National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Andexanet alfa for reversing anticoagulation [ID1101]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Portola	Yes, it is appropriate that NICE reviews andexanet alfa. Factor Xa-inhibitor (FXa) anticoagulants are increasingly being used in clinical practice for the prevention and treatment of thrombotic events since they possess distinct advantages over older therapies. However, FXa inhibitors are associated with major and even fatal bleeding events. As such there is a high unmet need for a reversal agent, particularly in situations of life threatening bleeding.	Comment noted. No changes to the scope required.
	British Cardiovascular Society	Yes	Comment noted.
	Anticoagulation UK	It is is relevant as we need antidotes to the full range of DOACS. Dabigatran has a reversal agent Idarucizumab. Patients who require anticoagulation therapy may not choose a factor XA inhibitor due to concerns around bleeding risk and reversal options. With update of Doacs for broad range of	Comment noted. No changes to the scope required.

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		conditions, opportunities to manage major bleeds safely and with efficacy is vital to patient welfare. We note that this technology is approved by USA FDA but has not yet gained marketing authorisation by CHMP of the EMA. The manufacturers issued a press release dated 11/12/18* stating an opinion is due end of Feb 2019	
	UKCPA (UK Clinical Pharmacy Association) Haemostasis, Anticoagulation and Thrombosis (HAT) group	Appropriate. No comments.	Comment noted.
	Royal College of Pathologists and British Society for Haematologists (RCPAth and BSH)	Yes	Comment noted.
	Thrombosis UK	Yes	Comment noted.
Wording	Portola	See comments below on individual sections.	Comment noted.
	British Cardiovascular Society	Yes	Comment noted.

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	Anticoagulation UK	The FDA marketing authorisation stated the use of Andexanet alfa(Andexxa) for Apixaban and Rivaroxaban only. Is 'Andexanet alfa for reversing anticoagulation' accurately representing which specific Factor XA inhibiting DOACs as mentioned in population section? Consider title of HTA to match Population wording	Comment noted. The remit is intended to be a broad outline of the appraisal and the technology will be appraised within its UK marketing authorisation.
	UKCPA	Paragraph 2 quotes bleeding rates of DOACs vs warfarin but this is an old reference. There is more up-to-date data and this needs to be reflected in the document. It is unclear why there is advice about reversal of antiplatelet therapy as this is a different drug group and does not relate to the consultation for andexanet alfa.	Comment noted. The background section has been updated more recent data on epidemiology.
	Royal College of Pathologists and British Society for Haematologists (RCPAth and BSH)	Yes. However, we expect cost effectiveness to be difficult to assess if it is compared with existing approaches as there was no head to head comparison and these are both expensive and of undetermined efficacy apart from observational cohort studies with no comparators or placebo arm	Comment noted. The cost-effectiveness of the technology will be considered by the appraisal committee based on the best available evidence and it will also take into consideration additional factors such as innovation and unmet medical need.
	Thrombosis UK	The wording is worryingly inaccurate and shows poor grasp of the issues	Comment noted. The background section has been updated with more

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		e.g. paragraph 2 'bleeding with DOACs is less than with warfarin'. Why is an old reference for the bleeding rates on warfarin used to talk about bleeding with DOACs? e.g para 3. Why is there a recommendation to antagonise antiplatelet therapy? Antiplatelet therapy is a different subject. This para does not make sense. e.g para 1 on page 2. Antithrombin is no longer known as antithrombin III, only as "antithrombin"	recent data on epidemiology.
Timing Issues	Portola	This proposed appraisal is urgent as there is no antidote currently available for the reversal of life-threatening bleeding caused by FXa inhibiting direct oral anticoagulants (DOACs), thus offering an important advance in addressing this unmet need as described above. [redacted]	Comment noted. NICE aims to provide guidance to the NHS within 6 months of the date when the marketing authorisation for a technology is granted. We note that the date of release of CHMP opinion has changed and is now expected for February 2019.
	British Cardiovascular Society	Moderate	Comment noted.

