National Institute for Health and Care Excellence

Health Technology Evaluation

Andexanet alfa for reversing anticoagulation from direct factor Xa inhibitors in people with intracranial haemorrhage (part review of TA697) [ID6335]
Response to stakeholder organisation comments on the draft remit and draft scope

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 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	AstraZeneca	AstraZeneca consider the proposed evaluation route to be appropriate.	Thank you for your comment. No action required.
Wording	AstraZeneca	The appropriate wording for this appraisal is andexanet alfa for reversing anticoagulation in people with intracranial haemorrhage (part review of TA697) [ID6335]". [redacted] AstraZeneca, therefore, kindly request the wording to be updated to "andexanet alfa for reversing anticoagulation in people with intracranial haemorrhage (part review of TA697) [ID6335]".	Thank you for your comment. The remit was changed to specify 'Andexanet alfa for reversing anticoagulation from direct factor Xa inhibitors in people with intracranial haemorrhage'

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Timing Issues	AstraZeneca	To date, there has been no National Institute for Health and Care Excellence (NICE) recommended therapy for the reversal of anticoagulation from direct factor Xa (FXa) inhibitors in people with intracranial haemorrhage (ICH). NICE have previously reviewed andexanet alfa as an option for reversing anticoagulation from apixaban or rivaroxaban in adults with ICH which led to a recommendation for research only. A direct oral anticoagulant (DOAC)-related major ICH is life-threatening, thus associated with high-mortality; approximately one out of three patients are likely to die while hospitalised for their DOAC-related ICH in clinical practice. The prevention of haematoma expansion is the most important therapeutic goal when treating patients with ICH as it is a validated predictor of functional outcome and mortality. As such, there is an urgent and critical need for NICE to appraise andexanet alfa within its [redacted] to provide a long-awaited, effective treatment for this condition	Thank you for your comment. No action required.
Additional comments on the draft remit	AstraZeneca	N/A	No action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	AstraZeneca	**AstraZeneca suggests the following additions/ amendments to the background information presented within the draft scope:** **DOAC prescriptions** According to the latest prescription cost analysis from the National Health Service (NHS) Business Services Authority from 2022 to 2023 in England, there were over 16.2 million DOAC prescriptions dispensed in the community, with over 15.9 million direct FXa inhibitors prescriptions (i.e., apixaban,	Thank you for your comment. The scope background information section has been updated to reflect the 2022 to 2023 prescription cost

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		rivaroxaban and edoxaban). 3 There has been an increase in DOAC prescriptions bolstered by the NHS priority to address the growing challenges of strokes and heart attacks through the improvement of anticoagulation medicine availability.4-10 Between January 2018 and July 2022, the proportion of patients prescribed a DOAC have almost doubled with 1.12% of the population receiving a DOAC in January 2018 to 1.97% in July 2022.9 AstraZeneca kindly request that prescription numbers in the background section are updated to align with the 2023 prescription cost analysis and specify that these numbers are likely to keep increasing in line with the NHS priorities and associated policies in place to tackle the growing cardiovascular disease burden. **Licensed reversal agents for DOAC-related major bleeds** Despite the increase in DOAC use and the associated serious risk of major bleeding, only two reversal agents of DOACs are licensed for use in the UK, namely andexanet alfa for the reversal of apixaban and rivaroxaban, and idarucizumab for the reversal of dabigatran.9,11-16 Although, andexanet alfa is routinely commissioned in clinical practice in England and Wales for the reversal of direct FXa inhibitors, namely apixaban and rivaroxaban, it is restricted to the gastrointestinal (GI) subpopulation.17,18 The increasing use of direct FXa inhibitors coupled with the restricted NICE recommendation of andexanet alfa, emphasises the urgent need for a specific reversal agent for patients with an ICH. Therefore, AstraZeneca suggest specifying in the background section that there is only one licensed reversal agent for major bleeding on a direct FXa inhibitor, namely andexanet alfa for the reversal of apixaban and rivaroxaban, although its use is restricted to the GI subpopulation. Thus, that there is no	analysis. The background information section has also been updated to include: *'Major bleeding events in the skull (intracranial haemorrhage), are associated with high mortality and morbidity'.*

