NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Andexanet alfa for reversing anticoagulation [ID1101]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Andexanet alfa for reversing anticoagulation [ID1101]

Contents:

The following documents are made available to consultees and commentators:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Appraisal title

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee	Anticoagulation UK	1.2 ACUK is concerned with the recommendation to use Adexanet alfa in adults with life-threatening or uncontrolled bleeding in the skull (intracranial haemorrhage) only for research and limitations to GI bleeds We seek clarification on the following: What settings will be eligible to participate in research i.e. all secondary care settings, major trauma/ stroke units? Where is current research taking place, i.e. geographical spread across the UK and, if at multiple centres, will any patient experiencing an ICH be able to access? Who will make the clinical decision as to whether a patient is eligible for the research and will consent be needed from the patient/patient's family or representative? Considering the situation where a person may be involved in an accident or trauma and confirmed as having an ICH, would the patient be disadvantaged in being able to access a research programme if not available within their geographical location. Patients should be reassured that in the event of a major bleed whilst on apixaban or rivaroxaban, they will not be compromised by where they live and encounter limitations on how they may be treated to reverse the event 3.2 The committee has acknowledged that the availability of an effective reversal agent would be greatly valued by people and HCPs. If clinicians are aware of the reversal agent being available for 'research purposes' for ICH as well as GI bleeds, will they be compromised in their clinical practice/judgement in being unable to access for a patient who they deem could benefit (younger patient, no comorbidities, with good chance of recovery) It could prove difficult and challenging to make this assessment in the knowledge that a treatment could make a difference to patient outcome. Are there any exceptional circumstances protocols that could override the research only recommendation? 3.4 We understand the implications of an ICH bleed can lead to mortality and long term disability. We note that GI bleeds may be able to be managed using endoscopy, embolization or surgery. In terms of other types of bleeds, could the limitations of availability of a reversal agent when other reversal methods have been utilised, be deemed detrimental to the patient's long term health outcomes. A bleed in the eye leading to blindness is considered a long term disability and would impact greatly on	Thank you for your comments Please see individual responses below. **1.2.** Please see section 6.4 of the NICE Guide to the methods of technology appraisal for further information on the factors considered by the appraisal committee when recommending a technology in research. Section 6.4.3 specifies that *"The Committee will need to be satisfied that the additional research is feasible in the circumstances in which the intervention has been recommended."*. However, the specific details of the research implementation are outside of the appraisal committee's remit. **3.2:** The committee noted that there is a clinical need for effective anticoagulation reversal agents after apixaban or rivaroxaban. At the third committee meeting clinical experts emphasised the difficulty in deciding when to use andexanet alfa in clinical practice, because treatment should be given as soon as possible and the decision may fall to relatively inexperienced doctors. So, it is likely all people would be offered treatment in the NHS, rather than the selected group included in ANNEXA-4. For further details of the committee

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			the individual. 3.9 The committee commented on reduction in mortality in ICH being plausible but size of benefit unclear as some patients may be left severely disabled who would otherwise die whilst some may make an excellent recovery. Given that a treatment could benefit a patient and whilst they may not return to the quality of life pre –bleeding event , we would hope that the access to treatment must take into account the patient's broader health profile e.g if a patient on a DOAC had a fall or trauma doing sport or a car accident and who was otherwise fit and well, the blanket decision of not being able to give Adexanet in these circumstances could be hugely detrimental to the individual. Each person is an individual and Doacs are prescribed to 18 yrs to 80 years plus; it seems inequitable that a firm NO is generalised for an anticoagulated person unable to fit 'research' criteria 3.16/3.20 Cost – What are the implications for clinicians to have to explain/ discuss with the patient's family or carer when advising that there is a treatment but not deemed to be cost effective use of NHS resources for ICH? 5.1 This recommendation is welcome and we look forward to seeing the published results when available. We would request that NICE commits to review this TA once results are published or earlier if available as this is of significance importance to the DOAC community and specialist clinicians. General comments We understand the risk of thrombosis from Adexanet alfa and how stopping a ICH bleed may actually cause distress and morbid disability to a patient along with costs of care to the NHS and society. From the patient perspective, if the treatment is going to be limited in how it will be used in a bleed scenario, it is important t that the patient be made aware of this before starting on a Doac and advised on the current bleed reversal options available including Adexanet alfa and its current licenced recommendations. From our AC community engagement, we know that patients are told of bleed risks but not advised of reversal options. (ACUK is a consultee to the QS for the recently published VTE guidelines NG158 and has prioritised standardising patient information as a key improvement priority) We note the recent SMC decision as below will be welcomed by patients and healthcare professionals in Scotland. As a patient organisation, how can we justify to our patient base the differences in the decision making processes between SMC and NICE and subsequent outcomes? 07 August 2020The 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 NHS SCOTLAND. The advice is summarised as follows: ADVICE: following a full submission andexanet alfa (Ondexxya®) is accepted for use within NHS	discussion see FAD section 3.9. **3.4**. As per Section 3.4 of the FAD, the committee noted that the effect of bleeding in other places in the body would vary considerably and that different types of bleeds should be considered separately for decision making. 3.9. Please see response to 3.2 3.16/3.20. The primary consideration underpinning NICE's guidance and standards is the overall population need. This means that sometimes we do not recommend an intervention because it does not provide enough benefit to justify its cost. See number 23 of NICE: Our principles **General comments** For the ICH cohort, the committee remained concerned that the extent of any mortality benefit from andexanet alfa for ICH bleeds is unclear and the benefit on long-term disability is not supported by clinical evidence. The committee considered the additional information presented by the company and responses to consultation but concluded that andexanet alfa should be recommended in the context of research for ICH bleeds**.** For further details of the committee discussion see FAD section 3.9 - 3.11. As per the NICE Guide to the methods of technology appraisal,

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			SCOTLAND 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 NHS Scotland 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	NICE's remit applies only to the NHS in England.
1	Consultee	Royal College of Pathologists and British Society for Haematology	We are concerned about these recommendations as approving Andexanet alfa for gastrointestinal bleeding at this stage means that there will not be clinical trials comparing the efficacy and safety of Andexanet alfa with prothrombin complex concentrate (PCC) in treatment of major or life threating GI bleeding related to rivaroxaban or apixaban. Therefore, we believe use of Andexanet alfa in GI bleeding should also include as research setting. Additionally, if the clinical trials comparing the use of Andexanet alfa in ICH failed to show better safety and efficacy compared to PCC in reversing the anticoagulant effect of rivaroxaban or apixaban, approval of Andexanet alfa would remain as approval drug for GI bleeding in the absence of proper randomised clinical trials. Furthermore, there is a possibility of discrimination in the use of Andexanet alfa for use in treatment of ICH related to rivaroxaban or apixaban based on which hospital patients get treated with this type of approval (postcode variation in treatment) as there is local approval of drug to use in ICH in addition to GI bleeding	Thank you for your comment. The committee considered this feedback and remains of the view that there is sufficient clinical evidence to recommend andexanet alfa in the gastrointestinal cohort. For further details of the committee discussion see FAD section 3.8.
1	Consultee	Thrombosis UK	1.2 Thrombosis UK would like to thank the NICE committee for reviewing all comments and considering patient benefit. We would like to seek clarification in regards to 1.2 recommendation 'Andexanet alfa is recommended only in research for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled bleeding in the skull (intracranial haemorrhage).' We understand there is no other therapy available for the treatment of intracranial haemorrhage and so would like to seek clarification on: • What settings would be permitted to participate in research? • Can NICE clarify how equity of access would be maintained? • Clarification on the process and guidance which will be needed to inform decision making by the clinician and in discussion with family, when a patient who had suffered an intracranial haemorrhage may be considered for andexanet alfa. We are concerned this may disadvantage patients, for example, geographically.	Please see section 6.4 of the NICE Guide to the methods of technology appraisal for further information on the factors considered by the appraisal committee when recommending a technology in research. Section 6.4.3 specifies that *"The Committee will need to be satisfied that the additional research is feasible in the circumstances in which the intervention has been recommended*.". Section 1.2 specifies that the research should be *'in the form of an ongoing randomised trial mandated by the regulator.'* However, the specific details of the research implementation are outside of the appraisal committee's remit.

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2	Consultee	Thrombosis UK	3.2 The committee acknowledged that the availability of an effective reversal agent would be 'greatly valued by people and HCPs'. If research restrictions are placed on access to the therapy for ICH, we are concerned patients who may benefit from the therapy, may be denied access not based on clinical judgement but on geographical access.	Thank you for your comment. The committee noted an equality concern that there would be national variation in access to andexanet alfa if recommended only in research. However, it understood that any variation in access was governed by entry to a randomised controlled trial which had been mandated by the regulator. It concluded that the ability to take part in this research was not an issue that needed its recommendation to be altered. For further details of the committee discussion see FAD section 3.19.
3	Consultee	Thrombosis UK	In line with NICE VTE Guidelines NG158, which advocates standardisation of patient information as a key improvement priority, we would like NICE to consider and include clear guidance on how decision making will be made in the event of an ICH, for sharing with patients during discussion about initiation of a DOAC therapy.	Thank you for your comment. The committee agreed that there was no robust evidence that andexanet alfa reduces long-term disability in ICH. It noted that there is a need for an effective reversal agent for direct factor Xa inhibitors, such as apixaban and rivaroxaban, in people with uncontrolled or life-threatening bleeding in ICH. It considered that it would be valuable to have studies which provided evidence on mortality and noted the ongoing randomised controlled trial will provide stronger evidence on short-term survival and neurological outcomes. The committee recommended andexanet alfa only in research in ICH, in the context of the ongoing randomised trial, but the specific details of the research implementation are outside of the appraisal committee's remit. For further details of the committee discussion see FAD section 3.2 and 3.11.
4	Consultee	Thrombosis UK	5.1 Thrombosis UK welcomes this recommendation	Thank you for your comment. No action required.
5	Consultee	Thrombosis UK	We would like to draw the Committees attention to the recent Scottish Medicines Consortium	Thank you for your comment. As per

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			decision: 07 August 2020 'Following a full submission andexanet alfa (Ondexxya®) is accepted for use within NHS Scotland 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.' We are concerned that this is a very difficult difference to explain to NHS patients in England and Wales considering taking a DOAC, or to families with a loved-one critically ill due to a life-threatening bleed.	the NICE Guide to the methods of technology appraisal, NICE's remit applies only to the NHS in England.
1	Web commentator	Guy's and St Thomas' NHS Foundation Trust	Comments from Guy's and St Thomas' NHS Foundation Trust in response to the National Institute for Health and Care Excellence (NICE) appraisal consultation document Andexanet alfa for reversing anticoagulation from apixaban and rivaroxaban We are surprised NICE have approved andexanet alfa in the management of gastrointestinal (GI) haemorrhage in those receiving apixaban and rivaroxaban. In the extensive analysis of the data for andexanet alfa, they identify most data is of poor quality, and the reason for advocating andexanet alfa for GI bleeding is because it is deemed cost effective. We are dismayed by this approach. If patients are having major haemorrhage from the GI tract, then we would consider the use of prothrombin complex concentrate (PCC) as a better option than andexanet alfa because in those with major blood loss, they will in addition to needing anticoagulation reversal also have deficiencies in clotting factors which PCC will be able to remedy, but andexanet alfa will not. PCC has been used as a substitute for fresh frozen plasma internationally in the management of massive bleeding, therefore in the setting of major bleeding in the GI tract, PCC fulfils two functions (reversing the effects of the factor Xa inhibitors apixaban and rivaroxaban, and repletion of clotting factors). Therefore, PCC appears to be a more logical approach to the management of GI haemorrhage than andexanet alfa.	Thank you for your comment. The committee considered this feedback and concluded that there is sufficient clinical evidence to recommend andexanet alfa in the gastrointestinal cohort. For further details of the committee discussion see FAD section 3.8.
1	Web commentator	David Lillicrap	**There is a clinical need for effective anticoagulation reversal agents:** The patient experts explained that anticoagulation treatments are accepted by people because they are lifesaving, but there are concerns about safely managing anticoagulation should a major bleed occur. If bleeding is life-threatening then anticoagulation needs to be reversed. Treatment is challenging if there is no reversal agent and relies on treating symptoms until the effects of the anticoagulant stop, in line with the normal half-life of the drug. The patient experts explained that there is an unmet need for a safe reversal agent for direct factor Xa anticoagulants such as apixaban and rivaroxaban. The committee concluded that the availability of an effective reversal agent would be greatly valued by people and healthcare professionals. I wish to reinforce the expert patient comments. The need for a reversal agent is critical for those, for	Thank you for your comment. The committee considered this feedback and concluded that there is a clinical need for effective anticoagulation reversal agents after apixaban or rivaroxaban. For further details of the committee discussion see FAD section 3.2.

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			example AF patients, who have a lifelong bleed problem when given long term aspirin, who also find they bleed when prescribed, say rivaroxaban, as their CHA 2 DS 2-VAS score rises dictating anticoagulation is necessary. They can find themselves on a less than therapeutic dose of an alternative, for instance apixaban, but still observe the occasional small bleed. I wish to reinforce the expert patient comments. The need for a reversal agent is critical for those, for example AF patients, who have a lifelong bleed problem when given long term aspirin, who also find they bleed when prescribed, say rivaroxaban, as their CHA 2 DS 2-VAS score rises dictating anticoagulation is necessary. They can find themselves on a less than therapeutic dose of an alternative, for instance apixaban, but still observe the occasional small blee**d.**	
1	Web commentator	King's Thrombosis Centre, Department of Haematological Medicine, King's College Hospital	Has all of the relevant evidence been taken into account? It is difficult to evaluate as most of the evidence presented is blocked out. There is no reference provided for the US 'real world' data. There are published cohort studies of real-world PCC use from US and Netherlands (summarised in this review article https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7354417/#rth212367-bib-0006), suggesting greater haemostatic efficacy than reported in ORANGE. It seems unusual that only 1 study of DOACs and PCC has been considered, along with unpublished data from real world US experience which has not been made publically available. A stronger comparison could be made by increasing the number of patients treated with PCC across broader care settings. Furthermore, a new publication of realworld use of andexanet with extracranial bleeding raises safety concerns with a 20% thrombosis rate and efficacy in less than 50% of the treated cohort (mortality 40%, see https://onlinelibrary.wiley.com/doi/10.1111/jth.15031).	Thank you for your comment. The committee considered this feedback during the third committee meeting. the committee considered the evidence presented and concluded that there is sufficient clinical evidence to recommend andexanet alfa in the gastrointestinal cohort. For the ICH cohort, the committee remained concerned that the extent of any mortality benefit from andexanet alfa in ICH is unclear and the benefit on long-term disability is not supported by clinical evidence. It concluded that andexanet alfa should be recommended in the context of research for ICH bleeds. For further details of the committee discussion see FAD section 3.8 - 3.11.
2	Web commentator	King's Thrombosis Centre, Department of Haematological Medicine, King's College Hospital	Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? No	Thank you for your comment. No further action required.
3	Web commentator	King's Thrombosis Centre, Department of Haematological Medicine, King's	Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? It is impossible to comment on this as the company have blacked out all numeric data to enable an evaluation. ORANGE reported data from 372 patients on rivaroxaban or apixaban GI bleeding, with 149 receiving PCC. 90 patients (with non-ICH bleeds) were included in the phase 2 Andexanet study and we note haemostatic efficacy was only reported for 60 of these. Subgroup mortality data was not	Thank you for your comment. The committee considered this feedback during the third committee meeting. Based on the evidence presented to it, the committee concluded that there is sufficient clinical evidence to

