocular bleeds.
- **Company**: 25% relative reduction mortality is a conservative assumption - substantially lower than the relative reduction observed for ICH and GI bleeds ([redacted]% and [redacted]% respectively).

[redacted]

Issue 4: Assumptions regarding andexanet alfa's effect on intraspinal and intraocular bleeds within 'other major bleeds'

Background

- Company assumed that
  - 50% of people will suffer from paralysis following intraspinal bleeds;
  - 25% of intraocular bleed survivors will have monocular blindness;
  - **andexanet alfa reduces paralysis and monocular blindness by 25%.**

- **Company:** justified approach with finding that 30-day mortality is reduced and from clinical expert input.

- **ERG: no clear clinical rationale** or evidence for these assumptions, **scenarios of 0% relative reduction in paralysis and blindness** more appropriate and conservative.

- **ICER increased** by £7,000 for 0% relative reduction in paralysis and blindness.

Stakeholder comments

- **Clinical experts:** Evidence too scarce to make assumptions of 25% relative reduction in paralysis and blindness.
- It is reasonable to assume a 0% relative reduction in absence of robust evidence.

- **Company**: Andexanet alfa's mechanism of action is to halt life-threatening bleeds, it would be clinically unrealistic to assume no benefit in preventing paralysis and monocular blindness.

[redacted]

Issue 5: Disability in ICH survivors

- Modified Rankin scale (mRS) scores reflect neurological outcomes and disability degree after ICH.
- Scale rank from 0 (no symptoms at all) to 6 (dead).
- Over the long-term, mRS scores affect utility, costs and mortality risk in the model.
- **Andexanet alfa**: Company used data from ANNEXA-4, collected from patients who had **ICH**, 30 days after the bleed event.
- **PCC**: Company used data from Øie 2018, collected from patients with **intracerebral haemorrhage**, 90 days after the bleed event.

mRS scores	Andexanet alfa (ANNEXA-4 distribution)	PCC (Øie 2018 distribution)
0	[redacted]	2%
1	[redacted]	8%
2	[redacted]	15%
3	[redacted]	20%
4	[redacted]	36%
5	[redacted]	20%
6	[redacted]	NA

[redacted]

Issue 5: Disability in ICH survivors

ERG comments

- Intracerebral haemorrhage is the **most severe type of ICH**, so mRS scores severity in PCC arm is **overestimated**.
- No evidence that people would have better mRS scores with andexanet alfa than PCC.
- **ERG's preferred scenarios**:
  - use the Øie 2018 mRS scores only for people who had intracerebral haemorrhage in the trial ([redacted]%) OR
  - use trial mRS scores for both treatment arms
- Both scenarios **increase the ICER.**

Stakeholder comments

- **Clinical experts**: Intracranial haemorrhage have the **highest mortality** and **worst morbidity** – hence generalising results from Øie 2018 to ICH may result in bias.
- To have an impact on mortality and morbidity, andexanet would have to **reduce haematoma expansion**.
- **Company**: Intracerebral bleed morbidity and mortality is expected to be similar to patients enrolled in ANNEXA-4 with life-threatening bleeding.
- It is plausible that a specific antidote which quickly reverses anti-activated FX activity and returns haemostasis to normal would lead to better outcomes including mRS scores.

[redacted]

Issue 6: Long-term utilities in ICH survivors

Background

- Long-term utility of ICH survivors for PCC obtained from NICE TA341 in 3-month post-acute care utility in people with ICH = 0.61
- Given the difference in mRS scores between andexanet alfa and PCC, **the company calculated that andexanet alfa increases utility by 0.11**→ long-term utility of ICH survivors post-andexanet alfa = 0.72.

ERG

- **ERG is concerned** that utility of **0.72** obtained for andexanet alfa **is 0.01 lower than UK general population aged 75 and above.**
- ERG's preferred scenario is to use the values based on mRS scores and Fletcher 2015 as source utilities.
- This **increases the ICER** by £2,805, £4,269 and £5,530 for the whole cohort, ICH plus GI cohort and ICH cohort, respectively.

Stakeholder comments

- **Clinical experts:** The ERG's assumption of using the weighted utilities by mRS scores seems more appropriate.
- **Company:** recognise that utilities used in base case analysis appear high for ICH survivor population but used the best available data.
- Utilities used in analysis from NICE TA341 were derived from EQ-5D.