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		routinely commissioned reversal agent for direct FXa inhibitor-related major ICH in clinical practice across England and Wales. **Unmet need and treatment management for DOAC-related major ICH** Due to the absence of a NICE recommended direct Fxa-inhibitor reversal agent for patients with a major ICH, clinicians use off-label four-factor prothrombin complex concentrate (4F-PCC)17 despite limited evidence being available to demonstrate the efficacy of PCC in these patients. 19-21 The substantial burden associated with major ICH coupled with the limited treatment options available to patients demonstrate the large unmet need for a routinely commissioned treatment. AstraZeneca, therefore, suggest presenting in the background section the high unmet need faced by these patients, including the associated high mortality and morbidity burden alongside the lack of routinely commissioned reversal agent for direct FXa inhibitor-related major ICH in clinical practice across England and Wales	
Population	AstraZeneca	AstraZeneca consider that the population is appropriately defined in the Draft scope. [redacted]	Thank you for your comment. The population has been updated to Adults needing reversal of anticoagulation from direct factor Xa inhibitors for life-threatening or uncontrolled bleeding in

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			the skull (intracranial haemorrhage).
Subgroups	AstraZeneca	AstraZeneca consider that no groups within this population should be considered separately.	Thank you for your comment. No action required.
Comparators	AstraZeneca	In TA697, 4F-PCC was considered as the appropriate comparator for andexanet alfa for reversing anticoagulation from apixaban or rivaroxaban. Of note, the Evidence Review Group (ERG) agreed that 4F-PCC is likely the most appropriate comparator for andexanet alfa in this indication.17 Therefore, AstraZeneca kindly request for the comparators to exclude tranexamic acid and amend comparator wording to: Established clinical management of uncontrolled or life-threatening bleeding without andexanet alfa (including PCC).	Thank you for your comment. No action required.
Outcomes	AstraZeneca	As the prevention of haematoma expansion is the most important therapeutic goal when treating patients with ICH and it is a validated predictor of functional outcome and mortality, 2 AstraZeneca kindly request to add haematoma expansion as part of “change in size of intracranial bleeding”.	Thank you for your comment. The scope outcomes have been updated ‘*change in size of intracranial bleeding’* has been removed and replaced with ‘*haematoma expansion’*.
Equality	AstraZeneca	Haemorrhagic stroke, which includes ICH, is an area with limited clinical innovation compared to ischemic stroke. Over the past decade, the mortality rate from ischemic stroke has decreased due to breakthroughs driven by multiple large randomised clinical trials (RCTs), however limited innovation	Thank you for your comment. No action required.

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		and, therefore, improvement in patient outcomes has been demonstrated for ICH. 21-24 Thus, there is a high unmet need associated with major ICH, putting patients at risk of mortality and morbidity. Moreover, the increase in DOAC prescription is likely associated with a rise in urgent admissions for bleeding complications. Between 2011 and 2016, each 10% rise in DOAC prescription led to an 0.8% increase in urgent admissions for bleeding in England.25 Increasing the risk of major ICH bleed and associated hospital admissions are counterproductive to the NHS long term plan that aims to boost 'out-of-hospital' care and reduce pressure on emergency hospital services.6 This is even more concerning considering the lack of routinely commissioned reversal agent for direct FXa inhibitor-related major ICH in clinical practice across England and Wales.	
Other considerations	AstraZeneca	None	No action needed.
Questions for consultation	AstraZeneca	**What does established clinical management without andexanet alfa include (specifically for reversing anticoagulation from apixaban or rivaroxaban in people with intracranial haemorrhage)?** To summarise, as noted in TA697, off-label PCC is used to reverse direct Fxa-inhibitor in patients with a major bleed, including ICH, 17 despite the limited evidence available to demonstrate its efficacy in these patients.19-21 Therefore, as PCC is the appropriate comparator for this appraisal, AstraZeneca request for the comparator section to be updated to exclude tranexamic acid and therefore state: Established clinical management of	Thank you for your comments. Details of any changes to the scope have been mentioned in the responses above. No further action required.