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		College Hospital	presented in either original publication. Propensity matching will further reduce the number included in analysis and it's difficult to imagine that this will provide convincing evidence of efficacy in such a small cohort. We note the planned recruitment size of the ongoing RCT of andexanet in ICH of 900. There is no data presented with regard to effect size to enable evaluation of how the evidence has been interpreted (and this is not presented by subgroup in the original publications). Without enabling clinicians to evaluate the data (or publications) to support their claims, it remains unconvincing. Given the majority of upper GI bleeds are due to gastric ulceration or variceal bleeding, it seems unlikely that reversal of anticoagulation will improve outcomes without definitive evaluation/intervention of the bleeding point. Lower GI bleeding is most commonly associated with benign anorectal conditions and has very low early mortality (with later deaths attributable to comorbid disease). There is no published subgroup data of 30d mortality following gastrointestinal bleeding in either study (as above no data has been made available to enable evaluation). The relevance of 30 day mortality as an outcome measure for GI bleeding is questionable, as most later deaths in this patient group relate to comorbid disease rather than bleeding, as highlighted by the recent HALT-IT study (https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(20)30848-5.pdf).	recommend andexanet alfa in the gastrointestinal cohort. For the 'other bleeds cohort' the committee concluded that andexanet alfa had not been proven to reduce mortality, so could not recommend the treatment in this population. For further details of the committee discussion see FAD section 3.8 and 3.12.
4	Web commentator	King's Thrombosis Centre, Department of Haematological Medicine, King's College Hospital	Are the recommendations sound and a suitable basis for guidance to the NHS? We agree with the recommendation wrt use of andexanet only in the research setting for patients with ICH and suggest the recommendation for GI bleeding should be similarly revised. There is more data for both andexanet use and PCC in the context of ICH. If this was viewed as inadequate by the committee, it seems unlikely there is adequate evidence based on retrospective propensity matching (using a single small observational cohort of PCC) to support a recommendation in favour of andexanet in GI bleeding. The significant thrombosis rates reported both in the phase 2 andexanet study and subsequent observational cohorts remain concerning. A RCT should be performed to establish both efficacy and safety of andexanet in the non-ICH cohort (including GI bleeding).	Thank you for your comment. The committee considered this feedback and, based on the evidence presented to it, concluded that there is sufficient clinical evidence to recommend andexanet alfa in the gastrointestinal cohort. For the ICH cohort, the committee remained concerned that the extent of any mortality benefit from andexanet alfa in ICH is unclear and the benefit on long-term disability is not supported by clinical evidence. It concluded that andexanet alfa should be recommended in the context of research for ICH bleeds. For further details of the committee discussion see FAD section 3.8 - 3.11.
1	Company	Portola Pharmaceuticals	**Executive summary** Portola would like to thank the committee for the opportunity to respond to the second Appraisal Consultation Document (ACD). We welcome the recommendation for the use of andexanet alfa for reversing anticoagulation with apixaban or rivaroxaban in adults with life-threatening or uncontrolled bleeding in the gastrointestinal	Thank you for your comments. The committee considered this feedback and remains of the view that there is a clinical need for effective anticoagulation reversal agents after apixaban or rivaroxaban. See FAD Section 3.2. Please see individual

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			tract. However, we are concerned that despite the substantial and statistically significant mortality benefit demonstrated for the intracranial haemorrhage (ICH) population, the recommendation for 'only in research' fails to address the needs of this important patient group. We would highlight that neither the ANNEXA-I study nor other planned research will address uncertainties related to long term morbidity in ICH, as this was not a concern for the regulators in the US or Europe. As recognised by the EMA, andexanet alfa is an innovative medicine, and no alternative options for effective FXa inhibitor reversal exist. As such, we are committed to providing a comprehensive response that will enable NICE to recommend access to andexanet alfa via routine commissioning; as a life-saving and disability reducing therapy for ICH patients. **As noted by the committee, there remains a significant unmet need for those with ICH who require reversal of apixaban or rivaroxaban anticoagulation** • The use of direct oral anticoagulants (DOACs) for anticoagulation has increased substantially in recent years, particularly in light of recent COVID 19-related guidance. There were an estimated [redacted] people treated with apixaban or rivaroxaban in 2018, compared to an estimated [redacted] in 2020, including the expected increased uptake due to COVID-19 [EPACT and NHSE].[1] • Despite increased availability and use of DOACs, major bleeding concurrent with the use of these medications remains a burden of clinical significance in the NHS. • In 2020, approximately [redacted] people in England who are being treated with apixaban or rivaroxaban experience an ICH that is life-threatening or uncontrollable,[1] resulting in an estimated [redacted] deaths (49%). • With the availability of an effective reversal agent such as andexanet alfa, many of these deaths (approximately [redacted]) could be avoided each year. **Current usual care in ICH does not address the unmet need** • As agreed by the committee, patient groups and clinical experts, the ICH population represents the population with the largest clinical unmet need across all life-threatening or uncontrolled bleeds. Approximately 50% of patients experiencing an ICH in the andexanet-eligible population died following PCC off-label treatment in the recent UK-based ORANGE study.[2,3] • In particular, intracerebral haemorrhage carries a very high mortality burden, which increases for anticoagulated populations.[4,5] Other treatments which limit haematoma	responses to comments 2 to 11 for further information. .

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			expansion in anticoagulated patients with non-FXa inhibitor-associated intracerebral bleeds, via a known mechanism of action (e.g. PCC reversal of warfarin) have demonstrated improved survival without worsened morbidity.[6] However, for FXa inhibitor bleeds, PCCs are unlicensed treatments with no known mechanism of action and with no evidence of any effect on limiting haematoma expansion nor associated mortality / morbidity improvement. • In contrast, andexanet alfa has a robust mechanism of action with immediate sequestration of FXa inhibitor within 2-5 minutes of bolus. Early administration of andexanet alfa in an ICH population with therapeutic FXa inhibitor anticoagulation drives thrombin generation and limits haematoma expansion. Consequently, mortality and morbidity benefits are to be expected. **The available evidence demonstrates that, as seen in those with gastrointestinal bleeding, andexanet alfa treatment results in substantially reduced mortality in people with ICH** • Despite the uncertainty of single-arm trial evidence, the committee accepted that: *"Andexanet alfa is likely to reduce 30-day mortality for people with GI bleeds"* [ACD, 3.8] • We note that the evidence base to support this comprises the propensity score matching analysis of ANNEXA-4 and ORANGE, a US multicentre real-world analysis study of patients receiving andexanet alfa within its licensed indication, and the predicted mortality outcomes of patients, estimated from the Rockall score at baseline in ANNEXA-4. • We acknowledge that the committee formed a similar conclusion on mortality in the ICH population: *"The indirect treatment comparison predicted that andexanet alfa reduces mortality in ICH. The committee considered this to be plausible."* [ACD, 3.9] • We note that the evidence base to support this comprises the same propensity score matching analysis of ANNEXA-4 and ORANGE, and US multicentre real-world analysis study of patients receiving andexanet alfa within its licensed indication. • We further note that the ACD states: "*the size of benefit was unclear*" [ACD 3.9] • We would respectfully refer to our response to the first ACD, whereby five indirect comparison approaches, including propensity score matching and inverse probability of treatment weighting, resulted in the same outcome[redacted]	

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			[redacted]. • With no evidence to the contrary, and supporting evidence of the robustness of results from the Rosenbaum sensitivity analysis and US multi-centre real-world analysis, it is clear that andexanet alfa would confer a substantial and significant mortality benefit in ICH patients. **Despite some uncertainty relating to the level of disability, andexanet alfa is a cost-effective treatment in patients with ICH, even under scenarios deemed most conservative by clinicians and the ERG** • We acknowledge that the conclusion of the ACD points to an uncertainty related to the disability of patients with andexanet alfa following treatment, despite the fact that the range of ICERs (even with the ERG's updated base case) lie within the bounds of what would usually be deemed cost-effective: "*The company's ICER was within the range NICE normally considers a cost-effective use of NHS resources. However, the committee had concerns about the methods and assumptions used in the model, particularly the assumption of a benefit from andexanet alfa on long-term disability after an ICH that had not been adequately justified or evidenced. The committee was concerned that it was unclear if people who had andexanet alfa would make a good recovery, or whether they would be severely disabled. The committee considered the ERG's updated base case for the ICH cohort, which resulted in a higher ICER. Therefore, the committee was not confident that the results for ICH were robust.*" [ACD, 3.6] • As part of this response, we present below compelling evidence to support the conclusion that andexanet alfa would improve morbidity and associated quality of life compared to PCC. This is congruent with the ERG's conclusion that assuming andexanet alfa would have no effect on morbidity and associated quality of life compared to PCC is a conservative assumption.[7] • We conducted a Delphi panel to elicit clinical consensus from 10 UK ICH experts including a contingent of ordinary, former and currently serving committee members of the British Association of Stroke Physicians (BASP) to understand the effect of andexanet alfa on morbidity and corresponding quality of life. • Of the 10 UK ICH experts, nine participated in a consensus meeting. **All nine experts agreed** that it is likely that andexanet alfa would shift the spectrum of disability, resulting in a positive quality of life outcome in comparison to PCCs in the population for which clinicians would consider treatment. See Appendix A for further details. • We also present multiple evidence sources to suggest that andexanet alfa would improve morbidity and corresponding quality of life in the population for which clinicians would	**Delphi panel results** The committee considered the results of the Delphi panel at the third committee meeting. However, it agreed that the Delphi panel represented opinion rather than offering robust evidence on key areas of uncertainty. For a full description of the committee's considerations, see FAD section 3.5.

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			consider treatment, demonstrating that the ICER lies within a cost-effective range and as such, andexanet can be recommended in the patient group which needs it the most. **A recommendation for the ICH population via routine commissioning has established pathways to facilitate successful implementation** • Currently, people with intracranial bleeding (including people with spontaneous intracerebral bleed) are treated throughout the UK through established clinical care pathways (e.g. stroke and neurosurgical pathways). Emergency departments can differentiate between intracranial bleed types with urgent scanning, and characterise ICH severity (clinically and through imaging) with urgent referral to the relevant stroke or neurosurgical team. • In clinical practice, resolving uncertainty in therapeutic decision making involves consideration of patients' baseline clinical severity, past medical history, premorbid function and treatment benefits versus risks, and patients' wishes (possibly expressed through advanced directives or family/carers) and consultation with colleagues. There was consensus reached on both of these topics raised in the Delphi panel (see Appendix A, Question 1a and Question 1c) • All nine ICH experts in the Delphi panel agreed that they would likely treat any patient with andexanet alfa provided that they had taken apixaban or rivaroxaban within the previous 12 hours or so and that they were deemed likely to experience long-term survival benefits (similar to eligibility criteria of GCS >7 and ICH volume <60 ml used in the ANNEXA-4 trial) (see Appendix A, Question 1b). • Failure to offer routine guidance for those with ICH will create inequity of care and access determined by a postcode lottery. As there is a high unmet need in this population clinical commissioning groups will make differing local commissioning decisions with the aim of saving lives and improving patient outcomes. • The potential to create further inequality exists since patients with a GI bleed will have access to treatment, and some groups of patients, for example Jehovah's witnesses, are unable to receive off-label treatment, PCCs, as they are blood product derivatives. **Other major bleeds** • We acknowledge the concerns of the committee in this patient population, and with no further evidence in this patient group, accept NICE's decision. Andexanet alfa's mode of action and speed of reversal andexanet alfa is likely to have benefits in this population. Therefore, we do not accept the wording stating that the indirect comparison suggests that andexanet alfa "*lowers survival for people with bleeds in other parts of the body*" [ACD 1.2]. At	

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			this time patient numbers are insufficient and bleed types are too heterogeneous in this group for an indirect comparison to provide conclusive results.	
2	Company	Portola Pharmaceuticals	**Andexanet alfa's known mechanism of action is specifically designed to rapidly arrest DOAC-related bleeding and limit haematoma expansion. PCCs have no mechanistic rationale to arrest DOAC-related bleeding or limit haematoma expansion.** • Where an anticoagulant reversal treatment has a known mechanism of action, if a defined 'to-benefit' population is treated early, it is possible to limit haematoma expansion and consequently improve mortality and morbidity: ○ A study of the reversal of warfarin-related intracerebral haemorrhage revealed that PCCs not only improved survival but that improved survival was not at the expense of increased disability. Patients who received PCCs had greater functional independence measure gains than those who did not receive PCCs (28.3 vs 12.3, p = 0.049). Furthermore, earlier treatment was associated with better survival after controlling for ICH score, compared with no treatment (p = 0.053).[6] • Andexanet alfa sequesters FXa inhibitor within 2-5 minutes of bolus administration and is sustained for the duration of infusion.[8] In contrast, PCCs are unable to affect FXa inhibitory activity with resultant delayed effects on thrombin generation.[9,10] • PCCs have no known mechanism of action for FXa inhibitor reversal. *In vitro* studies have shown PCCs are unable to overcome FXa inhibition through exogenous supplementation of FX (not FXa) at commonly used doses of 50 IU/Kg at therapeutic FXa inhibitor levels. PCC supplemented FX cannot bind and neutralise FXa inhibitors. Furthermore, any overloading with prothrombin from PCCs is limited through FXa inhibition.[11] • The known mechanism of action for andexanet alfa as a FX decoy protein with demonstrable dose-dependent decrease in FXa inhibitory activity results in reduction of haematoma expansion. Therefore, through its known mechanism of action, andexanet alfa will result in a clinically meaningful reduction in haematoma expansion in its licensed indication. In contrast, PCCs have failed to demonstrate any plausible mechanism of action and any corresponding impact on haematoma expansion, mortality or morbidity in persons with ICH receiving a DOAC.[12]	Thank you for your comment. The committee considered this feedback in the third committee meeting. It noted that PCC has a different mechanism of action to andexanet alfa, is used off-label and is supported by limited clinical evidence. However, no data on intracranial haematoma growth was available for people on anticoagulants not treated with andexanet alfa. The committee also noted clinical expert comments that haemostatic efficacy as defined in the trial could not be considered directly predictive of clinical outcomes. For further details of the committee discussion see FAD section 3.2 and 3.5.
3	Company	Portola Pharmaceuticals	**Haematoma expansion is a key prognostic factor for mortality and morbidity. The ANNEXA-4 study demonstrated a clinically meaningful effect on limiting haematoma expansion in a population at high risk of haematoma expansion.** In Section 3.5 of the ACD, it was noted that: "*the evidence on clinical events was limited to 30-day mortality*" and "*a large bleed volume at first*	Thank you for your comments. The committee considered this feedback at the third appraisal meeting. The committee noted that there is limited data about the expected size of haematoma growth in people treated with both andexanet alfa and

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			presentation is an important indicator of a poor prognosis, and patients with large bleeds were excluded from ANNEXA-4." [ACD, 3.5] • In clinical studies of intracerebral haemorrhage, haematoma expansion has been shown to result in worsening mortality and morbidity: o In a meta-analysis of patients with spontaneous intracerebral haemorrhage, mortality was significantly related to percentage change in haemorrhage growth at 24 hours indicating that for each 10% increase in growth, the mortality hazard rate increased by 5%.[13] o For each ml increase in baseline intracerebral haemorrhage volume and for each 10% increase in growth, patients were 6% and 16% more likely to increase 1 point on the outcome mRS, respectively. In addition, for each 10% increase in intracerebral haemorrhage growth, patients were 18% more likely to worsen from independence to assisted independence or from assisted independence to poor outcome. • The use of anticoagulants, baseline haematoma volume and earlier time from symptom to baseline imaging increases are associated with greater likelihood of haematoma expansion, where early treatment is all the more necessary.[14,15] • Despite the committee's reservation on the severity and generalisability of the ICH population recruited in ANNEXA-4, patients enrolled in ANNEXA-4 entered early at onset and were at high risk of haematoma expansion: o ANNEXA-4 **recruited patients early after symptom onset** when haematoma expansion is known to occur within the first 24 hours of haemorrhagic stroke symptom onset, with the highest probability within the first 5 hours of the onset of the bleed in non-anticoagulated patients.[15] o ANNEXA-4 **recruited patients with bleed volumes that are at a high risk of expanding**. Haematoma expansion is known to occur with increasing baseline bleed volume, with likelihood of haematoma expansion to a peak and then plateau at around a 75 ml baseline bleed volume.[13] • ANNEXA-4 was designed to demonstrate the effect of andexanet alfa on haemostatic outcomes in a relevant population that was most likely to benefit from rapid reversal, that is, those with a high risk of haematoma expansion. o This objective was achieved as people with spontaneous intracranial bleeding including intracerebral bleeding received andexanet alfa within 3-4 hours of	standard care. The committee also noted clinical expert comments that haemostatic efficacy as defined in the trial could not be considered directly predictive of clinical outcomes. For further details of the committee discussion see FAD section 3.5.

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			symptom onset and baseline haematoma volume in ANNEXA-4 included a spectrum of bleed volumes up to 60 ml. It was further noted in Section 3.5 of the ACD that: *"Not all bleeds enlarge, and it is difficult to say that a haematoma growth of less than 35% for intracerebral haemorrhage can be considered a positive outcome or a good haemostatic efficacy as defined in the trial." [ACD, 3.5]* • Haematoma expansion is a modifiable clinical predictor of disability and death in intracerebral haemorrhage. Therefore, early limitation of haematoma expansion is a desired therapeutic goal to prevent death and limit disability when assessing intracerebral haemorrhage treatment.[16,17] • As such, haematoma expansion has been a clinical endpoint in studies of therapeutic interventions for intracerebral bleeding including haemostatic therapies including aggressive blood pressure control.[16,18-21] • The definition of haemostatic efficacy for intracerebral bleeding utilised in ANNEXA-4 is consistent with other intracerebral bleed research[18-21] with use of absolute cut-offs (typically ≥3, ≥6 ml), proportional cut-offs (typically >26% or >33%), or a combination of both from baseline growth on follow-up imaging within the first 24 hours. • All previous haematoma expansion thresholds proposed have been shown to be associated with poor outcomes (defined as mRS 4-6). Definitions of haematoma expansion using larger haematoma volume increases predict greater changes in outcomes than lower thresholds. Furthermore, baseline haematoma size has little bearing on the ability of haematoma expansion (defined absolutely or relatively) to predict outcomes.[22] • Therefore, the definition of haematoma expansion used in ANNEXA-4 can be considered clinically relevant across the entire spectrum of baseline haematoma volume sizes. This conclusion is supported by a Delphi panel of 10 UK ICH experts (see Appendix A, Question 2). • The ANNEXA-4 study demonstrated a clinically meaningful effect on limiting haematoma expansion in a population at high risk of haematoma expansion. o Of 99 efficacy-evaluable patients with spontaneous ICH, a limitation in haematoma expansion of less than 35% between baseline and at 12 hours (as per the Sarode criteria) was achieved in 79% of patients with spontaneous intracerebral haemorrhage.	