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	Anticoagulation UK	A reversal agent for factor XA doacs is welcome for existing patients on these treatments, for new patients when considering DOAC choice and for patients who may be considering switching from a VKA warfarin to a DOAC but with the lack of reversal agent being a key concern/barrier For clinicians who are currently managing DOAC bleeds, this is a treatment which will be available in clinical situations when other reversal options are inappropriate due to the patient's health state	Comment noted. NICE aims to provide guidance to the NHS within 6 months of the date when the marketing authorisation for a technology is granted.
	UKCPA	This appraisal is urgently warranted as DOACs are a mainstay of treatment for the management of VTE and AF and the guidance needs to be available for reversal of the factor Xa inhibitors.	Comment noted. NICE aims to provide guidance to the NHS within 6 months of the date when the marketing authorisation for a technology is granted.
	RCPAth and BSH	Use of DOACs including factor Xa inhibitors is increasing for various indications. At present, there is no specific antidote for patients on factor Xa inhibitors, presenting with major or life-threatening bleeding or requiring urgent surgery. Therefore, this proposal is very important and addresses an urgent clinical need.	Comment noted. NICE aims to provide guidance to the NHS within 6 months of the date when the marketing authorisation for a technology is granted.
	Thrombosis UK	Very urgent	Comment noted. NICE aims to provide guidance to the NHS within 6 months of the

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			date when the marketing authorisation for a technology is granted.

Comment 2: the draft scope

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Background information	Portola	• Portola believes that the use of DOACs in the U.K. has grown beyond the 200,000 to 350,000 patients estimates referenced in the Draft Scoping Document • Major bleeding with FXa inhibitors has ranged from 1 to 3% in the large randomized Phase 3 studies conducted for labeled indications. Additional real-world registry data confirms this range for major bleeding • Intracranial haemorrhage rates for FXa inhibitors range from 0.3% to 0.5% in large Phase 3 studies and registries • The 2018 updated European Society of Cardiology (ESC) Practical Guide on use of DOACs recommends reversal with andexanet alfa for FXa patients experiencing a life threatening bleed • The ESC Guide notes that in cases of urgent surgery andexanet alfa has not been studied in this population and usefulness will need to be re-evaluated after approval • At the current time, andexanet alfa is not under review by CHMP for use in patients requiring urgent surgery.	Comment noted. The background section has been updated with more recent data on epidemiology.

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	Anticoagulation UK	See note in comparators section *	Comment noted.
	UKCPA	There is insufficient information on the rationale for scoping the use of andexanet alfa.	Comment noted.
	Royal College of Pathologists and British Society for Haematologists (RCPAth and BSH)	Paragraph 3 line 5, it says ''oral charcoal intake followed by antagonisation of antiplatelet therapy with'', this should be changed to anticoagulant from antiplatelet Other guidelines on management of major bleeding on DOACs such BSH guidelines are not mentioned. The merits of emergency reversal should always be weighed against the risk of thrombosis.	Comment noted. The background section has been updated to reflect this.
	Thrombosis UK	This is poorly written see comments above	Comment noted.
The technology/ intervention	Portola	The paragraph below seems incomplete as it does not include all the relevant clinical trials: Andexanet alfa does not currently have a marketing authorisation in the UK for reversing anticoagulation. It has been studied in a single arm trial in adults who had acute major bleeding episode within 18 hours after administration of an anticoagulant. The phase 2 and 3 studies of andexanet alfa in healthy adults should also be added here. They are prospective, randomized, placebo-controlled studies that provide key evidence on the reversal of anticoagulation that was used to support the regulatory assessment. We would suggest revising to:	Thank you for your comment. The scope is intended to provide a brief description of the technology and not a complete list the clinical trials. As it was discussed at the scoping workshop the population of this scope is reflected in the ANNEXA-4 clinical trial.

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		"Andexanet alfa does not currently have a marketing authorisation in the UK for reversing anticoagulation. It has been studied in randomized, placebo-controlled, phase 2 and 3 studies in healthy adults receiving direct and indirect factor Xa inhibitors, and in a prospective single arm trial in adult patients receiving a factor Xa inhibitor who require urgent reversal of anticoagulation due to life-threatening bleeding." It is also important to note that ANNEXA-4 is the only prospective clinical trial to date that has used robust, adjudicated outcomes to assess the effect of reversal of anticoagulation in patients receiving a FXa inhibitor. The mechanism of action for andexanet alfa could be referenced to: Lu et al. A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa. Nat Med. 2013 Apr;19(4):446-51	References are normally included only for epidemiology data.
	British Cardiovascular Society	Yes	Comment noted.
	Anticoagulation UK	American brand name is ANDEXXA. According to manufacturers press release,* the proposed brand name for EMA is Ondexxya???	Thank you for your comment. The brand name of the technology has been amended in the scope.
	UKCPA	The description of the technology should be: "For use in severe or life threatening bleeding in patients who have recently received a factor Xa direct oral anticoagulant"	Thank you for your comment. The exact wording of the eligibility criteria in the clinical trial was '*people with acute major bleeding episode requiring*