[redacted]

Additional areas of uncertainty

Issue	Why issue is important	Impact on ICER
Protocol amendment 4 in ANNEXA-4	• In the trial, the criteria for determining the dose of andexanet alfa was changed midway; under Amendment 4, the threshold time to determining low vs high dose andexanet was changed from 7 to 8 hours and the specific doses of the last FXa inhibitor were added to determine a low vs high dose. There were 139 patients enrolled under Amendment 4 of the study protocol. • The ERG considers that some patients enrolled earlier than the amendment may not have received the licensed dose, however the impact of the resulting bias is unclear.	Unknown

[redacted]

ERG corrections and additional assumption

Corrections	Comments
Mortality probability for ICH survivors implementation	• The mortality probability for ICH survivors was incorrectly implemented in the model. The ERG corrected this to ensure the probability was appropriately applied.
Paralysis cost calculation	• The company used an annual cost for the first year of paralysis but applied the yearly cost as a per cycle cost. The ERG corrected this by taking the annual cost and diving it by 12, to ensure the cost was correctly applied in the first 12 cycles of the model.
Additional assumption	**Comments**
ICH rehabilitation length and costs are overestimated	• The company included a rehabilitation cost for the ICH survivor which was applied for a lifetime in the model. The ERG is concerned with this assumption and believes that ICH rehabilitation costs should not be applied for lifetime. • The ERG's preferred assumption is that rehabilitation costs are applied for 12 months.

[redacted]

Assumptions included in base case analyses

Assumptions	Included?		
	Company's base case	ERG's base case	ERG's alternative base case
25% relative reduction in 30-day mortality for 'other major bleeds' (Issue 4)	Y	N	N
25% relative reduction of paralysis and blindness for andexanet alfa (Issue 4)	Y	N	N
Utility values based on NICE TA341 (Issue 6)	Y	N	N
mRS scores based on Oie 2018 for PCC (Issue 5)	Y	N	N
0% relative reduction in 30-day mortality for 'other major bleeds' (Issue 4)	N	Y	Y
0% relative reduction of paralysis and blindness for andexanet alfa (Issue 4)	N	Y	Y
ICH rehabilitation 12 months	N	Y	Y
Weighted utility values by mRS (Issue 6)	N	Y	N
Intracerebral-specific mRS results to [redacted]% of ICH patients (Issue 5)	N	Y	N
mRS distributions from ANNEXA-4 applied to both treatment arms (alternative ERG base case, Issue5)	N	N	Y

[redacted]

Cost effectiveness results by cohort – ICER vs PCC (£/QALY)

- Company's updated base-case (after clarification and ERG corrections)

Population	deterministic	probabilistic
Whole cohort	£12,489	£12,535
ICH plus GI cohort	£18,663	£18,642
ICH cohort	£18,640	£18,691
GI cohort	£19,568	£19,602
Other major bleeds (ERG scenario)	*Andexanet alfa dominating*	-

- ERG's alternative base case (mRS distributions from trial applied to both treatment arms)

Population	deterministic	probabilistic
Whole cohort	£26,806	£26,779
ICH plus GI cohort	£25,880	£25,870
ICH cohort	£28,244	£28,333
GI cohort	£19,568	£19,602
Other major bleeds	Andexanet alfa dominated	-

- ERG's base case (using intracerebral-specific mRS results to [redacted]% of ICH patients)

Population	deterministic	probabilistic
Whole cohort	£31,044	£31,203
ICH plus GI cohort	£30,110	£30,249
ICH cohort	£34,933	£35,107
GI cohort	£19,568	£19,602
Other major bleeds	Andexanet alfa dominated	-

Scenarios assuming no benefit on 30-day mortality and alternative mRS

ICER vs PCC	Deterministic (£/QALY)	Probabilistic (£/QALY)
No benefit in 30-day mortality + other company's assumptions		
Whole cohort	£26,499	£26,472
ICH plus GI cohort	£52,281	£52,474
ICH cohort	£39,697	£39,629
GI cohort	Andexanet alfa dominated	Andexanet alfa dominated
Other major bleeds	Andexanet alfa dominating	-
No benefit in mRS scores (same mRS scores) + other company's assumptions		
Whole cohort	£18,964	£18,998
ICH plus GI cohort	£28,277	£28,270
ICH cohort	£31,377	£31,236
GI cohort	£19,568	£19,643
Other major bleeds	Andexanet alfa dominating	-
No benefit in 30-day mortality and same mRS scores + other company's assumptions		
Whole cohort	£977,602	£741,072
ICH plus GI cohort	Andexanet alfa dominated	Andexanet alfa dominated
ICH cohort	Andexanet alfa dominated	£31,981,120
GI cohort	Andexanet alfa dominated	Andexanet alfa dominated
Other major bleeds	Andexanet alfa dominating	-
No benefit in 30-day mortality, use intracerebral-specific mRS + other company's assumptions		
Whole cohort	£149,501	£154,746
ICH plus GI cohort	£345,128	£331,838
ICH cohort	£286,819	£267,845
GI cohort	Andexanet alfa dominated	£5,237,826
Other major bleeds	Andexanet alfa dominating	-