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			○ Of patients with a limitation in haematoma expansion of less than 35%, 91% of these patients demonstrated 'excellent' haematoma expansion, defined as <20% at 1 hour from baseline sustained at 12 hours following andexanet. ○ Finally, the magnitude of the reduction in anti–Factor Xa activity was a predictor\\a of ICH haemostatic efficacy[8] and therefore supportive of andexanet alfa's mechanism of action in reducing haematoma expansion and improving clinical outcomes (see Comment Note 2). **Therefore, andexanet alfa's effects on reducing haematoma expansion are robust, and would translate into a mortality and morbidity benefit compared to PCC.**	
4	Company	Portola Pharmaceuticals	**Andexanet alfa will improve morbidity and associated quality of life in ICH patients for its anticipated use in the UK.** In Section 3.9 of the ACD it is stated that: *"The committee considered that the aim of treatment is to improve survival with less risk of long-term disability. But the survival improvement may lead to people being alive but with severe disability... it was unclear whether andexanet alfa improves very disabled survival in people who would otherwise die, or is improving the number of people with excellent recovery." [ACD, 3.9]* • We acknowledge the concern raised in the ACD. However, clinical expert consultation, consideration of andexanet alfa's mechanism of action, and demonstrated effect on haematoma expansion, suggest that an improvement in morbidity would be expected across the spectrum of disability. • The modified Rankin Scale (mRS) is a well-known neurological scale that incorporates the full spectrum of functional impairment from having no symptoms (score 0) to death (score of 6). See Appendix A, Table 12 for further information. Since haematoma expansion is linked to mRS outcomes, we would expect treatment with andexanet alfa to shift mRS scores down across the entire population. • In a Delphi panel of 10 UK ICH experts, all nine experts that attended the consensus meeting agreed that in the population for which clinicians would consider treatment with andexanet alfa, the rapid administration of andexanet alfa would likely have a better morbidity and quality of life outcome compared with PCCs based on the published data that andexanet alfa is effective in limiting the haematoma expansion, (see Appendix A, Question 2). ○ "I would expect a shift of mRS across all categories. For example, it may prevent those on track for mRS 1-3 worsening to mRS 4-5 and so forth. So mRS 5 may not	Thank you for your comment. In light of the uncertainty surrounding the effect of andexanet alfa on morbidity, NICE ensured that experts were invited to all three committee meetings. The committee heard from a clinical expert that for an effective intervention that improves mortality, all people with an ICH would be expected to have an improved level of disability on their baseline. However, the committee agreed that the size of any mortality benefit was uncertain and there was no robust clinical evidence for a benefit in morbidity. For this reason, it concluded that the benefit of andexanet alfa on long-term disability after ICH is unproven. For further details of the committee discussion see FAD section 3.10.

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			increase overall or at least as much as one might think." o One expert quoted that: "The overall outcome from any brain injury is a spectrum. By preventing mortality which results in a patient with severe disability, you shift the whole spectrum. Therefore, some severely disabled patients will become moderately disabled, some moderately disabled will become mildly disabled etc." • In the same panel, there was consensus that in the population for which clinicians would consider treatment with andexanet alfa, a positive clinical benefit for 30-day mortality in ICH patients would likely shift in the modified Rankin score across the entire population (net positive impact on disability) (see Appendix A, Question 3). • Furthermore, there is additional evidence to support the ICH experts view, as evidenced by the study by Oie et al.[23] o Average mRS scores for the intracerebral population were higher in Oie et al. than those for intracerebral patients in ANNEXA-4: mRS was [redacted] at day 30 in ANNEXA-4 and 4.41 at day 90 in the Oie et al. study. o In a Delphi panel of 10 UK ICH experts, all nine experts that attended the consensus meeting agreed that mRS score would improve for patients with an ICH or intracerebral haemorrhage only between 30 days and 90 days by at least 1 mRS category (see Appendix A, Question 4). o Furthermore, evidence has been shown to suggest that mRS improves by at least 1 point between 30 days and 90 days, and then post 90 days.[24,25] o This would mean that andexanet alfa intracerebral patients predicted mRS at day 90 would be ~[redacted], equating to an average mRS benefit of 2 or more compared to PCC. o Once again, this suggests that andexanet alfa would have a net-positive impact on morbidity and associated quality of life in the ICH population for which it will be used. • Therefore, <u>andexanet alfa will reduce mortality and improve morbidity and corresponding quality of life in surviving patients for its intended use in the UK</u> based on the following evidence: o Andexanet alfa's mechanism of action (see Comment Notes 2) o Andexanet alfa's demonstrated limitation of haematoma expansion (see Comment	

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			Notes 3) ○ **<u>Complete clinical consensus</u>** from a Delphi panel of 10 UK experts Comparison of intracerebral bleeds with andexanet alfa (ANNEXA-4) versus PCC (Oie et al.)	
5	Company	Portola Pharmaceuticals	**Andexanet alfa is used to limit further neurological deterioration in persons likely to survive. *A priori* clinical assumptions of functional recovery and patient adaptability post ICH are imprecise. Clinicians will engage patients and their relatives (where possible) in joint clinical decision making accounting for patient values and treatment preferences.** In Section 3.9, the ACD states: "*The committee was concerned by comments received at consultation from the British Association of Stroke Physicians, stating that it was unclear whether andexanet alfa improves 'very disabled survival in people who would otherwise die, or is improving the number of people with excellent recovery'. This uncertainty would make treatment decisions difficult and might involve discussions with relatives about whether to use andexanet alfa for ICH." [ACD, 3.9]* • We appreciate the committee's concern around the uncertainty of andexanet alfa on morbidity where the risk of long-term disability may outweigh any survival benefit, and in a Delphi panel with 10 experts in ICH, there was consensus that treating clinicians involve patients and their relatives or carers in their clinical decision making when possible (see Appendix A, Question 1c). • However, the same panel were in consensus that andexanet alfa would be given regardless if there is a chance of survival, only with the exception of cases characterised with poor premorbid function (e.g. mRS >4) and/or an advance directive. ○ The experts stated that decisions in the emergency setting are focused on probability of survival in first 72 hours, rather than attempting to estimate morbidity following treatment, and that prior clinical assumptions on likely disability have been wrong. ○ "The aim must be to try to urgently normalise the coagulation to prevent further haematoma expansion (a decision in patient's best interest), before attempting to consult the relatives" ○ They also stated that deciding not to reverse anticoagulation is essentially allowing a higher risk of deterioration to occur, and that 'Time is brain', where any delay in treatment may result in worse outcomes. • The issue of trading severe disability for death has been highlighted in relation to a number	Thank you for your comment. At the third committee meeting clinical experts emphasised the difficulty in deciding when to use andexanet alfa in clinical practice, because treatment should be given as soon as possible and the decision may fall to relatively inexperienced doctors. So, it is likely all people would be offered treatment in the NHS, rather than the selected group included in ANNEXA-4. For further details of the committee discussion see FAD section 3.9. The committee also agreed that it is uncertain whether or to what extent andexanet alfa would reduce long-term mortality and morbidity in ICH, but acknowledged that the ongoing RCT in ICH will provide further data on short-term mortality and neurological outcomes. For this reason, the committee agreed that andexanet alfa should be recommended in research for ICH. See FAD section 3.9 and 3.11.

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			of other interventions in stroke, most notably hemicraniectomy for malignant middle cerebral artery syndrome. o Hemicraniectomy is a treatment that is recommended in the Royal College of Physicians Guideline for stroke and is a widely accepted, live-saving treatment for selected patients.[26] Studies have shown that despite high rates of physical disability and depression, the vast majority of patients that underwent this emergency live-saving surgery are satisfied with life and do not regret having undergone surgery.[27] • There is an inherent assumption that, given the choice of being left with severe disability or death, patients may prefer not to be resuscitated, and that with respect to quality of life, surviving patients may consider themselves to be in a state "worse than death'. However, studies of patients surviving an intracerebral haemorrhage demonstrate that this is not the case: o Reported utility scores were high in many patients at 3 months following an intracerebral haemorrhage, with means (SD) 0.82 (0.28) and 0.62 (0.3)[28,29] – far from zero with utilities increasing over time. o Further, utilities were associated with factors that determine functional outcome, reinforcing the need for careful patient selection. • Therefore, patients who survive ICH adapt with a quality of life acceptable for most patients and certainly, on average, more desirable outcome than death. • This suggests that patients' perceptions of personal health, well-being, and satisfaction with life are often discordant with their objective health status and that many individuals appear to adapt to life-changing events and subsequently accept a degree of disability that they would previously have judged to be unacceptable. The reasons may be due to the following considerations: o Firstly, there is considerable statistical and clinical uncertainty about prognosis after stroke. o Secondly, individuals place different values on different outcomes after stroke. This is because different outcomes (e.g. ability to talk, walk) may impact differently on different individuals' quality of life. Many factors can affect this including culture and religion. o Thirdly, it may be difficult to elicit patient values after a stroke and be certain of the accuracy of previously expressed wishes. This is because, those severely affected	

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			from their stroke may have dysphasia or cognitive impairments, preventing them from communicating their values. In these circumstances, clinicians often rely on proxies who may not know the patient's values well. Even where a patient has expressed a previous wish, this may change over time or when faced with the reality. • Therefore, the reality is that for patients where andexanet alfa would be used as a life-saving therapy, it would be administered to those likely to survive and have prior good functional baseline (premorbid mRS <=4), to prevent further neurological deterioration. It would be erroneous for the clinician to presume to be able to predict accurately any likely functional recovery and patients' adaption to their disability *a priori*. In these circumstances, treating clinicians would involve patients and their relatives or carers in their clinical decision making when possible to clarify patient wishes and pre-morbid function, and this should not adversely affect the decision to provide andexanet alfa to the vast majority of patients where quality of life is acceptable compared to death.	
6	Company	Portola Pharmaceuticals	**The uncertainty related to quality of life is by how much andexanet alfa will improve quality of life in surviving ICH patients compared to PCC** In Section 3.14 of the ACD it stated that: "*The committee concluded that differences in the long-term outcomes and utilities for people after an ICH, depending on the treatment they had, are highly uncertain.*" [ACD, 3.14] • We acknowledge the concern raised in the ACD. To help address this concern, we conducted a Delphi panel with 10 UK ICH experts to understand the probable long-term outcomes and utilities for patients with an ICH following treatment with andexanet alfa compared to treatment with PCCs, for the population in which it is to be used (see Appendix A, Question 5). • All nine experts who attended the consensus meeting agreed they would expect a morbidity benefit associated with andexanet alfa compared with PCCs based on published data that andexanet alfa is effective in limiting haematoma expansion. • There was a consensus that difference in average quality of life between patients receiving andexanet alfa and PCCs utility would be between the range of 0.05 and 0.1 based on the average shift of mRS score between 0.5 and 1. • Summaries of the probable long-term morbidity outcomes and utilities are provided below: o Baseline utility among ICH survivors in the long term is 0.61 for both andexanet alfa and PCC, as per NICE TA341 [company base case assumption]:	Thank you for your comment. Given the uncertainty surrounding a quality-of-life benefit with andexanet alfa, NICE ensured that experts were invited to all three committee meetings. The committee noted that the results of the Delphi panel supported a utility benefit following treatment with andexanet alfa but was concerned that any increase in benefit was uncertain, as was the size of the benefit. The committee noted that the company scenarios with varying utility benefits for andexanet alfa compared with PCC also assumed a 30-day mortality benefit for andexanet alfa over PCC. Because a mortality benefit was uncertain, the committee was not confident that the scenarios for ICH were robust. For further details of the committee discussion see FAD section 3.9 and 3.17.

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			▪ Utility benefit = 0.05, lower end of expert range: ICER = [redacted] ▪ Utility benefit = 0.075, mid-point of expert range: ICER = [redacted] ▪ Utility benefit = 0.10, higher end of expert range: ICER = [redacted] o Baseline utility among ICH survivors in the long term is 0.53 for both andexanet alfa and PCC, mapped ANNEXA-4 [ERG base case assumption]: ▪ Utility benefit = 0.05, lower end of expert range: ICER = [redacted] ▪ Utility benefit = 0.075, mid-point of expert range: ICER = [redacted] ▪ Utility benefit = 0.10, higher end of expert range: ICER = [redacted] • The ICER ranges are as follows: o Baseline utility among ICH survivors in the long term is 0.61 for both andexanet alfa and PCC (NICE TA341) = [redacted] o Baseline utility among ICH survivors in the long term is 0.53 for both andexanet alfa and PCC (ANNEXA-4) = [redacted] • Therefore, the uncertainty in quality of life does not translate into large differences in cost-effectiveness – all estimates provided by the Delphi panel fall within a range that would be considered a cost-effective use of NHS resources.	
7	Company	Portola Pharmaceuticals	**Base case cost-effectiveness results and scenario analyses for ICH, show that andexanet alfa is a cost-effective use of NHS resources** • Following review of the second ACD, the revised base case presented in the first ACD response remains unchanged. • We are largely in agreement with the ERG's preferred base case. There are only two assumptions of difference: o The ERG applies ANNEXA-4 mRS distributions in both treatment arms; this assumes no benefit with andexanet alfa on morbidity and associated quality of life – for which no clinician agreed this was likely in the Delphi panel, and for which the ERG acknowledges is highly conservative. o The company derives a benefit utilising the published Oie et al. study, comparing day 30 mRS from ANNEXA-4 with day 90 mRS from Oie et al. Consensus from the Delphi panel was in complete agreement that day 30 mRS would improve by an average of at least 1 on the mRS – hence this comparison, may indeed be	Thank you for your comment. The committee considered the company base case and scenarios with varying utility benefits for andexanet alfa compared with PCC. The ICERs which all included the 30-day mortality benefit from the indirect comparison, either with no utility benefit, as preferred by the ERG, or the modal benefit as suggested by the Delphi panel, were above what NICE normally considers a cost-effective use of NHS resources. The committee recalled that the extent to which andexanet alfa reduces mortality is uncertain and that reducing the 30-day mortality benefit for andexanet alfa compared with established clinical management

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			conservative and bias in favour of PCC. See Appendix A Question 4. ○ The ERG derives long term utility among ICH survivors by mapping the mRS score to EQ-5D from the ANNEXA-4 study at day 30. As a result, utility of an ICH survivor is 0.53 in both treatment arms. Considering the Delphi panel consensus that mRS would improve by at least 1 between day 30 and day 90, the utility of 0.53 would improve to ~0.63 by day 90 (and possibly further thereafter). See Appendix A, Question 4 ○ The company uses a baseline utility of 0.61 accepted as a generalisable UK utility for ICH in a prior NICE technology assessment (TA341). This broadly aligns with the predicted day 90 value from the mapped mRS of ANNEXA-4 (=0.63), per the ERG's assumption. • The results of our base case are as follows; ○ Base case = [redacted] ○ Threshold analyses varying morbidity benefit associated with andexanet alfa relative to PCCs, considering the Delphi panel results = [redacted] • The results of the ERG revised base case are as follows; ○ Base case = [redacted] ○ Threshold analyses varying morbidity benefit associated with andexanet alfa relative to PCCs = [redacted], as published by the ERG[7] • Even under the extreme clinical assumption of no morbidity benefit, which was deemed conservative by the ERG,[7] clinically implausible by UK clinicians engaged during the first ACD response,[30] and subsequent Delphi panel conducted as part of this response (Appendix A), both our base case and the ERG revised base case result in ICERs within the range of what NICE would consider cost-effective - under [redacted] • The more likely clinical scenario of a baseline utility of ~0.61, and some form of clinical benefit on quality of life for andexanet alfa results in ICERs under [redacted] Therefore, it can be concluded that andexanet alfa is a cost-effective use of NHS resources in ICH.	including PCC would further increase the ICER. Therefore, the committee was not confident that any of the ICERs for ICH were robust, and those presented may well be underestimates. So, it could not recommend andexanet alfa for routine commissioning in ICH. For further details of the committee discussion see FAD section 3.17.
8	Company	Portola Pharmaceuticals	**To minimise the risk of improved survival at the expense of increased disability, optimise clinical outcomes, and ensure the guidance will be easy to implement, andexanet alfa should only be used in its licensed indication, where there is potential for benefit.**	Thank you for your comment. At the third committee meeting clinical experts emphasised the difficulty in deciding when to use andexanet alfa