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			urgent reversal of anticoagulation and who have received one of the following anticoagulant agents: apixaban rivaroxaban, edoxaban or enoxaparin'. Currently the scope reflects this wording, therefore no update is needed to the wording.
	Royal College of Pathologists and British Society for Haematologists (RCPAth and BSH)	Yes	Comment noted.
	Thrombosis UK	No. This would be better phrased as "For use in severe or life-threatening bleeding in patients who have recently received a direct oral agent with anti Xa activity"	Thank you for your comment. The exact wording of the eligibility criteria in the clinical trial was '*people with acute major bleeding episode requiring urgent reversal of anticoagulation and who have received one*

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			of the following anticoagulant agents: apixaban rivaroxaban, edoxaban or enoxaparin'. Currently the scope reflects this wording, therefore no update is needed to the wording.
Population	Portola	The population is appropriate. It is important to note that andexanet alfa treatment would not be required for all cases of severe or life-threatening bleeds. Please see comment on the definition of severe or life-threatening bleeds in the 'Questions for consultation' section.	Comment noted.
	Anticoagulation UK	Yes	Comment noted.
	UKCPA	The timeframe of treatment with andexanet alfa should include a statement 'for patients would have recently had a factor Xa direct oral anticoagulant	Thank you for your comment. The population section of the scope is intended to be a broad outline of the population that the technology is expected to receive its marketing authorisation for.
	Royal College of Pathologists and	Package insert of andexanet alfa states that ANDEXXA has not been shown to be effective for, and is not indicated for, the treatment of bleeding related to	Thank you for your comment. The

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	British Society for Haematologists (RCPAth and BSH)	any FXa inhibitors other than apixaban and rivaroxaban. Therefore, population should be defined as Adults requiring urgent reversal of anticoagulation in case of severe or life-threatening bleeding, after treatment rivaroxaban and apixaban. This should not be left as generic factor Xa-inhibiting DOAC	population section of the scope is intended to be a broad outline of the population that the technology is expected to receive its marketing authorisation for. As andexanet alfa does not have a marketing authorisation at the current time, it is appropriate that the population section is left broad and in line with the clinical trial population.
	Thrombosis UK	Not quite. ..last phrase needs to say “after RECENT” treatment with a factor Xa inhibiting DOAC”- see statement in above box which would be preferable. For use in severe or life-threatening bleeding in patients who have recently received a direct oral agent with anti Xa activity BUT THERE HAVE NEVER BEEN TRIALS IN TRAUMA PATIENTS! - all the issues in trauma are summarised in Hunt BJ, Neal MD, Stensballe J in a Blood article published Dec 6th 2018, entitled “Reversing anti-factor Xa agents and the unmet need in trauma patients” The following recently published paper also provides evidence of real-life data suggesting our current use of prothrombin complex concentrate (PCC) is	Thank you for your comment. The population section of the scope is intended to be a broad outline of the population that the technology is expected to receive its marketing authorisation for. The best available evidence will be considered by the appraisal committee alongside any analysis

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		providing efficacy and also have a low rate of thrombosis after reversal. We are concerned that there is no comparative data comparing PCC with andexanet as regards efficacy and safety (rates of thrombosis after reversal). This comparative data is very important for 1) in the US andexanet is set at $26,000 for low dose and the cost of PCC is about £1,000. 2) There is a signal from the limited data on andexanet that there is a high thrombosis rate after using andexanet than after PCC, but data is from v small numbers. 'Efficacy & safety of prothrombin complex concentrate in patients treated with rivaroxaban or apixaban compared to warfarin presenting with major bleeding" DRJ Arachchillage, S Alvian, J Griffin, K Gurung, R Szydlo, N Karawitage, M Laffan, Nov 2018 **(https://onlinelibrary.wiley.com/doi/pdf/10.1111/bjh.15705**	to establish comparative effectiveness evidence between andexanet alfa and its comparators, in line with the methods outlined in the Guide to the methods of technology appraisal 2013.
Comparators	Portola	In clinical practice Fresh Frozen Plasma and supportive care are widely used to treat a range of patients who experience bleeds. In a subset of patients (who experience life- threatening bleeds), prothrombin complex concentrate is often used without tranexamic acid. Therefore, we would suggest rewording to: "Established clinical management of life-threatening bleeds without andexanet alfa (including prothrombin complex concentrate with or without tranexamic acid) despite lack of prospective clinical data or label."	Thank you for your comment. The comparators section of the scope has been updated in line with these suggestions.
	Anticoagulation UK	*It is stated that prothrombin complex concentrate with tranexamic acid is established clinical management. There is reference (in the background) to ESC guidelines recommending oral charcoal intake followed by	Thank you for your comment. Attendees at the scoping workshop