Scenarios assuming no benefit on 30-day mortality and alternative mRS and using ERG's assumptions

ICER vs PCC	Deterministic (£/QALY)	Probabilistic (£/QALY)
No benefit in 30-day mortality + ERG's base case assumptions (intracerebral-specific mRS)		
Whole cohort	£347,973	£346,056
ICH plus GI cohort	£348,317	£362,128
ICH cohort	£290,600	£295,864
GI cohort	Andexanet alfa dominated	£43,426,263
Other major bleeds	Andexanet alfa dominated	-
No benefit in mRS scores (same mRS scores) + ERG's base case assumptions (intracerebral-specific mRS)		
Whole cohort	£39,260	£39,169
ICH plus GI cohort	£38,198	£38,166
ICH cohort	£49,996	£50,371
GI cohort	£19,568	£19,582
Other major bleeds	Andexanet alfa dominated	-
No benefit in 30-day mortality and same mRS scores + ERG's base case assumptions (intracerebral-specific mRS)		
Whole cohort	Andexanet alfa dominated	-
ICH plus GI cohort	Andexanet alfa dominated	-
ICH cohort	Andexanet alfa dominated	-
GI cohort	Andexanet alfa dominated	-
Other major bleeds	Andexanet alfa dominated	-

Key cost-effectiveness issues

1. For ICH and GI bleeds, the model uses the 30-day mortality rates from the propensity score matching analysis. What is the impact of the uncertainty in this analysis on the robustness of the cost-effectiveness results?
2. Is it reasonable to assume that, for pericardial and retroperitoneal bleeds, that andexanet alfa reduces 30-day mortality by 25%?
3. Is it reasonable to assume that, for intraspinal and intraocular bleeds, andexanet alfa reduces paralysis and monocular blindness by 25%?
4. Whether and how should the model consider that andexanet alfa affects the severity of disability in ICH survivors?
5. How valid are the utility estimates for ICH survivors with and without andexanet alfa?

Back up slides

Clinical evidence – definition of excellent haemostasis in the trial

Excellent (effective)	• Visible: Cessation of bleeding ≤ 1 hour after end of infusion and no plasma, coagulation factor or blood products (excludes pRBCs)
	• Muscular/skeletal: pain relief or no increase in swelling or unequivocal improvement ≤1 hour after the end of infusion; and condition has not deteriorated during the 12-hour period
	• ICH:
	  • Intracerebral haemorrhage: ≤ 20% increase in haematoma volume compared to baseline on a repeat CT or MRI scan performed at both the 1- and 12-hour post infusion time points.
	  • Subarachnoid bleeding: ≤ 20% increase in maximum thickness using the most dense area on the follow-up vs baseline at both the 1- and 12-hour post infusion time points.
	  • Subdural haematoma: ≤ 20% increase in maximum thickness at both the 1- and 12-hour post infusion assessments compared to baseline.
	• Pericardial bleed. No increase in the size of pericardial effusion on repeat echocardiogram done within 12 hours of the end of infusion.
	• Intra-spinal bleed. No increase in haematoma size on repeat CT or MRI scan done within 12 hours of the end of infusion.
	Other bleeds: ≤ 10% decrease in both corrected haemoglobin/haematocrit at 12 hours compared to baseline.