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			• Andexanet alfa would fit into current clinical pathways in the UK for patients with life threatening or uncontrolled bleeding who require immediate resuscitation, including intracerebral haemorrhage protocols. • The uncertainty regarding disability outcomes will be minimised as all nine ICH experts in the Delphi panel agreed that they would likely treat any patient with andexanet alfa provided that they had taken apixaban or rivaroxaban within the previous 12 hours or so and that they were deemed likely to experience long-term survival benefits (similar to eligibility criteria of GCS >7 and ICH volume <60 ml used in the ANNEXA-4 trial) (see Appendix A, Question 1b) • This recommendation is based on the availability of prognostic indicators related to ICH morbidity and mortality in patients with intracerebral haemorrhage which have been explored in Comment Note 3. • Recommending treatment as per the licensed indication and having this recommendation fit into existing protocols, will ensure that physicians use andexanet alfa where there is the potential for benefit. • Time bound and severity dependent protocols already exist in stroke thrombolysis and ischemic stroke pathways. Treatment criteria will also help clinicians with their discussion regarding treatment options with family and relatives, and where appropriate make the decision to put patients on a palliation pathway.	in clinical practice, because treatment should be given as soon as possible and the decision may fall to relatively inexperienced doctors. So, it is likely all people would be offered treatment in the NHS, rather than the selected group included in ANNEXA-4. For further details of the committee discussion see FAD section 3.9.
9	Company	Portola Pharmaceuticals	**The ANNEXA-I study will not address uncertainties related to long term morbidity in ICH, and a recommendation for andexanet alfa 'only in research' in people with ICH is not appropriate.** In the Section 5.1 of the ACD it states that: "*The committee noted an ongoing randomised controlled trial of the effectiveness of andexanet alfa compared with prothrombin complex concentrate in people with ICH. The main outcomes of interest are mortality, long-term disability and the risk of thromboses and thromboembolic events.*'' [ACD, 5.1] • ANNEXA-I was not designed to address uncertainties regarding long term disability as it was not a concern for the regulators. • As such, no outcomes on long term disability >30 days being collected in ANNEXA-I (trial of andexanet in ICH patients receiving an oral FXa inhibitor; ClinicalTrials.gov Identifier: NCT03661528). • In brief, the requirement to perform ANNEXA-I at the time of authorisation was to address	Thank you for your comment. The committee considered this feedback and re-examined the ANNEXA-I study during the third committee meeting. It recognised that although the randomised controlled trial will not resolve the uncertainty on long-term morbidity or mortality, it will provide stronger evidence of haemostatic efficacy and short-term mortality and neurological outcomes. The committee concluded that additional data collection is needed compared with standard management in ICH, therefore it recommended andexanet alfa in the context of the research mandated by

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			the following uncertainties: ○ Establish the FXa inhibitory activity to haemostatic efficacy relationship. This relationship is important to support the proposed dosing regimen for andexanet. ○ Thrombotic rate of andexanet alfa in comparison to a comparable patient population. In the ACD, it is also is noted that: *"the European Stroke Organisation 2019 guideline on reversal of oral anticoagulants for ICH recommended early reversal 'using andexanet alfa if available'. However, it also recommended 'randomising into trials as based on the low quality of evidence' because 'there is significant uncertainty whether desirable outweigh undesirable effects". [ACD 3.9]* • However, these recommendations were based on interim analyses from ANNEXA-4. The publication of the full ANNEXA-4 trial results has since been added to the evidence base and other recommendations have been updated to reflect use preferential use of Andexanet over PCCs where available including 2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants.[31]	the regulator. For further details of the committee discussion see FAD section 3.9.
10	Company	Portola Pharmaceuticals	**Although we accept the decision in patients with 'other bleeds', we would like to note that andexanet alfa is expected to benefit these patients, despite the limited evidence in this group** • Clinicians contacted following the first appraisal committee meeting stated that they would expect andexanet alfa treatment to be beneficial in this population. However, we acknowledge the limitations in the evidence base. • Section 1.2 of the ACD states that the results of the indirect comparison suggest *"that andexanet alfa lowers survival for people with bleeds in other parts of the body*." ○ As described in the original submission, and all post submission document, the results of the propensity score matching analysis was not considered robust in patients with other major bleed. ○ Namely, heterogeneity in the bleed types in this subgroup and extremely small sample size rendered these results unreliable, as corroborated by their clinically implausible values (andexanet alfa being associated with greater mortality relative to PCCs). As a result, we did not apply results in the cost effectiveness model. Hence, whilst it is appropriate to	Thank you for your comment. The committee considered this feedback and concluded that there is a clinical need for effective anticoagulation reversal agents after apixaban or rivaroxaban in people with other bleeds, but that the clinical evidence presented is insufficient to recommend the technology in this cohort. For further details of the committee discussion see FAD section 3.12 and 3.14. In light of your comments on andexanet alfa in other bleeds, section 3.12 of the FAD has been amended to read '*The company stated that it expected andexanet alfa treatment to be beneficial in this population'*. Section 3.14 of the FAD

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			consider the evidence generated using propensity score matching analysis in ICH/GI where these limitations do not apply, we maintain that the analysis in other bleeds should be disregarded and request that the limitations of analysis so far in this group be characterised more accurately, as a lack of robustness.	has been amended to read: '*At consultation, the company agreed that its assumptions were uncertain because of the limited evidence available*.'
11	Company	Portola Pharmaceuticals	**The recommendations in their current form raise concerns over equality.** As noted in Section 3.18 of the ACD, the lack of an alternative to PCCs raises an equality concern. • Inequality would arise where people with rivaroxaban or apixaban related major gastrointestinal bleeding will be able to access a life-saving treatment, whereas those with intracranial bleeding will not. o The likely impact on the UK population is that approximately [redacted] ICH-related deaths are occurring each year in people in England who are being treated with apixaban or rivaroxaban, of which approximately two-thirds could be avoided with availability of andexanet alfa. • Some groups of people refuse blood products and their derivatives due to religious reasons (e.g. Jehovah's witnesses) even in life-threatening situations such as major bleeding. Although these reasons do not impact on the economic models proposed to NICE, if NICE decide not to allow routine reimbursement for andexanet in intracranial haemorrhage, it would mean these people would not have access to an additional therapeutic option where PCC use is not acceptable.	Thank you for your comment. The committee considered this feedback at the third committee meeting. It noted the national variation in access to andexanet alfa if recommended only in research for ICH, but noted that this variation is governed by entry to a randomised controlled trial which had been mandated by the regulator. It concluded that the ability to take part in this research was not an issue that needed its recommendation to be altered. The committee also noted that treatment options were limited for people who cannot have PCC. The committee was aware that people who would not be able to have PCC would have alternative clinical management. It noted that no data had been presented that compared established clinical management outcomes with and without blood products. The committee noted that data from the ongoing randomised controlled trial might reduce this uncertainty in ICH, because it compares andexanet alfa with standard care, which is not limited to PCC. However, the committee concluded that the effectiveness of andexanet alfa in ICH and other bleeds was still highly uncertain for people who could and could not have blood products. Therefore, there was no need to alter its recommendation. For further details of the committee

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				discussion see FAD section 3.19.

NICE National Institute for Health and Care Excellence

Andexanet alfa for reversing anticoagulation [ID1101]

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Portola Pharmaceuticals (a wholly owned subsidiary of Alexion Pharmaceuticals)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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Andexanet alfa for reversing anticoagulation [ID1101]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Executive summary** Portola would like to thank the committee for the opportunity to respond to the second Appraisal Consultation Document (ACD). We welcome the recommendation for the use of andexanet alfa for reversing anticoagulation with apixaban or rivaroxaban in adults with life-threatening or uncontrolled bleeding in the gastrointestinal tract. However, we are concerned that despite the substantial and statistically significant mortality benefit demonstrated for the intracranial haemorrhage (ICH) population, the recommendation for 'only in research' fails to address the needs of this important patient group. We would highlight that neither the ANNEXA-I study nor other planned research will address uncertainties related to long term morbidity in ICH, as this was not a concern for the regulators in the US or Europe. As recognised by the EMA, andexanet alfa is an innovative medicine, and no alternative options for effective FXa inhibitor reversal exist. As such, we are committed to providing a comprehensive response that will enable NICE to recommend access to andexanet alfa via routine commissioning; as a life-saving and disability reducing therapy for ICH patients. **As noted by the committee, there remains a significant unmet need for those with ICH who require reversal of apixaban or rivaroxaban anticoagulation** • The use of direct oral anticoagulants (DOACs) for anticoagulation has increased substantially in recent years, particularly in light of recent COVID 19-related guidance. There were an estimated [redacted] people treated with apixaban or rivaroxaban in 2018, compared to an estimated [redacted] in 2020, including the expected increased uptake due to COVID-19 [EPACT and NHSE].[1] • Despite increased availability and use of DOACs, major bleeding concurrent with the use of these medications remains a burden of clinical significance in the NHS. • In 2020, approximately [redacted] people in England who are being treated with apixaban or rivaroxaban experience an ICH that is life-threatening or uncontrollable,[1] resulting in an estimated [redacted] deaths (49%). • With the availability of an effective reversal agent such as andexanet alfa, many of these deaths (approximately [redacted]) could be avoided each year. **Current usual care in ICH does not address the unmet need** • As agreed by the committee, patient groups and clinical experts, the ICH population represents the population with the largest clinical unmet need across all life-threatening or uncontrolled bleeds. Approximately 50% of patients experiencing an ICH in the andexanet-eligible population died following PCC off-label treatment in the recent UK-based ORANGE study.[2,3] • In particular, intracerebral haemorrhage carries a very high mortality burden, which increases for anticoagulated populations.[4,5] Other treatments which limit haematoma expansion in anticoagulated patients with non-FXa inhibitor-associated intracerebral bleeds, via a known

mechanism of action (e.g. PCC reversal of warfarin) have demonstrated improved survival without worsened morbidity.[6] However, for FXa inhibitor bleeds, PCCs are unlicensed treatments with no known mechanism of action and with no evidence of any effect on limiting haematoma expansion nor associated mortality / morbidity improvement.

- In contrast, andexanet alfa has a robust mechanism of action with immediate sequestration of FXa inhibitor within 2-5 minutes of bolus. Early administration of andexanet alfa in an ICH population with therapeutic FXa inhibitor anticoagulation drives thrombin generation and limits haematoma expansion. Consequently, mortality and morbidity benefits are to be expected.

The available evidence demonstrates that, as seen in those with gastrointestinal bleeding, andexanet alfa treatment results in substantially reduced mortality in people with ICH

- Despite the uncertainty of single-arm trial evidence, the committee accepted that:

  "Andexanet alfa is likely to reduce 30-day mortality for people with GI bleeds" [ACD, 3.8]

- We note that the evidence base to support this comprises the propensity score matching analysis of ANNEXA-4 and ORANGE, a US multicentre real-world analysis study of patients receiving andexanet alfa within its licensed indication, and the predicted mortality outcomes of patients, estimated from the Rockall score at baseline in ANNEXA-4.

- We acknowledge that the committee formed a similar conclusion on mortality in the ICH population:

  "The indirect treatment comparison predicted that andexanet alfa reduces mortality in ICH. The committee considered this to be plausible." [ACD, 3.9]

- We note that the evidence base to support this comprises the same propensity score matching analysis of ANNEXA-4 and ORANGE, and US multicentre real-world analysis study of patients receiving andexanet alfa within its licensed indication.

- We further note that the ACD states:

  "*the size of benefit was unclear*" [ACD 3.9]

- We would respectfully refer to our response to the first ACD, whereby five indirect comparison approaches, including propensity score matching and inverse probability of treatment weighting, resulted in the same outcome:

  [redacted]

- With no evidence to the contrary, and supporting evidence of the robustness of results from the Rosenbaum sensitivity analysis and US multi-centre real-world analysis, it is clear that andexanet alfa would confer a substantial and significant mortality benefit in ICH patients.

Despite some uncertainty relating to the level of disability, andexanet alfa is a cost-effective treatment in patients with ICH, even under scenarios deemed most conservative by clinicians and the ERG

- We acknowledge that the conclusion of the ACD points to an uncertainty related to the disability of patients with andexanet alfa following treatment, despite the fact that the range of ICERs

(even with the ERG's updated base case) lie within the bounds of what would usually be deemed cost-effective:

"*The company's ICER was within the range NICE normally considers a cost-effective use of NHS resources. However, the committee had concerns about the methods and assumptions used in the model, particularly the assumption of a benefit from andexanet alfa on long-term disability after an ICH that had not been adequately justified or evidenced. The committee was concerned that it was unclear if people who had andexanet alfa would make a good recovery, or whether they would be severely disabled. The committee considered the ERG's updated base case for the ICH cohort, which resulted in a higher ICER. Therefore, the committee was not confident that the results for ICH were robust.*" [ACD, 3.6]

- As part of this response, we present below compelling evidence to support the conclusion that andexanet alfa would improve morbidity and associated quality of life compared to PCC. This is congruent with the ERG's conclusion that assuming andexanet alfa would have no effect on morbidity and associated quality of life compared to PCC is a conservative assumption.[7]

- We conducted a Delphi panel to elicit clinical consensus from 10 UK ICH experts including a contingent of ordinary, former and currently serving committee members of the British Association of Stroke Physicians (BASP) to understand the effect of andexanet alfa on morbidity and corresponding quality of life.

- Of the 10 UK ICH experts, nine participated in a consensus meeting. **All nine experts agreed** that it is likely that andexanet alfa would shift the spectrum of disability, resulting in a positive quality of life outcome in comparison to PCCs in the population for which clinicians would consider treatment. See Appendix A for further details.

- We also present multiple evidence sources to suggest that andexanet alfa would improve morbidity and corresponding quality of life in the population for which clinicians would consider treatment, demonstrating that the ICER lies within a cost-effective range and as such, andexanet can be recommended in the patient group which needs it the most.

A recommendation for the ICH population via routine commissioning has established pathways to facilitate successful implementation

- Currently, people with intracranial bleeding (including people with spontaneous intracerebral bleed) are treated throughout the UK through established clinical care pathways (e.g. stroke and neurosurgical pathways). Emergency departments can differentiate between intracranial bleed types with urgent scanning, and characterise ICH severity (clinically and through imaging) with urgent referral to the relevant stroke or neurosurgical team.

- In clinical practice, resolving uncertainty in therapeutic decision making involves consideration of patients' baseline clinical severity, past medical history, premorbid function and treatment benefits versus risks, and patients' wishes (possibly expressed through advanced directives or family/carers) and consultation with colleagues. There was consensus reached on both of these topics raised in the Delphi panel (see Appendix A, Question 1a and Question 1c)

- All nine ICH experts in the Delphi panel agreed that they would likely treat any patient with andexanet alfa provided that they had taken apixaban or rivaroxaban within the previous 12 hours or so and that they were deemed likely to experience long-term survival benefits (similar to eligibility criteria of GCS >7 and ICH volume <60 ml used in the ANNEXA-4 trial) (see Appendix A, Question 1b).