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		antagonisation of antiplatelet therapy with specific antidote if available? What is the standardised practice is the UK?	suggested that in the case a life threatening bleeding or emergency surgery prothrombin complex concentrate (PCC) is used in high dose (50 units/kg) with supportive treatment including tranexamic acid. No changes to the scope needed.
	UKCPA	PCC –partial reversal. Tranexamic acid- used to reverse bleeding anyway, so would be used for DOAC associated bleeding.	Comment noted.
	Royal College of Pathologists and British Society for Haematologists (RCPAth and BSH)	In absence of a specific antidote, PCC with tranexamic acid is considered to be the best alternative care. Activated factors such as FEIBA and rfVIIa are also used in some circumstances.	It was discussed at the scoping workshop that FEIBA and recombinant factor VIIa are rarely used in this population.
	Thrombosis UK	The standard treatment is PCC, NOT “PCC and tranexamic acid”. Medical staff would give tranexamic acid to anyone who is bleeding anyway, that would include those receiving andexanet	Thank you for your comment. Attendees at the scoping workshop suggested that in the case a life-threatening bleeding or emergency surgery prothrombin

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			complex concentrate (PCC) is used in high dose (50 units/kg) with supportive treatment including tranexamic acid. The comparator section of the scope has been updated to say PCC with or without tranexamic acid is established management of life-threatening bleeding.
Outcomes	Portola	There are further measures that should be included. We suggest the following as outcome measures: • Reversal of anticoagulation effect as measured by anti-factor X activity, unbound anticoagulant plasma levels and thrombin generation • Haemostatic efficacy as measured by hematoma expansion in intracranial hemorrhage and re-bleeding • Modified Rankin Score as a measurement of functional neurologic outcomes.	It was discussed at the scoping workshop that anti-factor Xa activity, anticoagulant plasma levels and thrombin generation are surrogate and pharmacokinetic outcomes. There is little real-world evidence for the link to final clinical outcomes. However the list of outcomes has been updated to include neurological outcomes (in people with intracranial bleeding).

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	British Cardiovascular Society	Yes	Comment noted.
	Anticoagulation UK	Requirement for blood product – is this because the treatment is a coagulation factor Xa(recombinant and derived from blood product) Risk of Thrombotic and ischemic risk, cardiac arrest and sudden death noted in adverse events.	Comment noted. These outcomes are covered by the current list of outcomes. No changes to the scope needed.
	UKCPA	Needs to reflect the long terms complications of intracranial haemorrhage.	Comment noted. This would be covered by the effects of intracranial haemorrhage outcome.
	Royal College of Pathologists and British Society for Haematologists (RCPAth and BSH)	Yes	Comment noted.
	Thrombosis UK	Outcomes measures is missing effect on DALYs, many patients after intracranial bleeds have long term disability. This does not seem to be captured with your current list	Thank you for your comment. As it is outlined in the Reference case in the Guide to the methods of technology appraisal 2013, for the cost-

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			effectiveness analysis health effects should be expressed in QALYs. Long term disability would be captured by the decrease in quality of life using the comparator compared with andexanet alfa.
Economic analysis	Portola	Aspects of the economic analysis, such as the time horizon, will be detailed in the submission.	Comment noted.
	Anticoagulation UK	Nothing noted	Comment noted.
	UKCPA	Is this data available?	The economic analysis should be conducted by the company and presented in the submission, using the methodologies that our outlined in the Reference Case, in the Guide to the methods of technology appraisal 2013.