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		uncontrolled or life- threatening bleeding without andexanet alfa (including PCC). **Do you consider that the use of andexanet alfa can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** In TA697, the committee recognised that the RCT mandated by the regulator (ANNEXA-I) was to provide stronger evidence of haemostatic efficacy in addition to the key clinical question of short-term mortality and neurological outcomes, however, the committee acknowledged that it may not resolve the long-term morbidity and mortality uncertainty, mainly due to the trial design itself. 17 The primary endpoint for ANNEXA-I is haemostatic efficacy26 which is recognised by the international Society on Thrombosis and Haemostasis (ISTH) as the most important parameter for evaluating the effectiveness of treatments for anticoagulant-related bleeding. 27 Haematoma expansion, which is a composite of haemostatic efficacy, is a validated predictor of functional outcomes and mortality, however, data is limited. Therefore, the use of andexanet alfa in patients with ICH may result in long-term health-related benefits that are unlikely to be included in the QALY calculation. 2 **Are the outcomes listed in the scope appropriate (specifically in people with intracranial haemorrhage)? Do any other outcomes need to be included?**	

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		The prevention of haematoma expansion is the most important therapeutic goal when treating patients with ICH and it is a validated predictor of functional outcome and mortality. 2 As outlined above, the ISTH has recognised haemostatic efficacy, which is inclusive of haematoma expansion, as the most important parameter for evaluating the effectiveness of treatments for anticoagulant-related bleeding.27 In addition, ANNEXA-I stopped early after achieving pre-specified criteria on haemostatic efficacy versus usual care. 26 Therefore, AstraZeneca kindly request to add haematoma expansion as part of change in size of intracranial bleeding" outcome measure. **Are there any subgroups of people in whom andexanet alfa is expected to be more clinically effective and cost effective or other groups that should be examined separately?** AstraZeneca consider that no groups within this population should be considered separately. **Would andexanet alfa be a candidate for managed access?** Based on the above, AstraZeneca will be seeking a recommendation for andexanet alfa in ICH into routine commissioning and do not consider andexanet alfa to be a candidate for managed access.	
Additional comments on the draft scope	AstraZeneca	AstraZeneca kindly request that the related NICE guidelines section is updated to include all relevant clinical guidelines relating to the management of major ICH bleed. These guidelines are:	Thank you for your comment. The related NICE guidelines have

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		• NICE. Major trauma: assessment and initial management (2016). [NG39] • NICE. Blood transfusion (2015). [NG24]. • NICE. Stroke and transient ischaemic attack in over 16s: diagnosis and initial management (2022). [NG128] • NICE. Head injury: assessment and early management (2023). [NG232] AstraZeneca kindly request the related national policy section is updated to include the anticoagulation policies in place from NHSE which include: • NHS. Operational note: Commissioning recommendations for national procurement for DOACs. 2022; https://www.england.nhs.uk/wp-content/uploads/2022/01/B1279-national-procurement-for-DOACs-commissioning-recommendations-v1.pdf. Accessed 4 October, 2023. • NHS. DOAC infographic. 2023; https://www.england.nhs.uk/long-read/direct-oral-anticoagulants-doac-infographic/. Accessed 4 October, 2023. • NHS. Clinical guide for the management of anticoagulant services during the coronavirus pandemic. 2021; https://www.nice.org.uk/Media/Default/About/COVID-19/Specialty-guides/specialty-guide-anticoagulant-services-and-coronavirus.pdf. Accessed 24 October, 2023. • • NHS. Quality and Outcomes Framework guidance for 2023/24. 2023; https://www.england.nhs.uk/wp-content/uploads/2023/03/PRN00289-quality-and-outcomes-	been added to the scope. National policy around commissioning around direct oral anticoagulants has not been added to the scope.

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		framework-guidance-for-2023-24.pdf. Accessed 01 November, 2023.	

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

N/A