	• Failure to offer routine guidance for those with ICH will create inequity of care and access determined by a postcode lottery. As there is a high unmet need in this population clinical commissioning groups will make differing local commissioning decisions with the aim of saving lives and improving patient outcomes. • The potential to create further inequality exists since patients with a GI bleed will have access to treatment, and some groups of patients, for example Jehovah's witnesses, are unable to receive off-label treatment, PCCs, as they are blood product derivatives. **Other major bleeds** • We acknowledge the concerns of the committee in this patient population, and with no further evidence in this patient group, accept NICE's decision. • Andexanet alfa's mode of action and speed of reversal andexanet alfa is likely to have benefits in this population. Therefore, we do not accept the wording stating that the indirect comparison suggests that andexanet alfa "*lowers survival for people with bleeds in other parts of the body*" [ACD 1.2]. At this time patient numbers are insufficient and bleed types are too heterogeneous in this group for an indirect comparison to provide conclusive results.
2	**Andexanet alfa's known mechanism of action is specifically designed to rapidly arrest DOAC-related bleeding and limit haematoma expansion. PCCs have no mechanistic rationale to arrest DOAC-related bleeding or limit haematoma expansion.** • Where an anticoagulant reversal treatment has a known mechanism of action, if a defined 'to-benefit' population is treated early, it is possible to limit haematoma expansion and consequently improve mortality and morbidity: o A study of the reversal of warfarin-related intracerebral haemorrhage revealed that PCCs not only improved survival but that improved survival was not at the expense of increased disability. Patients who received PCCs had greater functional independence measure gains than those who did not receive PCCs (28.3 vs 12.3, p = 0.049). Furthermore, earlier treatment was associated with better survival after controlling for ICH score, compared with no treatment (p = 0.053).[6] • Andexanet alfa sequesters FXa inhibitor within 2-5 minutes of bolus administration and is sustained for the duration of infusion.[8] In contrast, PCCs are unable to affect FXa inhibitory activity with resultant delayed effects on thrombin generation.[9,10] • PCCs have no known mechanism of action for FXa inhibitor reversal. *In vitro* studies have shown PCCs are unable to overcome FXa inhibition through exogenous supplementation of FX (not FXa) at commonly used doses of 50 IU/Kg at therapeutic FXa inhibitor levels. PCC supplemented FX cannot bind and neutralise FXa inhibitors. Furthermore, any overloading with prothrombin from PCCs is limited through FXa inhibition.[11] • The known mechanism of action for andexanet alfa as a FX decoy protein with demonstrable dose-dependent decrease in FXa inhibitory activity results in reduction of haematoma expansion. • Therefore, through its known mechanism of action, andexanet alfa will result in a clinically meaningful reduction in haematoma expansion in its licensed indication. In contrast, PCCs have failed to demonstrate any plausible mechanism of action and any corresponding impact on haematoma expansion, mortality or morbidity in persons with ICH receiving a DOAC.[12]

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3	**Haematoma expansion is a key prognostic factor for mortality and morbidity. The ANNEXA-4 study demonstrated a clinically meaningful effect on limiting haematoma expansion in a population at high risk of haematoma expansion.** In Section 3.5 of the ACD, it was noted that: "*the evidence on clinical events was limited to 30-day mortality*" and "*a large bleed volume at first presentation is an important indicator of a poor prognosis, and patients with large bleeds were excluded from ANNEXA-4*." [ACD, 3.5] • In clinical studies of intracerebral haemorrhage, haematoma expansion has been shown to result in worsening mortality and morbidity: o In a meta-analysis of patients with spontaneous intracerebral haemorrhage, mortality was significantly related to percentage change in haemorrhage growth at 24 hours indicating that for each 10% increase in growth, the mortality hazard rate increased by 5%.[22] o For each ml increase in baseline intracerebral haemorrhage volume and for each 10% increase in growth, patients were 6% and 16% more likely to increase 1 point on the outcome mRS, respectively. In addition, for each 10% increase in intracerebral haemorrhage growth, patients were 18% more likely to worsen from independence to assisted independence or from assisted independence to poor outcome. • The use of anticoagulants, baseline haematoma volume and earlier time from symptom to baseline imaging increases are associated with greater likelihood of haematoma expansion, where early treatment is all the more necessary.[13,14] • Despite the committee's reservation on the severity and generalisability of the ICH population recruited in ANNEXA-4, patients enrolled in ANNEXA-4 entered early at onset and were at high risk of haematoma expansion: o ANNEXA-4 **recruited patients early after symptom onset** when haematoma expansion is known to occur within the first 24 hours of haemorrhagic stroke symptom onset, with the highest probability within the first 5 hours of the onset of the bleed in non-anticoagulated patients.[13] o ANNEXA-4 **recruited patients with bleed volumes that are at a high risk of expanding**. Haematoma expansion is known to occur with increasing baseline bleed volume, with likelihood of haematoma expansion to a peak and then plateau at around a 75 ml baseline bleed volume.[13] • ANNEXA-4 was designed to demonstrate the effect of andexanet alfa on haemostatic outcomes in a relevant population that was most likely to benefit from rapid reversal, that is, those with a high risk of haematoma expansion. o This objective was achieved as people with spontaneous intracranial bleeding including intracerebral bleeding received andexanet alfa within 3-4 hours of symptom onset and baseline haematoma volume in ANNEXA-4 included a spectrum of bleed volumes up to 60 ml. It was further noted in Section 3.5 of the ACD that:

	"Not all bleeds enlarge, and it is difficult to say that a haematoma growth of less than 35% for intracerebral haemorrhage can be considered a positive outcome or a good haemostatic efficacy as defined in the trial." [ACD, 3.5] • Haematoma expansion is a modifiable clinical predictor of disability and death in intracerebral haemorrhage. Therefore, early limitation of haematoma expansion is a desired therapeutic goal to prevent death and limit disability when assessing intracerebral haemorrhage treatment.[15,16] • As such, haematoma expansion has been a clinical endpoint in studies of therapeutic interventions for intracerebral bleeding including haemostatic therapies including aggressive blood pressure control.[15,17-20] • The definition of haemostatic efficacy for intracerebral bleeding utilised in ANNEXA-4 is consistent with other intracerebral bleed research[17-20] with use of absolute cut-offs (typically ≥3, ≥6 ml), proportional cut-offs (typically >26% or >33%), or a combination of both from baseline growth on follow-up imaging within the first 24 hours. • All previous haematoma expansion thresholds proposed have been shown to be associated with poor outcomes (defined as mRS 4-6). Definitions of haematoma expansion using larger haematoma volume increases predict greater changes in outcomes than lower thresholds. Furthermore, baseline haematoma size has little bearing on the ability of haematoma expansion (defined absolutely or relatively) to predict outcomes.[21] • Therefore, the definition of haematoma expansion used in ANNEXA-4 can be considered clinically relevant across the entire spectrum of baseline haematoma volume sizes. This conclusion is supported by a Delphi panel of 10 UK ICH experts (see Appendix A, Question 2). • The ANNEXA-4 study demonstrated a clinically meaningful effect on limiting haematoma expansion in a population at high risk of haematoma expansion. o Of 99 efficacy-evaluable patients with spontaneous ICH, a limitation in haematoma expansion of less than 35% between baseline and at 12 hours (as per the Sarode criteria) was achieved in 79% of patients with spontaneous intracerebral haemorrhage. o Of patients with a limitation in haematoma expansion of less than 35%, 91% of these patients demonstrated 'excellent' haematoma expansion, defined as <20% at 1 hour from baseline sustained at 12 hours following andexanet. o Finally, the magnitude of the reduction in anti–Factor Xa activity was a predictor of ICH haemostatic efficacy[8] and therefore supportive of andexanet alfa's mechanism of action in reducing haematoma expansion and improving clinical outcomes (see Comment Note 2). • **Therefore, andexanet alfa's effects on reducing haematoma expansion are robust, and would translate into a mortality and morbidity benefit compared to PCC.**
4	**Andexanet alfa will improve morbidity and associated quality of life in ICH patients for its anticipated use in the UK.** In Section 3.9 of the ACD it is stated that: *"The committee considered that the aim of treatment is to improve survival with less risk of long-term disability. But the survival improvement may lead to people being alive but with severe disability... it was*

unclear whether andexanet alfa improves very disabled survival in people who would otherwise die, or is improving the number of people with excellent recovery." [ACD, 3.9]

- We acknowledge the concern raised in the ACD. However, clinical expert consultation, consideration of andexanet alfa's mechanism of action, and demonstrated effect on haematoma expansion, suggest that an improvement in morbidity would be expected across the spectrum of disability.

- The modified Rankin Scale (mRS) is a well-known neurological scale that incorporates the full spectrum of functional impairment from having no symptoms (score 0) to death (score of 6). See Appendix A, Table 12 for further information. Since haematoma expansion is linked to mRS outcomes, we would expect treatment with andexanet alfa to shift mRS scores down across the entire population.

- In a Delphi panel of 10 UK ICH experts, all nine experts that attended the consensus meeting agreed that in the population for which clinicians would consider treatment with andexanet alfa, the rapid administration of andexanet alfa would likely have a better morbidity and quality of life outcome compared with PCCs based on the published data that andexanet alfa is effective in limiting the haematoma expansion, (see Appendix A, Question 2).

    - "I would expect a shift of mRS across all categories. For example, it may prevent those on track for mRS 1-3 worsening to mRS 4-5 and so forth. So mRS 5 may not increase overall or at least as much as one might think."

    - One expert quoted that: "The overall outcome from any brain injury is a spectrum. By preventing mortality which results in a patient with severe disability, you shift the whole spectrum. Therefore, some severely disabled patients will become moderately disabled, some moderately disabled will become mildly disabled etc."

- In the same panel, there was consensus that in the population for which clinicians would consider treatment with andexanet alfa, a positive clinical benefit for 30-day mortality in ICH patients would likely shift in the modified Rankin score across the entire population (net positive impact on disability) (see Appendix A, Question 3).

- Furthermore, there is additional evidence to support the ICH experts view, as evidenced by the study by Oie et al.[24]

    - Average mRS scores for the intracerebral population were higher in Oie et al. than those for intracerebral patients in ANNEXA-4: mRS was [redacted] at day 30 in ANNEXA-4 and 4.41 at day 90 in the Oie et al. study.

    - In a Delphi panel of 10 UK ICH experts, all nine experts that attended the consensus meeting agreed that mRS score would improve for patients with an ICH or intracerebral haemorrhage only between 30 days and 90 days by at least 1 mRS category (see Appendix A, Question 4).

    - Furthermore, evidence has been shown to suggest that mRS improves by at least 1 point between 30 days and 90 days, and then post 90 days.[25,26]

    - This would mean that andexanet alfa intracerebral patients predicted mRS at day 90 would be ~[redacted], equating to an average mRS benefit of 2 or more compared to PCC.

    - Once again, this suggests that andexanet alfa would have a net-positive impact on morbidity and associated quality of life in the ICH population for which it will be used.

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	• Therefore, andexanet alfa will reduce mortality and improve morbidity and corresponding quality of life in surviving patients for its intended use in the UK based on the following evidence: o Andexanet alfa's mechanism of action (see Comment Notes 2) o Andexanet alfa's demonstrated limitation of haematoma expansion (see Comment Notes 3) o **Complete clinical consensus** from a Delphi panel of 10 UK experts o Comparison of intracerebral bleeds with andexanet alfa (ANNEXA-4) versus PCC (Oie et al.)
5	**Andexanet alfa is used to limit further neurological deterioration in persons likely to survive. *A priori* clinical assumptions of functional recovery and patient adaptability post ICH are imprecise. Clinicians will engage patients and their relatives (where possible) in joint clinical decision making accounting for patient values and treatment preferences.** In Section 3.9, the ACD states: "*The committee was concerned by comments received at consultation from the British Association of Stroke Physicians, stating that it was unclear whether andexanet alfa improves 'very disabled survival in people who would otherwise die, or is improving the number of people with excellent recovery'. This uncertainty would make treatment decisions difficult and might involve discussions with relatives about whether to use andexanet alfa for ICH." [ACD, 3.9]* • We appreciate the committee's concern around the uncertainty of andexanet alfa on morbidity where the risk of long-term disability may outweigh any survival benefit, and in a Delphi panel with 10 experts in ICH, there was consensus that treating clinicians involve patients and their relatives or carers in their clinical decision making when possible (see Appendix A, Question 1c). • However, the same panel were in consensus that andexanet alfa would be given regardless if there is a chance of survival, only with the exception of cases characterised with poor premorbid function (e.g. mRS >4) and/or an advance directive. o The experts stated that decisions in the emergency setting are focused on probability of survival in first 72 hours, rather than attempting to estimate morbidity following treatment, and that prior clinical assumptions on likely disability have been wrong. o "The aim must be to try to urgently normalise the coagulation to prevent further haematoma expansion (a decision in patient's best interest), before attempting to consult the relatives" o They also stated that deciding not to reverse anticoagulation is essentially allowing a higher risk of deterioration to occur, and that 'Time is brain', where any delay in treatment may result in worse outcomes. • The issue of trading severe disability for death has been highlighted in relation to a number of other interventions in stroke, most notably hemicraniectomy for malignant middle cerebral artery syndrome. o Hemicraniectomy is a treatment that is recommended in the Royal College of Physicians Guideline for stroke and is a widely accepted, live-saving treatment for selected patients.[27] Studies have shown that despite high rates of physical disability and

	depression, the vast majority of patients that underwent this emergency live-saving surgery are satisfied with life and do not regret having undergone surgery.[28] • There is an inherent assumption that, given the choice of being left with severe disability or death, patients may prefer not to be resuscitated, and that with respect to quality of life, surviving patients may consider themselves to be in a state "worse than death'. However, studies of patients surviving an intracerebral haemorrhage demonstrate that this is not the case: o Reported utility scores were high in many patients at 3 months following an intracerebral haemorrhage , with means (SD) 0.82 (0.28) and 0.62 (0.3)[29,30] – far from zero with utilities increasing over time. o Further, utilities were associated with factors that determine functional outcome, reinforcing the need for careful patient selection. • Therefore, patients who survive ICH adapt with a quality of life acceptable for most patients and certainly, on average, more desirable outcome than death. • This suggests that patients' perceptions of personal health, well-being, and satisfaction with life are often discordant with their objective health status and that many individuals appear to adapt to life-changing events and subsequently accept a degree of disability that they would previously have judged to be unacceptable. The reasons may be due to the following considerations: o Firstly, there is considerable statistical and clinical uncertainty about prognosis after stroke. o Secondly, individuals place different values on different outcomes after stroke. This is because different outcomes (e.g. ability to talk, walk) may impact differently on different individuals' quality of life. Many factors can affect this including culture and religion. o Thirdly, it may be difficult to elicit patient values after a stroke and be certain of the accuracy of previously expressed wishes. This is because, those severely affected from their stroke may have dysphasia or cognitive impairments, preventing them from communicating their values. In these circumstances, clinicians often rely on proxies who may not know the patient's values well. Even where a patient has expressed a previous wish, this may change over time or when faced with the reality. • Therefore, the reality is that for patients where andexanet alfa would be used as a life-saving therapy, it would be administered to those likely to survive and have prior good functional baseline (premorbid mRS <=4), to prevent further neurological deterioration. It would be erroneous for the clinician to presume to be able to predict accurately any likely functional recovery and patients' adaption to their disability *a priori*. • In these circumstances, treating clinicians would involve patients and their relatives or carers in their clinical decision making when possible to clarify patient wishes and pre-morbid function, and this should not adversely affect the decision to provide andexanet alfa to the vast majority of patients where quality of life is acceptable compared to death.
6	**The uncertainty related to quality of life is by how much andexanet alfa will improve quality of life in surviving ICH patients compared to PCC** In Section 3.14 of the ACD it stated that: "*The committee concluded that differences in the long-term outcomes and utilities for people after an ICH, depending on the treatment they had, are highly uncertain.*" [ACD, 3.14]