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	Royal College of Pathologists and British Society for Haematologists (RCPAth and BSH)	One critical risk for patients taking all anticoagulants is intracerebral haemorrhage. If it is concluded that the technology will reduce the risk of disabling stroke then the horizon may need to be several years. In other forms of haemorrhage, the horizon is unlikely to be longer than the admission. This analysis is virtually impossible in the absence of a randomised controlled trial. Although, use of PCC reverse the effect of warfarin analysis of published data does not show any proven survival or outcome benefit	Thank you for your comment. In line with the Reference Case of the Guide to the methods of technology appraisal 2013, the time horizon should be long enough to reflect all important differences in costs or outcomes between the technologies being compared.
	Thrombosis UK	In our opinion, economic analysis is likely to be extremely challenging as we do not think the available data is adequate to do an ICER	The economic analysis should be conducted by the company and presented in the submission, using the methodologies that our outlined in the Reference Case, in the Guide to the methods of technology appraisal 2013.
Equality and Diversity	Portola	No issues have been identified regarding equality.	Comment noted.
	Anticoagulation UK	Patients should be made aware of the side effects of this agent and options available. We presume that clinical assessment will be undertaken and this	Thank you for your comment. No changes to the scope are

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		may not be the first line treatment but used when other bleeding reversal options have been explored. If possible and dependent on the circumstances of the patient's status at the time of the bleed, how will patients consent to this treatment (with risk and benefit explained) be obtained. Protocol for administration and management and clarity around life – threatening and severe risk needed. If this treatment is derived from human blood product, this may not be acceptable to some groups of the population. If a patient is unable to consent to the treatment at the time of administration, could this have implications later down the line.	needed. The appraisal committee will take into account potential equality issues relevant to their recommendations. Andexanet alfa is a recombinant technology, and it is not derived from human blood product, therefore this is not likely to be an equality issue.
	UKCPA	No additional comments.	Comment noted.
	Royal College of Pathologists and British Society for Haematologists (RCPAth and BSH)	No specific comments to add	Comment noted.
	Thrombosis UK	WE believe the wording is fine, although it is perhaps wise to note that the majority of those receiving reversal will be the geriatric population	Thank you for your comment. No changes to the scope are needed. The appraisal committee will take into account potential equality issues relevant

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			to their recommendations.
Other considerations	Portola	No additional issues have been identified.	Comment noted.
	British Cardiovascular Society	See below	Comment noted.
	UKCPA	Use in trauma patients, when there is little RCTs in this area.	Comments noted. Technology will be appraised within its marketing authorisation.
	Royal College of Pathologists and British Society for Haematologists (RCPAth and BSH)	complexity of different regimens of the IV infusion of andexanet alfa Possible rebound once the infusion is stopped application andexanet alfa to factor Xa inhibitors other than rivaroxaban and apixaban	Comments noted. Technology will be appraised within its marketing authorisation, and based on the best available evidence on the technology.
	Thrombosis UK	There are no trials in trauma patients, where there is a significant need to carry them out. For this reason, we are concerned whether the therapy can be used in this situation without a trial? Especially as the trauma community use PCC	Comments noted. Technology will be appraised within its marketing authorisation.
Innovation	Portola	Yes, andexanet alfa is a highly innovative technology and is an FDA-designated breakthrough therapy. Andexanet alfa is the only agent that has been demonstrated to directly reverse the inhibitory effects of apixaban and rivaroxaban on FXa, their target.	Comment noted. Innovation will be considered by the appraisal committee

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		In randomized clinical trials, FXa inhibitors have been shown to be safe and effective for the treatment and prevention of venous thromboembolism and for stroke prevention in patients with atrial fibrillation. However, FXa inhibitors are associated with major and even fatal bleeding events. These bleeding patients suffer poor outcomes and high mortality rates. Such episodes of acute major bleeding may be difficult to treat because there is no reversal agent. In addition, agents with no efficacy evidence to support their use are given in clinical practice; this is a consequence of the urgent nature of treatment and the high unmet need for a reversal agent. As the first agent specifically developed to reverse the effects of FXa inhibitors, andexanet alfa represents a step-change in therapy. The ability to have a standard of care which is effective in reversing FXa inhibiting DOACs will create a standardisation which will facilitate timely effective treatment and within hospital efficiencies. This change in service would not be captured in the QALY calculation but will represent significant benefits to patients and the NHS.	when formulating its recommendations. The consultees and commentators will have an opportunity to provide evidence on the innovative nature of the product in their submissions. No changes to the scope are needed.
	Anticoagulation UK	Yes	Comment noted.
	UKCPA	This is innovative.	Comment noted, no changes to the scope are needed. Consultees are encouraged to describe the innovative nature of the technology in their evidence submissions. The appraisal committee will consider the innovative nature of andexanet