Clinical evidence – definition of good haemostasis in the trial

Good (effective)	• Visible: Cessation of bleeding between > 1 and ≤ 4 hours after end of infusion and ≤ 2 units plasma, coagulation factor or blood products (excludes pRBCs).
	• Muscular/skeletal: pain relief or no increase in swelling or unequivocal improvement in objective signs of bleeding >1 and ≤4 hours after end of infusion; and the condition has not deteriorated during the 12-hour period
	• ICH:
	  • Intracerebral haematoma: > 20% but ≤ 35% increase in haematoma volume compared to baseline on a repeat CT or MRI scan at +12-hour time point.
	  • Subarachnoid bleeding: > 20% but < 35% increase in maximum thickness using the most dense area on the follow-up at +12 hours vs baseline.
	  • Subdural haematoma: > 20% but < 35% increase in maximum thickness at +12 hours compared to baseline.
	• Pericardial bleed. < 10% increase in the size of pericardial effusion on repeat echocardiogram done within 12 hours of the end of infusion.
	• Intra-spinal bleed. < 10% increase in haematoma size on repeat CT or MRI scan done within 12 hours of the end of infusion.
	Other: > 10% to ≤ 20% decrease in both corrected haemoglobin/haematocrit at 12 hours compared to baseline.

Clinical evidence – definition of poor haemostasis in the trial

Poor (not effective)	• Visible: Cessation of bleeding > 4 hours after end of the infusion and /or >2 units plasma, coagulation factor or blood products (excludes pRBCs)
	• Muscular/skeletal: No improvement by 4 hours after end of infusion and/or condition has deteriorated during the 12-hour period
	• ICH:
	  • Intracerebral haematoma: > 35% increase in haematoma volume on a CT or MRI compared to baseline on a repeat CT or MRI scan at +12-hour time point.
	  • Subarachnoid bleeding: > 35% increase in maximum thickness using the most dense area on the +12 hours vs at baseline.
	  • Subdural haematoma: > 35% increase in maximum thickness at +12 hours compared to baseline.
	• Pericardial bleed. 10% or more increase in the size of pericardial effusion on repeat echocardiogram done within 12 hours of the end of infusion.
	• Intra-spinal bleed. 10% or more increase in haematoma size on repeat CT or MRI scan done within 12 hours of the end of infusion.
	Other: > 20% decrease in both corrected haemoglobin/haematocrit.

Cost effectiveness results – Whole cohort

Scenario	Cumulative ICER vs PCC (£/QALY)
Company's base case	£11,636/QALY
Company's updated base case (after clarification and ERG corrections)	**£12,489/QALY**
0% relative reduction in 30-day mortality for 'other major bleeds'	£12,577/QALY
0% relative reduction of paralysis and blindness for andexanet alfa	£19,306/QALY
ICH rehabilitation 12 months	£18,095/QALY
Weighted utility values by mRS	£22,233/QALY
Alternative mRS distributions	
ERG base case: Intracerebral-specific mRS results to [redacted]% of ICH patients	**£31,044/QALY**
Alternative ERG base case: mRS distributions from ANNEXA-4 applied to both treatment arms	£26,806/QALY

[redacted]

Cost effectiveness results – ICH and GI

Scenario	Cumulative ICER vs PCC (£/QALY)
Company's base case	£18,741/QALY
Company's updated base case (after clarification and ERG corrections)	**£18,663/QALY**
ICH rehabilitation 12 months	£17,453/QALY
Weighted utility values by mRS	£21,445/QALY
Alternative mRS distributions	
ERG base case: Intracerebral-specific mRS results to [redacted]% of ICH patients	**£30,110/QALY**
Alternative ERG base case: mRS distributions from ANNEXA-4 applied to both treatment arms	£25,880/QALY

[redacted]

Cost effectiveness results – ICH only

Scenario	Cumulative ICER vs PCC (£/QALY)
Company's base case	£18,738/QALY
Company's updated base case (after clarification and ERG corrections)	**£18,640/QALY**
ICH rehabilitation 12 months	£17,190/QALY
Weighted utility values by mRS	£22,124/QALY
Alternative mRS distributions	
ERG base case: Intracerebral-specific mRS results to [redacted]% of ICH patients	**£34,933/QALY**
Alternative ERG base case: mRS distributions from ANNEXA-4 applied to both treatment arms	£28,244/QALY

[redacted]

Cost-effectiveness results - Additional scenarios

- ERG's scenario – 'other major bleeds' cohort

Scenario	Cumulative ICER (£/QALY)
Base case using company's preferred assumptions	Andexanet alfa dominating
0% relative reduction in 30-day mortality for 'other major bleeds'	Andexanet alfa dominating
0% relative reduction of paralysis and blindness for andexanet alfa	Andexanet alfa dominated

- Company's scenario – bleed types distribution from ORANGE

Population	ICER vs PCC, deterministic (£/QALY)
Whole cohort	£10,303
ICH plus GI cohort	£18,717

[redacted]