	• We acknowledge the concern raised in the ACD. To help address this concern, we conducted a Delphi panel with 10 UK ICH experts to understand the probable long-term outcomes and utilities for patients with an ICH following treatment with andexanet alfa compared to treatment with PCCs, for the population in which it is to be used (see Appendix A, Question 5). • All nine experts who attended the consensus meeting agreed they would expect a morbidity benefit associated with andexanet alfa compared with PCCs based on published data that andexanet alfa is effective in limiting haematoma expansion. • There was a consensus that difference in average quality of life between patients receiving andexanet alfa and PCCs utility would be between the range of 0.05 and 0.1 based on the average shift of mRS score between 0.5 and 1. • Summaries of the probable long-term morbidity outcomes and utilities are provided below: o Baseline utility among ICH survivors in the long term is 0.61 for both andexanet alfa and PCC, as per NICE TA341 [company base case assumption]: ▪ Utility benefit = 0.05, lower end of expert range: ICER = [redacted] ▪ Utility benefit = 0.075, mid-point of expert range: ICER = [redacted] ▪ Utility benefit = 0.10, higher end of expert range: ICER = [redacted] o Baseline utility among ICH survivors in the long term is 0.53 for both andexanet alfa and PCC, mapped ANNEXA-4 [ERG base case assumption]: ▪ Utility benefit = 0.05, lower end of expert range: ICER = [redacted] ▪ Utility benefit = 0.075, mid-point of expert range: ICER = [redacted] ▪ Utility benefit = 0.10, higher end of expert range: ICER = [redacted] • The ICER ranges are as follows: o Baseline utility among ICH survivors in the long term is 0.61 for both andexanet alfa and PCC (NICE TA341) = [redacted] o Baseline utility among ICH survivors in the long term is 0.53 for both andexanet alfa and PCC (ANNEXA-4) = [redacted] • Therefore, the uncertainty in quality of life does not translate into large differences in cost-effectiveness – all estimates provided by the Delphi panel fall within a range that would be considered a cost-effective use of NHS resources.
7	**Base case cost-effectiveness results and scenario analyses for ICH, show that andexanet alfa is a cost-effective use of NHS resources** • Following review of the second ACD, the revised base case presented in the first ACD response remains unchanged. • We are largely in agreement with the ERG's preferred base case. There are only two assumptions of difference: o The ERG applies ANNEXA-4 mRS distributions in both treatment arms; this assumes no benefit with andexanet alfa on morbidity and associated quality of life – for which no

	clinician agreed this was likely in the Delphi panel, and for which the ERG acknowledges is highly conservative. ○ The company derives a benefit utilising the published Oie et al. study, comparing day 30 mRS from ANNEXA-4 with day 90 mRS from Oie et al. Consensus from the Delphi panel was in complete agreement that day 30 mRS would improve by an average of at least 1 on the mRS – hence this comparison, may indeed be conservative and bias in favour of PCC. See Appendix A Question 4. ○ The ERG derives long term utility among ICH survivors by mapping the mRS score to EQ-5D from the ANNEXA-4 study at day 30. As a result, utility of an ICH survivor is 0.53 in both treatment arms. Considering the Delphi panel consensus that mRS would improve by at least 1 between day 30 and day 90, the utility of 0.53 would improve to ~0.63 by day 90 (and possibly further thereafter). See Appendix A, Question 4 ○ The company uses a baseline utility of 0.61 accepted as a generalisable UK utility for ICH in a prior NICE technology assessment (TA341). This broadly aligns with the predicted day 90 value from the mapped mRS of ANNEXA-4 (=0.63), per the ERG's assumption. • The results of our base case are as follows; ○ Base case = [redacted] ○ Threshold analyses varying morbidity benefit associated with andexanet alfa relative to PCCs, considering the Delphi panel results = [redacted] • The results of the ERG revised base case are as follows; ○ Base case = [redacted] ○ Threshold analyses varying morbidity benefit associated with andexanet alfa relative to PCCs = [redacted], as published by the ERG[7] [redacted]Even under the extreme clinical assumption of no morbidity benefit, which was deemed conservative by the ERG,[7] clinically implausible by UK clinicians engaged during the first ACD response,[23] and subsequent Delphi panel conducted as part of this response (Appendix A), both our base case and the ERG revised base case result in ICERs within the range of what NICE would consider cost-effective - under [redacted] • The more likely clinical scenario of a baseline utility of ~0.61, and some form of clinical benefit on quality of life for andexanet alfa results in ICERs under [redacted] • Therefore, it can be concluded that andexanet alfa is a cost-effective use of NHS resources in ICH.
8	**To minimise the risk of improved survival at the expense of increased disability, optimise clinical outcomes, and ensure the guidance will be easy to implement, andexanet alfa should only be used in its licensed indication, where there is potential for benefit.** • Andexanet alfa would fit into current clinical pathways in the UK for patients with life threatening or uncontrolled bleeding who require immediate resuscitation, including intracerebral haemorrhage protocols.

	• The uncertainty regarding disability outcomes will be minimised as all nine ICH experts in the Delphi panel agreed that they would likely treat any patient with andexanet alfa provided that they had taken apixaban or rivaroxaban within the previous 12 hours or so and that they were deemed likely to experience long-term survival benefits (similar to eligibility criteria of GCS >7 and ICH volume <60 ml used in the ANNEXA-4 trial) (see Appendix A, Question 1b) • This recommendation is based on the availability of prognostic indicators related to ICH morbidity and mortality in patients with intracerebral haemorrhage which have been explored in Comment Note 3. • Recommending treatment as per the licensed indication and having this recommendation fit into existing protocols, will ensure that physicians use andexanet alfa where there is the potential for benefit. • Time bound and severity dependent protocols already exist in stroke thrombolysis and ischemic stroke pathways. • Treatment criteria will also help clinicians with their discussion regarding treatment options with family and relatives, and where appropriate make the decision to put patients on a palliation pathway.
9	**The ANNEXA-I study will not address uncertainties related to long term morbidity in ICH, and a recommendation for andexanet alfa 'only in research' in people with ICH is not appropriate.** In the Section 5.1 of the ACD it states that: "*The committee noted an ongoing randomised controlled trial of the effectiveness of andexanet alfa compared with prothrombin complex concentrate in people with ICH. The main outcomes of interest are mortality, long-term disability and the risk of thromboses and thromboembolic events.*'' [ACD, 5.1] • ANNEXA-I was not designed to address uncertainties regarding long term disability as it was not a concern for the regulators. • As such, no outcomes on long term disability >30 days being collected in ANNEXA-I (trial of andexanet in ICH patients receiving an oral FXa inhibitor; ClinicalTrials.gov Identifier: NCT03661528). • In brief, the requirement to perform ANNEXA-I at the time of authorisation was to address the following uncertainties: o Establish the FXa inhibitory activity to haemostatic efficacy relationship. This relationship is important to support the proposed dosing regimen for andexanet. o Thrombotic rate of andexanet alfa in comparison to a comparable patient population. In the ACD, it is also is noted that: *"the European Stroke Organisation 2019 guideline on reversal of oral anticoagulants for ICH recommended early reversal 'using andexanet alfa if available'. However, it also recommended 'randomising into trials as based on the low quality of evidence' because 'there is significant uncertainty whether desirable outweigh undesirable effects". [ACD 3.9]* • However, these recommendations were based on interim analyses from ANNEXA-4. The publication of the full ANNEXA-4 trial results has since been added to the evidence base and

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	other recommendations have been updated to reflect use preferential use of Andexanet over PCCs where available including 2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants.[31]
10	**Although we accept the decision in patients with 'other bleeds', we would like to note that andexanet alfa is expected to benefit these patients, despite the limited evidence in this group** • Clinicians contacted following the first appraisal committee meeting stated that they would expect andexanet alfa treatment to be beneficial in this population. However, we acknowledge the limitations in the evidence base. • Section 1.2 of the ACD states that the results of the indirect comparison suggest *"that andexanet alfa lowers survival for people with bleeds in other parts of the body*." o As described in the original submission, and all post submission document, the results of the propensity score matching analysis was not considered robust in patients with other major bleed. o Namely, heterogeneity in the bleed types in this subgroup and extremely small sample size rendered these results unreliable, as corroborated by their clinically implausible values (andexanet alfa being associated with greater mortality relative to PCCs). o As a result, we did not apply results in the cost effectiveness model. Hence, whilst it is appropriate to consider the evidence generated using propensity score matching analysis in ICH/GI where these limitations do not apply, we maintain that the analysis in other bleeds should be disregarded and request that the limitations of analysis so far in this group be characterised more accurately, as a lack of robustness.
11	**The recommendations in their current form raise concerns over equality.** As noted in Section 3.18 of the ACD, the lack of an alternative to PCCs raises an equality concern. • Inequality would arise where people with rivaroxaban or apixaban related major gastrointestinal bleeding will be able to access a life-saving treatment, whereas those with intracranial bleeding will not. o The likely impact on the UK population is that approximately [redacted] ICH-related deaths are occurring each year in people in England who are being treated with apixaban or rivaroxaban, of which approximately two-thirds could be avoided with availability of andexanet alfa. • Some groups of people refuse blood products and their derivatives due to religious reasons (e.g. Jehovah's witnesses) even in life-threatening situations such as major bleeding. • Although these reasons do not impact on the economic models proposed to NICE, if NICE decide not to allow routine reimbursement for andexanet in intracranial haemorrhage, it would mean these people would not have access to an additional therapeutic option where PCC use is not acceptable.

Insert extra rows as needed

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
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Appendix A. Delphi panel consensus results

A.1. Background and Delphi panel objectives

[redacted]

A.2. Methodology

[redacted]

Figure 1: Overview of Delphi panel methodology

A.2.1. Expert recruitment

[redacted]

A.2.2. Round One

[redacted]

A.2.3. Round Two

[redacted][1]

A.2.4. Consensus meeting

[redacted]

A.3. Results

[redacted]

Table 1: Delphi panel participants

[redacted]
[redacted]
[redacted]
[redacted]
[redacted]
[redacted]

[redacted]

A.3.1. Question 1a

[redacted]

[redacted]

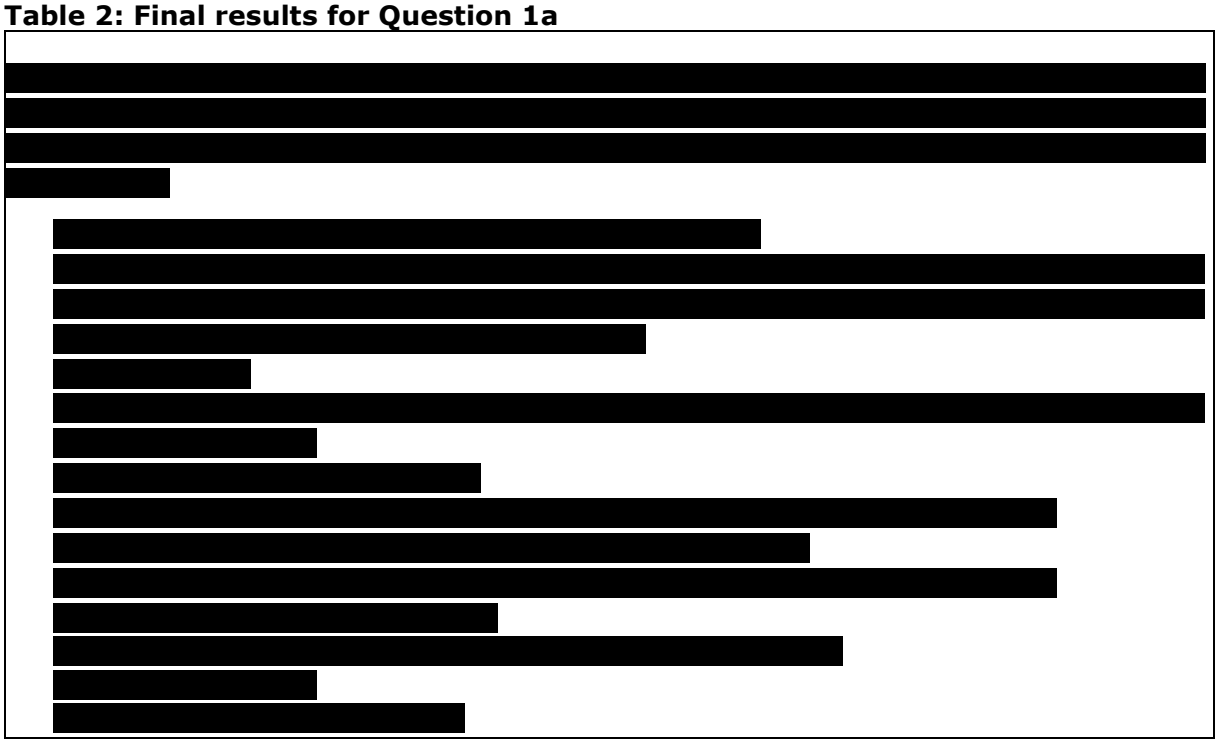
[redacted]

[redacted]

[redacted][2]

[redacted]

Table 2: Final results for Question 1a



[redacted]

Table 3: Final Likert scale results for Question 1a

Likert scale	Number of experts
Strongly disagree	[redacted]
Disagree	[redacted]
Somewhat disagree	[redacted]
Neither agree nor disagree	[redacted]
Somewhat agree	[redacted]
Agree	[redacted]
Strongly agree	[redacted]

A.3.2. Question 1b

[redacted]

Table 4: Final results for Question 1b

Answer	Reasons
[redacted]	• [redacted]
[redacted]	[redacted] • [redacted]

[redacted]

Table 5: Final Likert scale results for Question 1b

Likert scale	Number of experts
Strongly disagree	[redacted]
Disagree	[redacted]
Somewhat disagree	[redacted]
Neither agree nor disagree	[redacted]
Somewhat agree	[redacted]
Agree	[redacted]
Strongly agree	[redacted]

A.3.3. Question 1c

[redacted]

Table 6: Final results for Question 1c

[redacted]

[redacted]

[redacted]

Table 7: Final Likert scale results for Question 1c

Likert scale	Number of experts
Strongly disagree	[redacted]
Disagree	[redacted]
Somewhat disagree	[redacted]
Neither agree nor disagree	[redacted]
Somewhat agree	[redacted]
Agree	[redacted]
Strongly agree	[redacted]

A.3.4. Question 2

[redacted]

[redacted][2]

[redacted]

[redacted]

[redacted][3]

[redacted][4]

[redacted][5] [redacted]

[redacted][6]

[redacted]

Table 8: Final results for Question 2

[redacted]

[redacted]

Table 9: Final Likert scale results for Question 2

Likert scale	Number of experts
Strongly disagree	[redacted]
Disagree	[redacted]
Somewhat disagree	[redacted]
Neither agree nor disagree	[redacted]
Somewhat agree	[redacted]
Agree	[redacted]
Strongly agree	[redacted]

A.3.5. Question 3

[redacted]

[redacted][2]

[redacted]

[redacted][2]

[redacted]

Table 10: Round 1 results for Question 3

[redacted]
Yes = [redacted]
No = [redacted]

[redacted]

Table 11: Final Likert scale results for Question 3

Likert scale	Number of experts
Strongly disagree	[redacted]
Disagree	[redacted]
Somewhat disagree	[redacted]
Neither agree nor disagree	[redacted]
Somewhat agree	[redacted]
Agree	[redacted]
Strongly agree	[redacted]

A.3.6. Question 4

[redacted]

Table 12: Modified Rankin Scale descriptions

mRS score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderate to severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

[redacted][7] [redacted]

Table 13: The modified Rankin Scale for andexanet alfa and PCCs

mRS	Andexanet alfa at 30 days for intracranial haemorrhage	Andexanet alfa at 30 days intracerebral haemorrhage	Øie et al. 2018 at 90 days intracerebral haemorrhage
0	[redacted]	[redacted]	1%
1	[redacted]	[redacted]	5%
2	[redacted]	[redacted]	9%
3	[redacted]	[redacted]	12%
4	[redacted]	[redacted]	22%
5	[redacted]	[redacted]	12%
6	[redacted]	[redacted]	39%
Average	[redacted]	[redacted]	**4.41**

[redacted]

Table 14: Round 1 results for Question 4

[redacted]	
Yes = X	[redacted]
No = X	[redacted]

[redacted]

Table 15: Final Likert scale results for Question 4

Likert scale	Number of experts
Strongly disagree	[redacted]

Disagree	[redacted]
Somewhat disagree	[redacted]
Neither agree nor disagree	[redacted]
Somewhat agree	[redacted]
Agree	[redacted]
Strongly agree	[redacted]

A.3.7. Question 5

[redacted]

[redacted]

[redacted]

[redacted][2]

[redacted]

Table 16: Round 1 results for Question 5

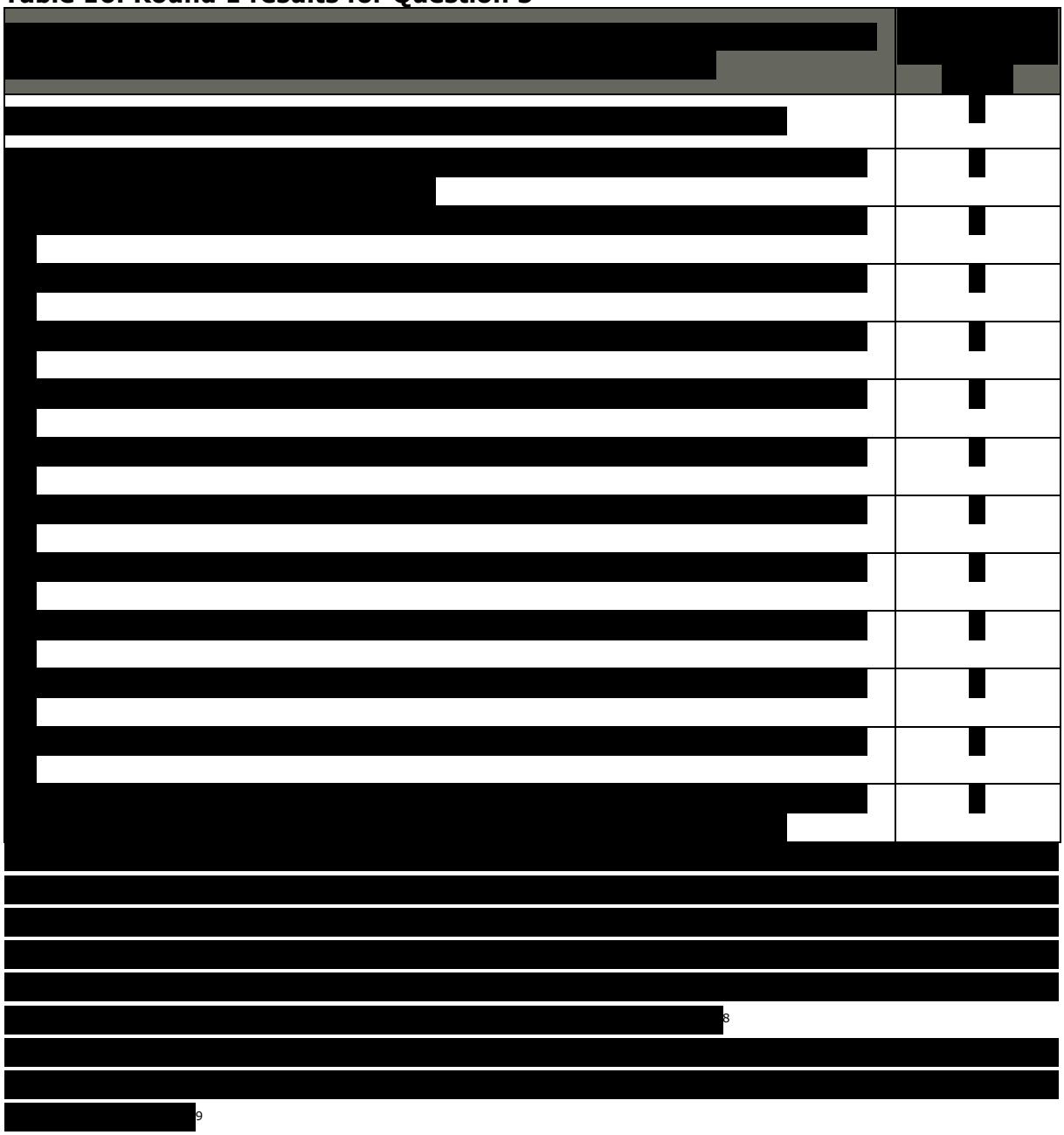


Table 17: Final Likert scale results for Question 5

Likert scale	Number of experts
Strongly disagree	[redacted]
Disagree	[redacted]
Somewhat disagree	[redacted]