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			alfa during the appraisal.
	Royal College of Pathologists and British Society for Haematologists (RCPAth and BSH)	At present there is no specific reversal agent for the factor Xa inhibitors which are approved by NICE. This is a barrier to their general adoption by prescribers despite their other advantages. If Andexanet is licensed then the availability of a specific antidote for reversal of direct factor Xa inhibitors, will put doctors and patients at ease. It may be of benefit particularly for the elderly population who are at increased risk of both bleeding and thrombosis.	Comment noted. Innovation will be considered by the appraisal committee when formulating its recommendations. The consultees and commentators will have an opportunity to provide evidence on the innovative nature of the product in their submissions. No changes to the scope are needed.
	Thrombosis UK	Yes, this is highly innovative	Comment noted.
Questions for consultation	Portola	**Questions for consultation** ***Would andexanet alfa be used only in case of severe or life-threatening bleeding? If so, how should severe or life-threatening bleeding be defined*?** Andexanet alfa would only be used only in case of severe or life-threatening bleeding. Not all cases of severe bleeding would be considered appropriate	Thank you for your comments. No changes to the scope needed. The technology will be

		for andexanet alfa treatment. Portola would suggest the following definition for severe or life-threatening bleeding: • Life threatening bleeds (e.g. with signs or symptoms of haemodynamic compromise, such as severe hypotension, poor skin perfusion, mental confusion, low urine output that cannot be otherwise explained) • Symptomatic bleeding in a critical area of organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome • Bleeding causing a fall in haemoglobin level of ≥ 20 g/L (2 g/dL or 1.24 mmol/L) OR a haemoglobin level ≤ 80 g/L if no baseline haemoglobin level is available OR in the opinion of the physician, the patient's hemoglobin will fall to ≤ 80 g/L with resuscitation OR leading to transfusion of two or more unit of whole blood or red cells ***What is established clinical management without andexanet alfa likely to include?*** The position statement from the European Society of Cardiology (Niessner et al, Eur Heart J. 2017) provides guidelines on the management of the reversal of non-vitamin K antagonist oral anticoagulants in the case of life threatening bleeding/emergency surgery antagonization of anticoagulant therapy includes: • Oral charcoal intake • Consider antagonization of concomitant antiplatelet therapy • Consider specific antidote if available. • If no antidote available, consider Prothrombin complex concentrate • Consider recombinant Factor VIIa if no effect of previous measures The evidence for the use of prothrombin complex and Factor VIIa is limited to small uncontrolled trials. In the position statement from the ESC it states that:	appraised within its marketing authorisation. Thank you for your comment. No changes to the scope needed.

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		Pending the availability of robust clinical evidence of a beneficial effect, if immediate haemostatic support is required due to a life- threatening situation, the choice of clotting factor concentrates may be based on its least pro-thrombotic effect, favouring PCCs over rFVIIa. ***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? Should people with intracranial bleeding be considered separately?*** • Andexanet alfa is expected to be clinically effective and cost effective in the subgroup of patients with severe or life-threatening bleeding, as defined above. • Given the high mortality and costs associated with intracranial bleeding, andexanet alfa may demonstrate a greater benefit in this subset of patients. ***Where do you consider andexanet alfa will fit into the existing NICE pathway, Trauma?]*** • We would consider andexanet alfa to fall under the category of 'anticoagulation reversal' falling under 'person with major haemorrhaging in hospital'. • The ANNEXA 4 study included patients with bleeds which resulted from trauma. • As the first approved FXa inhibitor antidote, andexanet alfa should be used as stated in the ESC position statement above. ***Do you consider that the use of andexanet alfa can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?*** • [redacted]	The subgroup of people with intracranial bleeding has been added to the scope. Thank you for your comment. No changes to the scope needed. Comment noted.

