National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism

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

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	AntiCoagulation Europe(ACE)	We note that Apixaban does not currently hold a UK Marketing authorisation for this indication. Have the manufacturers submitted an application which is in progress? If this is a high priority area for VTE prevention, then it is appropriate for consideration (pending authorisation).	Thank you for your comments. No action required.
	Bristol-Myers Squibb and Pfizer	We consider it appropriate for this topic to be referred to NICE for appraisal.	Thank you for your comment. No action required.
	British Society for Haemostasis and Thrombosis	Yes. Currently, there is a need for more convenient oral anticoagulant which does not need frequent monitoring for the treatment and prevention of venous thromboembolism	Thank you for your comment. No action required.
	Clinical Leaders of Thrombosis	Yes	Thank you for your comment. No action required.
	Leo Pharma	The topic is appropriate to be referred to NICE.	Thank you for your comment. No action required.
	RCPath and BSH	This is an appropriate referral	Thank you for your comment. No action required.
	Royal College of Nursing	This seems appropriate	Thank you for your comment. No action required.

Section	Consultees	Comments	Action
Wording	AntiCoagulation Europe (ACE)	Yes	Thank you for your comment. No action required.
	Bristol-Myers Squibb and Pfizer	We agree.	Thank you for your comment. No action required.
	British Society for Haemostasis and Thrombosis	Yes, it does	Thank you for your comment. No action required.
	Clinical Leaders of Thrombosis	Wording is appropriate	Thank you for your comment. No action required.
	Leo Pharma	The wording is appropriate.	Thank you for your comment. No action required.
	RCPath and BSH	The draft remit anticipates that Apixaban will receive UK marketing authorisation	Thank you for your comment. No action required.
Timing Issues	Bristol-Myers Squibb and Pfizer	The final guidance in the technology appraisal (TA) of apixaban should be published as close to the launch as possible given that the VTE prevention is a Department of Health high priority area, as previously noted by NICE in response to stakeholder comments on the draft scope for dabigatran etexilate.	Thank you for your comment. No action required.
	British Society for Haemostasis and Thrombosis	This is possibly due to the fact that the marketing company has performed clinical trials and wanted to consider the possibility of use in UK	Thank you for your comment. No action required.
	Clinical Leaders of Thrombosis	We do not feel it is of any urgency as effective treatments are currently in use.	Thank you for your comment. No action required.
	Leo Pharma	The STA timing framework is appropriate.	Thank you for your comment. No action required.
	RCPath and BSH	Not urgent	Thank you for your comment. No action required.

Section	Consultees	Comments	Action
Additional comments on the draft remit	Bristol-Myers Squibb and Pfizer	None	Noted.
	British Society for Haemostasis and Thrombosis	None	Noted.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	AntiCoagulation Europe (ACE)	agree	Thank you for your comment. No action required.
	Bristol-Myers Squibb and Pfizer	None	Noted.
	British Society for Haemostasis and Thrombosis	Pulmonary embolism does not always have to develop from deep vein thrombosis It may be useful to expand on the statement, 'For people in whom a vitamin K antagonist is not considered an appropriate treatment' this is not clear	Thank you for your comments. The wording has been amended.
	Clinical Leaders of Thrombosis	Accurate and complete	Thank you for your comment. No action required.
	Leo Pharma	The information is adequate.	Thank you for your comment. No action required.
	RCPath and BSH	This is accurate. The published trials are AMPLIFY and AMPLIFY-EXT (NEJM 2013;369:799 and NEJM 2013;368)	Thank you for your comment. No action required.
	Royal College of Nursing	The draft scope appears to be robust. Routine practice in the NHS is to treat patients as outlined in the scope, however, Low-molecular-weight heparin (LMWH) and warfarin is now more	Thank you for your comment. No action required.