Neither agree nor disagree	
Somewhat agree	
Agree	
Strongly agree	

Appendix B. References

1. Hsu C-C & Sandford BA. The Delphi technique: making sense of consensus. *Practical Assessment, Research, and Evaluation* 2007. 12: 10.
2. NICE. Appraisal consultation document – Andexanet alfa for reversing anticoagulation from apixaban or rivaroxaban. 2020. at <https://www.nice.org.uk/guidance/GID-TA10440/documents/129-2>
3. Davis SM, Broderick J, Hennerici M, *et al.* Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. *Neurology* 2006. 66: 1175–1181.
4. Connolly SJ, Crowther M & Eikelboom JW. Treatment of Factor Xa Inhibitor-Associated Bleeding with Andexanet Alfa: Full Results of ANNEXA-4. in (2019).
5. Gerner ST, Kuramatsu JB, Sembill JA, *et al.* Association of prothrombin complex concentrate administration and hematoma enlargement in non–vitamin K antagonist oral anticoagulant–related intracerebral hemorrhage. *Annals of Neurology* 2018. 83: 186–196.
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7. Øie LR, Madsbu MA, Solheim O, *et al.* Functional outcome and survival following spontaneous intracerebral hemorrhage: A retrospective population-based study. *Brain and Behavior* 2018. 8: e01113.
8. Kind P, Hardman G & Macran S. *UK population norms for EQ-5D*. (Centre for Health Economics, University of York, 1999). at <https://econpapers.repec.org/paper/chyrespap/172chedp.htm>
9. Overview | Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism | Guidance | NICE. at <https://www.nice.org.uk/guidance/ta341>

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Andexanet alfa for reversing anticoagulation [ID1101]

Consultation on the appraisal consultation document – deadline for comments 5pm on Friday 2 October 2020 **email:** NICE DOCS

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Anticoagulation UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**Nothing to declare**
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	1.2 ACUK is concerned with the recommendation to use Adexanet alfa in adults with life-threatening or uncontrolled bleeding in the skull (intracranial haemorrhage) only for research and limitations to GI bleeds We seek clarification on the following: What settings will be eligible to participate in research i.e. all secondary care settings, major trauma/ stroke units? Where is current research taking place, i.e. geographical spread across the UK and, if at multiple centres, will any patient experiencing an ICH be able to access? Who will make the clinical decision as to whether a patient is eligible for the research and will consent be needed from the patient/patient's family or representative? Considering the situation where a person may be involved in an accident or trauma and confirmed as having an ICH, would the patient be disadvantaged in being able to access a research programme if not available within their geographical location. Patients should be reassured that in the event of a major bleed whilst on apixaban or rivaroxaban, they will not be compromised by where they live and encounter limitations on how they may be treated to reverse the event 3.2 The committee has acknowledged that the availability of an effective reversal agent would be greatly valued by people and HCPs. If clinicians are aware of the reversal agent being available for 'research purposes' for ICH as well as GI bleeds, will they be compromised in their clinical practice/judgement in being unable to access for a patient who they deem could benefit (younger patient, no comorbidities, with good chance of recovery) It could prove difficult and challenging to make this assessment in the knowledge that a treatment could make a difference to patient outcome. Are there any exceptional circumstances protocols that could override the research only recommendation? 3.4 We understand the implications of an ICH bleed can lead to mortality and long term disability. We note that GI bleeds may be able to be managed using endoscopy, embolization or surgery. In terms of other types of bleeds, could the limitations of availability of a reversal agent when other reversal methods have been utilised, be deemed detrimental to the patient's long term health outcomes. A bleed in the eye leading to blindness is considered a long term disability and would impact greatly on the individual. 3.9 The committee commented on reduction in mortality in ICH being plausible but size of benefit unclear as some patients may be left severely disabled who would otherwise die whilst some may make an excellent recovery. Given that a treatment could benefit a patient and whilst they may not return to the quality of life pre –bleeding event , we would hope that the access to treatment must take into account the patient's broader health profile e.g if a patient on a DOAC had a fall or trauma doing sport or a car accident and who was otherwise fit and well, the blanket decision of not being able to give Adexanet in these circumstances could be hugely detrimental to the individual. Each person is an individual and Doacs are prescribed to 18 yrs to 80 years plus; it seems inequitable that a firm NO is generalised for an anticoagulated person unable to fit 'research' criteria

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	3.16/3.20 Cost – What are the implications for clinicians to have to explain/ discuss with the patient's family or carer when advising that there is a treatment but not deemed to be cost effective use of NHS resources for ICH? 5.1 This recommendation is welcome and we look forward to seeing the published results when available. We would request that NICE commits to review this TA once results are published or earlier if available as this is of significance importance to the DOAC community and specialist clinicians. **General comments** We understand the risk of thrombosis from Adexanet alfa and how stopping a ICH bleed may actually cause distress and morbid disability to a patient along with costs of care to the NHS and society. From the patient perspective, if the treatment is going to be limited in how it will be used in a bleed scenario, it is important t that the patient be made aware of this before starting on a Doac and advised on the current bleed reversal options available including Adexanet alfa and its current licenced recommendations. From our AC community engagement, we know that patients are told of bleed risks but not advised of reversal options. (ACUK is a consultee to the QS for the recently published VTE guidelines NG158 and has prioritised standardising patient information as a key improvement priority) **We note the recent SMC decision as below will be welcomed by patients and healthcare professionals in Scotland. As a patient organisation, how can we justify to our patient base the differences in the decision making processes between SMC and NICE and subsequent outcomes?** *07 August 2020The 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 NHS SCOTLAND. The advice is summarised as follows: ADVICE: following a full submission andexanet alfa (Ondexxya®) is accepted for use within NHS SCOTLAND 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 NHS Scotland 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*
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Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Thrombosis UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row.

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Consultation on the appraisal consultation document – deadline for comments 5pm on Friday 2 October 2020 **email:** NICE DOCS

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	1.2 Thrombosis UK would like to thank the NICE committee for reviewing all comments and considering patient benefit. We would like to seek clarification in regards to 1.2 recommendation '*Andexanet alfa is recommended only in research for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled bleeding in the skull (intracranial haemorrhage).'* We understand there is no other therapy available for the treatment of intracranial haemorrhage and so would like to seek clarification on: • What settings would be permitted to participate in research? • Can NICE clarify how equity of access would be maintained? • Clarification on the process and guidance which will be needed to inform decision making by the clinician and in discussion with family, when a patient who had suffered an intracranial haemorrhage may be considered for andexanet alfa. We are concerned this may disadvantage patients, for example, geographically.
2	**3.2** The committee acknowledged that the availability of an effective reversal agent would be 'greatly valued by people and HCPs'. If research restrictions are placed on access to the therapy for ICH, we are concerned patients who may benefit from the therapy, may be denied access not based on clinical judgement but on geographical access.
3	In line with NICE VTE Guidelines NG158, which advocates standardisation of patient information as a key improvement priority, we would like NICE to consider and include clear guidance on how decision making will be made in the event of an ICH, for sharing with patients during discussion about initiation of a DOAC therapy.
4	5.1 Thrombosis UK welcomes this recommendation
5	We would like to draw the Committees attention to the recent Scottish Medicines Consortium decision: *07 August 2020* *'Following a full submission andexanet alfa (Ondexxya®) is accepted for use within NHS Scotland 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.'* We are concerned that this is a very difficult difference to explain to NHS patients in England and Wales considering taking a DOAC, or to families with a loved-one critically ill due to a life-threatening bleed.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Royal College of Pathologists and British Society for Haematology
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Dr Deepa Jayakody Arachchillage

Comment number	**Comments** Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned about these recommendations as approving Andexanet alfa for gastrointestinal bleeding at this stage means that there will not be clinical trials comparing the efficacy and safety of Andexanet alfa with prothrombin complex concentrate (PCC) in treatment of major or life threating GI bleeding related to rivaroxaban or apixaban. Therefore, we believe use of Andexanet alfa in GI bleeding should also include as research setting. Additionally, if the clinical trials comparing the use of Andexanet alfa in ICH failed to show better safety and efficacy compared to PCC in reversing the anticoagulant effect of rivaroxaban or apixaban, approval of Andexanet alfa would remain as approval drug for GI bleeding in the absence of proper randomised clinical trials. Furthermore, there is a possibility of discrimination in the use of Andexanet alfa for use in treatment of ICH related to rivaroxaban or apixaban based on which hospital patients get treated with this type of approval (postcode variation in treatment) as there is local approval of drug to use in ICH in addition to GI bleeding
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Insert extra rows as needed

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Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Role	
Other role	
Organisation	Guy's and St Thomas' NHS Foundation Trust
Location	
Conflict	
Notes	

Comments on the ACD:

Comments from Guy's and St Thomas' NHS Foundation Trust in response to the National Institute for Health and Care Excellence (NICE) appraisal consultation document Andexanet alfa for reversing anticoagulation from apixaban and rivaroxaban

We are surprised NICE have approved andexanet alfa in the management of gastrointestinal (GI) haemorrhage in those receiving apixaban and rivaroxaban. In the extensive analysis of the data for andexanet alfa, they identify most data is of poor quality, and the reason for advocating andexanet alfa for GI bleeding is because it is deemed cost effective. We are dismayed by this approach.

If patients are having major haemorrhage from the GI tract, then we would consider the use of prothrombin complex concentrate (PCC) as a better option than andexanet alfa because in those with major blood loss, they will in addition to needing anticoagulation reversal also have deficiencies in clotting factors which PCC will be able to remedy, but andexanet alfa will not.

PCC has been used as a substitute for fresh frozen plasma internationally in the management of massive bleeding, therefore in the setting of major bleeding in the GI tract, PCC fulfils two functions (reversing the effects of the factor Xa inhibitors apixaban and rivaroxaban, and repletion of clotting factors). Therefore, PCC appears to be a more logical approach to the management of GI haemorrhage than andexanet alfa.

Written on behalf of the Trust Thrombosis and Thromboprophylaxis committee

[redacted]

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

There is a clinical need for effective anticoagulation reversal agents:
The patient experts explained that anticoagulation treatments are accepted by people because they are lifesaving, but there are concerns about safely managing anticoagulation should a major bleed occur. If bleeding is life-threatening then anticoagulation needs to be reversed. Treatment is challenging if there is no reversal agent and relies on treating symptoms until the effects of the anticoagulant stop, in line with the normal half-life of the drug. The patient experts explained that there is an unmet need for a safe reversal agent for direct factor Xa anticoagulants such as apixaban and rivaroxaban. The committee concluded that the availability of an effective reversal agent would be greatly valued by people and healthcare professionals.

I wish to reinforce the expert patient comments. The need for a reversal agent is critical for those, for example AF patients, who have a lifelong bleed problem when given long term aspirin, who also find they bleed when prescribed, say rivaroxaban, as their CHA 2 DS 2-VAS score rises dictating anticoagulation is necessary. They can find themselves on a less than therapeutic dose of an alternative, for instance apixaban, but still observe the occasional small bleed.

Has all of the relevant evidence been taken into account?
My reading of the documents suggests YES.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Even though not proven cost effective when compared to PCC treatment in ICH and other major bleeds, nevertheless, can Andexanet alfa be proposed as therapy in those patients who will not accept treatment using blood products?

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

Possibly, but redaction made in depth assessment of cost effectiveness difficult.

Are the recommendations sound and a suitable basis for guidance to the NHS?

Yes, but with the proviso that Andexanet alfa be offered as an alternative to PCC therapy for patients who will not accept blood products.

Name	[redacted]
Role	
Other role	
Organisation	King's Thrombosis Centre, Department of Haematological Medicine, King's College Hospital
Location	
Conflict	
Notes	

Comments on the ACD:

Has all of the relevant evidence been taken into account?
It is difficult to evaluate as most of the evidence presented is blocked out. There is no reference provided for the US 'real world' data. There are published cohort studies of real-world PCC use from US and Netherlands (summarised in this review article https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7354417/#rth212367-bib-0006), suggesting greater haemostatic efficacy than reported in ORANGE. It seems unusual that only 1 study of DOACs and PCC has been considered, along with unpublished data from real world US experience which has not been made publically available. A stronger comparison could be made by increasing the number of patients treated with PCC across broader care settings. Furthermore, a new publication of realworld use of andexanet with extracranial bleeding raises safety concerns with a 20% thrombosis rate and efficacy in less than 50% of the treated cohort (mortality 40%, see https://onlinelibrary.wiley.com/doi/10.1111/jth.15031).

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
No

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

It is impossible to comment on this as the company have blacked out all numeric data to enable an evaluation. ORANGE reported data from 372 patients on rivaroxaban or apixaban GI bleeding, with 149 receiving PCC. 90 patients (with non-ICH bleeds) were included in the phase 2 Andexanet study and we note haemostatic efficacy was only reported for 60 of these. Subgroup mortality data was not presented in either original publication. Propensity matching will further reduce the number included in analysis and it's difficult to imagine that this will provide convincing evidence of efficacy in such a small cohort. We note the planned recruitment size of the ongoing RCT of andexanet in ICH of 900. There is no data presented with regard to effect size to enable evaluation of how the evidence has been interpreted (and this is not presented by subgroup in the original publications). Without enabling clinicians to evaluate the data (or publications) to support their claims, it remains unconvincing. Given the majority of upper GI bleeds are due to gastric ulceration or variceal bleeding, it seems unlikely that reversal of anticoagulation will improve outcomes without definitive evaluation/intervention of the bleeding point. Lower GI bleeding is most commonly associated with benign

anorectal conditions and has very low early mortality (with later deaths attributable to comorbid disease). There is no published subgroup data of 30d mortality following gastrointestinal bleeding in either study (as above no data has been made available to enable evaluation). The relevance of 30 day mortality as an outcome measure for GI bleeding is questionable, as most later deaths in this patient group relate to comorbid disease rather than bleeding, as highlighted by the recent HALT-IT study (https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(20)30848-5.pdf).

Are the recommendations sound and a suitable basis for guidance to the NHS?

We agree with the recommendation wrt use of andexanet only in the research setting for patients with ICH and suggest the recommendation for GI bleeding should be similarly revised. There is more data for both andexanet use and PCC in the context of ICH. If this was viewed as inadequate by the committee, it seems unlikely there is adequate evidence based on retrospective propensity matching (using a single small observational cohort of PCC) to support a recommendation in favour of andexanet in GI bleeding. The significant thrombosis rates reported both in the phase 2 andexanet study and subsequent observational cohorts remain concerning. A RCT should be performed to establish both efficacy and safety of andexanet in the non-ICH cohort (including GI bleeding).

BMJ TAG

Andexanet alfa for reversing anticoagulation [ID1101]

ERG review of company's response to the second ACD

November 2020

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 16/168/04T.

1 Introduction

This document provides the ERG's response in relation to the company's comments and additional data presented in relation to the second appraisal consultation document (ACD).