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		NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. • Portola would agree that the STA process is the most appropriate route for andexanet alfa [redacted]	Comment noted. No changes to the scope needed.
	British Cardiovascular Society	"• Would andexanet alfa be used only in case of severe or life-threatening bleeding? If so, how should severe or life-threatening bleeding be defined? Yes, usage likely to be restricted to lifethreatening bleeding or bleeding on closed space (the eye, the spinal cord, intracranial bleeding). Suggest use same definitions of life-threatening bleeding as used in main Factor Xa inhibitor trials. • What is established clinical management without andexanet alfa likely to include? For Xa-inhibitor bleeding at present it would mainly be supportive care (blood transfusion and fluids for example). Beriplex (prothrombin complesx concentrate) can be used but it is not a specific reversal agent and trials of its use are quite conflicting. • in theory Beriplex shouldn't work as it replaces Factor X but the active inhibitor drug will still be there to provide ongoing inhibition. • Human trials are mainly healthy volunteers monitoring their coagulation results – tend to improve this measure but not a	Comment noted. No changes to the scope needed. Comment noted. No changes to the scope needed.

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		good surrogate outcome. Difficult to know therefore how helpful the drug would be in real clinical situations therefore. • Animal studies are various bleeding models in various mammals – sometimes helps, sometimes doesn't. Uncertainty therefore in how animal models may predict usefulness in clinical practice. An alternative is to consider the use of Novoseven (recombinant Coagulation Factor VIIa), but this carries a high risk of arterial or venous thrombosis ~5-10%, especially in the elderly.	
		• Are the outcomes listed appropriate? Do any other outcomes need to be included? BCS considers that the outcome measures being considered are appropriate	Comment noted.
		• 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? Should people with intracranial bleeding be considered separately? Unknown	Comment noted.
		• Where do you consider andexanet alfa will fit into the existing NICE pathway, Trauma? BCS is unable to comment on trauma pathways	Comment noted.
		• could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which andexanet alfa will be licensed; Does not seem likely. May allow for better treatment for patient's currently unable to benefit from existing blood-based products (e.g. Jehovah's Witnesses)	Comment noted.
		• could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider	

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		population, e.g. 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. No • Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. • Do you consider andexanet alfa to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? If this product can be shown to make meaningful reductions in bleeding/death/disability due to bleeding in real clinical practice, then this would indeed be a major improvement in anticoagulation management. Fear of bleeding problems is a common reason to avoid the use of FXa antagonists, which may prevent those patients benefitting from the benefits of anticoagulation • Do you consider that the use of andexanet alfa can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? Possibly. The absence of a reversal agent for some of the Novel oral anticoagulants is used as a justification to block the adoption of their use over Warfarin. Whilst this level of prescriber block is decreasing, it is still present. As such the availability of Andexanet Alfa may encourage the use of Anti factor Xa anticoagulants, as opposed to Warfarin. This potentially decreases the overall risk of intracranial bleeding in the anticoagulated population. Whilst rare, intracranial bleeding can have catastrophic consequences to individual patients, as well as putting great costs on the NHS in resource use. This indirect benefit is unlikely to be picked up by the QALY calculation	Comment noted. Comment noted. Innovation will be considered by the appraisal committee when formulating its recommendations. Comment noted. No changes to the scope needed. The consultees and commentators will have an opportunity to provide evidence on the additional factors that should be considered during the appraisal.

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	Anticoagulation UK	Assuming the progress of the HTA will align with licencing considerations of EMA As these are treatments which will be used in emergency situations, will they only be available in secondary care settings and what is the shelf life of the product to avoid wastage if high end point cost	Comment noted. The technology will be appraised within its UK marketing authorisation. Dosing and the time of administration will be considered in line with the summary of product characteristics.
	UKCPA	Use of andexanet alfa in reversal of trauma-associated bleeding.	Comment noted.
	Royal College of Pathologists and British Society for Haematologists (RCPAth and BSH)	What is the cost per person in reversing the anticoagulant effect using Andexanet alfa vs use of PCC and tranexamic acid? What are the adverse effects of Andexanet alfa so far from clinical studies including antibody formation and thrombotic events? Will the guidance consider re-introduction of anticoagulation?	Comments noted. These aspects are going to be considered by the appraisal committee during the appraisal. Consultees are encouraged to describe these additional factors in their evidence submissions.
	Thrombosis UK	What do we do with bleeding trauma patients when there is no trial data on this group?	Comment noted. Consultees are encouraged to describe these additional factors in their evidence submissions.

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

None