2 ERG review of comments

2.1 Comment 1: Executive summary

The ERG notes the company's comments but considers it important to highlight that no new clinical trial data on andexanet alfa have been provided in the company response. However, the company has conducted a Delphi panel in an attempt to [redacted] The Delphi panel resulted in [redacted]

[redacted]

[redacted]The results of the Delphi process and ERG's view are discussed in more detail under the relevant sections below. In addition, based on the clinical expert consensus obtained from the Delphi panel, the ERG considers some scenario analysis around morbidity benefits in ICH survivors to be worthwhile. These are given in Sections 2.6 and 2.7. However, the ERG's preferred base case assumptions are unchanged as no new clinical trial data on andexanet alfa have been provided in the company response. The ERG considers the responses provided by the Delphi panel to be plausible interpretations of the questions presented to them. However, they do not directly address the lack of evidence to support these plausible, albeit hypothesis generating, assumptions that can only be obtained by future research.

The conditional European marketing authorisation for andexanet alfa requires the company to submit the final results of the ongoing ANNEXA-I global randomised controlled trial (RCT) investigating the use of andexanet alfa versus standard care in patients with ICH taking apixaban, rivaroxaban, or edoxaban, in order to substantiate correlation of antiFXa-activity with haemostatic efficacy and to clarify the risk of thromboses and thromboembolic events.[1] However, the ERG notes that ANNEXA-I is not expected to complete until 2024/2025[2] and the ERG is also unclear as to what data are being collecting on thromboses and thromboembolic events. Nevertheless, ANNEXA-I is an RCT and thus will provide stronger evidence in support of the clinical benefit of andexanet alfa compared to standard care in terms of haemostatic efficacy at 12 hours and neurological deficit at 24 hours.

The company also raised concern about the 'only in research' recommendation for andexanet alfa in the ICH population. The ERG considers it important to highlight that ANNEXA-4, the key study informing the clinical effectiveness of andexanet alfa is a single arm trial and the propensity score matching that was presented in the company submission (using the ORANGE study to represent PCC) was associated with high levels of clinical heterogeneity. In particular, the ERG considers the differences in inclusion criteria between ORANGE and ANNEXA-4 (as discussed in the ERG review of company's response to technical engagement report), severely impact on the results of the 30-day

mortality propensity score matching analysis. The ERG therefore maintains the view that the propensity score matching results are highly uncertain and as detailed in the ERG report, the ERG also has concerns that matching with replacement was used and in the 30-day mortality analyses over 60% of individuals in the PCC group were matched multiple times. The ERG additionally noted in the ERG report that unobserved confounders due to the non-randomised study design are likely to be present and so the results of the propensity score matching analyses are subject to inherent bias.

However, as discussed in the ERG review of the company's response to the first ACD, the ERG considers the indirect comparison results are [redacted] in 30-day mortality with andexanet alfa compared to PCC across the ERG's preferred three analyses (Base case, Scenario 1 and Scenario 4) for the whole cohort, ICH + GI subgroup and ICH subgroup. In terms of other major bleeds, as discussed in the ERG report, the ERG does not consider the data on other major bleeds to be suitable for PSM analysis or any other analysis given the [redacted]

2.2 Comment 2: Andexanet alfa's known mechanism of action is specifically designed to rapidly arrest DOAC-related bleeding and limit haematoma expansion. PCCs have no mechanistic rationale to arrest DOAC-related bleeding or limit haematoma expansion.

The company reported that, "*through its known mechanism of action, andexanet alfa will result in a clinically meaningful reduction in haematoma expansion in its licensed indication*". The ERG notes that clinical haemostasis (as adjudicated by an independent and blinded endpoint adjudication committee) was rated as excellent or good in 81.4% (n = 250) of the safety population subgroup of patients who had received apixaban or rivaroxaban (n = 307), 12 hours after andexanet alfa infusion. However, the ERG also notes that there was no significant relationship between haemostatic efficacy and a reduction in anti-factor Xa activity during andexanet treatment in ANNEXA-4[3] and the company has not provided any comparative evidence to confirm any benefit of andexanet alfa in reducing haematoma expansion compared to PCC.

2.3 Comment 3: Haematoma expansion is a key prognostic factor for mortality and morbidity. The ANNEXA-4 study demonstrated a clinically meaningful effect on limiting haematoma expansion in a population at high risk of haematoma expansion.

The ERG notes that from the apixaban and rivaroxaban subgroup of ANNEXA-4, out of 119 ICH patients, [redacted] had haematoma expansion when defined as intracerebral volume >35% increase from baseline to 1 and 12 hours. The ERG also notes that reduction in anti-factor Xa activity was not predictive of haemostatic efficacy in the overall population of ANNEXA-4, although it was considered modestly predictive in patients with intracranial haemorrhage.[3]

No data were provided on mortality and morbidity of patients in ANNEXA-4 specifically in relation to volume of haematoma expansion and the absolute number of patients with haematoma expansion was relatively small albeit [redacted] of the ICH patients with data for this outcome. As discussed in Section 2.1, the company conducted a Delphi panel comprising of 10 clinical experts with the aim of obtaining clinical expert consensus on [redacted] in patients treated with andexanet alfa.

[redacted] However, as discussed in Section 2.1, the ERG considers the Delphi panel statements to be plausible, albeit hypothesis generating, assumptions that require confirmation through further research.

The company also cite a paper by Davis *et al.* 2006[4] that suggests haematoma expansion in patients with intracerebral haemorrhage is likely to be related to mortality and morbidity. However, the ERG notes that the study by Davis *et al.* was conducted in patients with spontaneous intracerebral haemorrhage rather than exclusively in patients on oral anticoagulants such as apixaban and rivaroxaban, and the ERG also notes that intracerebral haemorrhage is just one subtype of ICH. As such, the ERG considers extrapolating the findings by Davis *et al.* to the population suitable for andexanet alfa would be purely speculative. In addition, the ERG considers the definition of a clinically meaningful reduction in haematoma expansion to be a matter for committee to decide.

2.4 Comment 4: Andexanet alfa will improve morbidity and associated quality of life in ICH patients for its anticipated use in the UK.

As discussed in Sections 2.1 and 2.3, the only new data presented relating to morbidity and associated quality of life in ICH patients treated with andexanet alfa are from the Delphi panel and the relevant statements relating to this comment are:

- [redacted]

[redacted]The ERG considers the results of the Delphi panel to be subjective and notes that the only outcomes for which comparative data from the propensity score matching of andexanet alfa and PCC were available are 30-day mortality and length of hospital stay. Scenario analysis showing what impact morbidity benefits in ICH survivors could have on the incremental cost-effectiveness ratio (ICER) are given in Sections 2.6 and 2.7.

2.5 Comment 5: Andexanet alfa is used to limit further neurological deterioration in persons likely to survive. *A priori* clinical assumptions of functional recovery and patient adaptability post ICH are imprecise. Clinicians will engage patients and their relatives (where possible) in joint clinical decision-making accounting for patient values and treatment preferences.

The company report the results of the Delphi panel consensus statements that:

[redacted]The

ERG considers that while the experts' statements appear plausible, they should be confirmed by further research.

2.6 Comment 6: The uncertainty related to quality of life is by how much andexanet alfa will improve quality of life in surviving ICH patients compared to PCC

To demonstrate that the ERG's assumption of no morbidity benefit in ICH survivors is highly conservative, the company provided results from the Delphi panel to demonstrate that there would be a morbidity benefit associated with andexanet alfa. The company reported a consensus that the difference in the average quality of life between patients receiving andexanet alfa and standard care would be between the range of 0.05 and 0.1 based on the average shift of a mRS between 0.5 and 1. Thus, the ERG considers the scenario analysis provided by the company (on top of the ERG's other preferred assumptions) to be useful to explore what the impact on the ICER could be in the absence of clinical trial data (Table 1). The ERG reiterates that these analyses are purely exploratory as the responses provided by the Delphi panel do not directly address the lack of evidence to support morbidity benefits in ICH survivors and this can only be obtained by future research. Additionally, the ERG was unable to verify the consensus obtained from the Delphi panel with its own clinical experts.

Upon inspection of the model, the ERG determined that the company applied the utility benefit to andexanet alfa by subtracting the benefit from standard care (a utility value of 0.53 is maintained for andexanet alfa). Given that the company has repeatedly argued that a utility value of 0.53 is too low for an ICH survivor, the ERG is surprised that the company took this approach. The ERG considers that a more suitable approach would be to add the utility benefit to andexanet alfa and maintain a utility value of 0.53 for standard care. The ERG has added the ICERs using this approach to Table 1.

Table 1. Exploratory scenarios changing the long-term utility among ICH survivors

Utility benefit*	ICER, company*	ICER, ERG**
0, ERG base case	[redacted]	[redacted]
0.05, lower end of expert range	[redacted]	[redacted]
0.075, mid-point of expert range	[redacted]	[redacted]
0.10, higher end of expert range	[redacted]	[redacted]

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ICH, intracranial haemorrhage

*Utility benefit subtracted from standard care, utility value for andexanet alfa remains at 0.53

**Utility benefit added to andexanet alfa, utility value for standard care remains at 0.53

Finally, the ERG notes that the company did not ask the Delphi panel if a long-term utility of 0.72 for an ICH survivor would be considered plausible. This utility value was applied in the company's base case analysis and noted in the second ACD as one of the ERG's concerns. Further details on this issue are given in Section 5.3.9 of the main ERG report. Overall, the ERG maintains that the company's approach to model HRQoL in ICH survivors is inappropriate.

2.7 Comment 7: Base case cost-effectiveness results and scenario analyses for ICH, show that andexanet alfa is a cost-effective use of NHS resources

Following review of the second ACD, the company's revised base case presented in the first ACD response remains unchanged. The company's base case ICER for the ICH population is [redacted].

To demonstrate that the ERG's assumption of no morbidity benefit in ICH survivors is highly conservative, the company provided results from the Delphi panel to demonstrate that mRS would improve by at least 1 between day 30 and day 90 in patients who receive andexanet alfa. Based on clinical expert comments in the full report (Question 4 in Appendix A of the company's response), the ERG is [redacted]. Due to time constraints, the ERG was unable to verify the consensus obtained from the Delphi panel with its own clinical experts. The ERG also considers that as this assumption has such a major impact in the analysis that should be validated by other clinical stakeholders for committee to make a more informed assessment.

Nonetheless, to explore what impact a mRS improvement of 1 for andexanet alfa could have on the cost-effectiveness results, the ERG ran a scenario analysis on top of its other preferred assumptions. This scenario involved changing the utility associated with andexanet alfa from 0.53 to 0.63 at cycle 4 (as suggested by the company). The results of the ERG's scenario analysis are given in Table 2.

Table 2. ERG scenario assuming a mRS improvement of 1 for andexanet alfa

	Andexanet alfa	Standard care	Incremental value
Total costs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]

ICER	-	-	[redacted]

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

The company also compared the mRS distributions recorded in ANNEXA-4 at day 30 with mRS distributions recorded in Øie *et al.* 2018[5] at day 90 (Table 3). The company included results from patients in ANNEXA-4 with an ICH and intracerebral haemorrhage separately in this comparison and concluded that average mRS scores for the intracerebral population were [redacted] in Oie *et al.* 2018 than those for intracerebral patients in ANNEXA-4: mRS was [redacted] at day 30 in ANNEXA-4 and 4.41 at day 90 in the Oie *et al.* 2018 study.

Table 3. mRs distributions for andexanet alfa and standard care (adapted from Table 13 of the company's additional information)

mRS	Andexanet alfa at 30 days for intracranial haemorrhage	Andexanet alfa at 30 days intracerebral haemorrhage	Øie *et al.* 2018 at 90 days intracerebral haemorrhage
0	[redacted]	[redacted]	1%
1	[redacted]	[redacted]	5%
2	[redacted]	[redacted]	9%
3	[redacted]	[redacted]	12%
4	[redacted]	[redacted]	22%
5	[redacted]	[redacted]	12%
6	[redacted]	[redacted]	39%
Average including death	[redacted]	[redacted]	4.41
Average excluding death	[redacted]	[redacted]	2.07

The ERG notes that this is not new data as mRS distributions from patients in ANNEXA-4 with an intracerebral haemorrhage were provided by the company at the clarification stage. As explained in Section 5.3.5 of the main ERG report, the company was asked to explore a scenario where intracerebral-specific mRS results from ANNEXA-4 were applied to the proportion of patients that experienced an intracerebral haemorrhage in ANNEXA-4 ([redacted]).

As part of this scenario, and the base case analysis, the mRS category associated with death (mRS 6) is excluded from the model because the consequences of ICH (long-term costs, HRQoL and mortality) are based on ICH survivors. Therefore, to better reflect how morbidity benefits are applied in the model, the ERG has added the average mRS excluding death to Table 3. This is important because removing mRS 6 has a large impact on the average mRS, and flips the average from favouring ANNEXA-4, to favouring Øie *et al.* 2018. Based on stakeholder responses at Technical Engagement, this scenario was not considered further as it was considered clinically implausible for patients to have greater morbidity benefits on standard care than andexanet alfa (i.e. a higher ICER compared to assuming no difference in morbidity). In consequence, the ERG considers that the feedback on this scenario supports its preferred base case assumption of using mRS distributions from ANNEXA-4 in both treatment arms (i.e. no morbidity benefit in ICH survivors).

2.8 Comment 8: To minimise the risk of improved survival at the expense of increased disability, optimise clinical outcomes, and ensure the guidance will be easy to implement, andexanet alfa should only be used in its licensed indication, where there is potential for benefit.

The ERG notes that the company's proposed positioning of andexanet alfa in NHS clinical practice remains unchanged and in keeping with its European marketing authorisation for use as a reversal agent in patients anticoagulated with the FXa inhibitors rivaroxaban or apixaban who experience a serious uncontrolled or life-threatening bleeding event. The ERG also notes that [redacted]

2.9 Comment 9: The ANNEXA-I study will not address uncertainties related to long term morbidity in ICH, and a recommendation for andexanet alfa 'only in research' in people with ICH is not appropriate.

As discussed in Section 2.1, the results of ANNEXA-I are required as part of the conditional marketing authorisation for andexanet alfa and the study is estimated to complete in 2024/2025. The ERG notes from the ClinicalTrials.gov listing of ANNEXA-I[2] (NCT03661528) that it is a randomised, multicentre clinical trial designed to determine the efficacy and safety of andexanet alfa compared to usual care in patients presenting with acute intracranial haemorrhage within 6 hours of symptom

onset and within 15 hours of taking an oral factor Xa inhibitor. The outcome measures for ANNEXA-I listed on ClinicalTrials.gov are as follows:

- Primary Outcome Measure:
    - Proportion of patients with good or excellent haemostatic efficacy as rated by an independent adjudication committee [Time Frame: 12 hours]; and
- Secondary Outcome Measures:
    - Change from baseline in anti-fXa activity [Time Frame: 1-3 hours];
    - Change from baseline in NIHSS [Time Frame: 24 hours];
    - Change from baseline in GCS [Time Frame: 24 hours]; and
    - Proportion of neurological deterioration, as defined by NIHSS increase > 4 or GCS decrease > 2 [Time Frame: 24 hours].

The ERG notes that all of the outcomes prespecified on ClinicalTrials.Gov for ANNEXA-I are planned to be assessed at a maximum of 24 hours after randomised study treatment and thus ANNEXA-I will not help to inform the long term outcomes of patients. However, ANNEXA-I is a randomised controlled trial and thus will provide stronger evidence in support of the clinical benefit of andexanet alfa compared to standard care. The ERG also notes that the comparator (standard care) is open label and that the comparator used in different countries to the UK may differ and so potentially this may lead to issues around the generalisability of the results from ANNEXA-I to the UK.

In relation to the existing recommendations elsewhere for andexanet alfa, as highlighted by the company, the ERG notes that the 2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants: A Report of the American College of Cardiology Solution Set Oversight Committee suggests andexanet alfa is preferable to 4F-PCC for treatment of patients with major bleeding on oral direct FXa inhibitors.[6] However, the ERG notes that evaluations undertaken by NICE are independent of other organisations and it is not unexpected for NICE to make different decisions based on the clinical- and cost-effectiveness of new technologies.

2.10 Comment 10: Although we accept the decision in patients with 'other bleeds', we would like to note that andexanet alfa is expected to benefit these patients, despite the limited evidence in this group.

The ERG notes that no new evidence has been presented and remains concerned that there is limited data for other bleeds and therefore does not consider it feasible to draw any strong conclusions as to the efficacy of andexanet alfa in this patient group.

2.11 Comment 11: The recommendations in their current form raise concerns over equality.

The ERG considers the issues raised by the company regarding equality are a matter for committee to consider.

3 References

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6. Tomaselli GF, Mahaffey KW, Cuker A, Dobesh PP, Doherty JU, Eikelboom JW, et al. 2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants: A Report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol* 2020; **76**: 594-622.