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		commonly being substituted with the use of Rivaroxaban as first line treatment.	
The technology/ intervention	AntiCoagulation Europe (ACE)	yes	Thank you for your comment. No action required.
	Bristol-Myers Squibb and Pfizer	We recommend the following description of the technology to be used in the NICE scope: Apixaban is a novel oral, highly selective inhibitor of factor Xa (FXa). It directly and reversibly binds to the active site of Factor Xa and exerts anticoagulant and antithrombotic effects by diminishing the conversion of prothrombin to thrombin.	Thank you for your comment. The description of the technology is intended to be brief and no changes are considered necessary.
	British Society for Haemostasis and Thrombosis	Yes	Thank you for your comment. No action required.
	Clinical Leaders of Thrombosis	Yes	Thank you for your comment. No action required.
	Leo Pharma	No comment.	Noted.
	RCPath and BSH	Yes. It should be noted that there were 2 doses of Apixaban used in the AMPLIFY-EXT trial - continuing a therapeutic dose (5mg bd) or a reduced dose of 2.5mg bd. We will need to establish whether both doses will be licensed for long term prevention of VTE.	The description has been amended to reflect the 2 doses studied in the trial.
Population	AntiCoagulation Europe (ACE)	yes	Thank you for your comment. No action required.
	Bristol-Myers Squibb and Pfizer	None	Noted.
	British Society for Haemostasis and Thrombosis	Yes	Thank you for your comment. No action required.
	Clinical Leaders	It may be useful to split the population by age group. Impaired renal function	Thank you for your comment.

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	of Thrombosis	should also be a consideration.	Attendees at the scoping workshop agreed that it was not necessary to divide the population by age or renal function.
	Leo Pharma	The appraisal should separate its analyses and guidance for patients with cancer and patients without cancer, not just because of the difference in comparators but also because of the difference in healthcare costs, causes of death, health-related utility, and baseline mortality risk.	The 'other considerations' section has been amended and now states that, if evidence allows, the analysis should consider separately people with cancer.
	RCPath and BSH	As noted in 'other considerations' Cancer related VTE should be considered as a separate population. Initial treatment (3-6 months) and long term prevention of VTE should also be considered separately in terms of economic analysis	The 'other considerations' section states that the appraisal should consider both those who require a limited period of anticoagulation (3–6 months) and those who require long-term anticoagulation (usually lifelong). It has also been amended to include people with cancer as a subgroup.
Comparators	AntiCoagulation Europe (ACE)	agree	Thank you for your comment. No action required.
	Bristol-Myers Squibb and Pfizer	We would like to propose that the comparators to be considered within the scope are amended to reflect treatments currently used in clinical practice and the evidence available. 1. We believe that fondaparinux does not represent a clinically meaningful comparator for the current appraisal. We note in TA287, section 4.2, that the NICE committee accepted that fondaparinux is rarely used and agreed that it was appropriate to consider only LWMH and a vitamin K antagonist as the	Thank you for your comments. Attendees at the scoping workshop considered that although fondaparinux is not extensively used in the UK, its

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		comparator as listed in the manufacturer's decision problem. We continue to believe this is the case with the number of patients prescribed fondaparinux was estimated to be approximately 0.04% days on therapy for patients treated for a VTE event in 2013 (source: BMS data on file). 2. Aspirin and 'no preventative therapy' should also be considered as relevant comparators for the long term prevention of recurrent VTE. Aspirin has been investigated in two recent large randomised control trials (WARFASA [Becattini et al, New England Journal of Medicine 2012 May 24;366(21):1959-67] and ASPIRE [Brighton et al New England Journal of Medicine. 2012 Nov 22;367(21):1979-87]) and has been shown to be superior to no treatment at all. It is also used as an option in clinical practice for patients who refuse anticoagulation. Furthermore, there are patients who may benefit from long term anticoagulation, but who do not currently receive this treatment due to an increased risk of bleeding associated with anticoagulation. 3. Dabigatran is currently being appraised for this indication and so, if guidance has been issued when the proposed apixaban STA begins, it should be regarded as a relevant comparator. 4. We request that reference to the cancer subgroup be moved from the 'Comparator' section to the 'Other considerations' section of the draft scope. This change would make this scope consistent with that issued for rivaroxaban (TA287), in which the consideration of an active cancer subgroup was referenced in the 'Other considerations' section. We also suggest the following wording be used in the 'Other Considerations' section: If evidence allows, subgroups can be considered by type of venous thromboembolism (pulmonary embolism or deep vein thrombosis) and presence of active cancer	use is established practice and a comparison with fondaparinux would be valuable. Attendees at the scoping workshop noted that aspirin and no preventative therapy are considered for long-term prevention of venous thromboembolism when other anticoagulants are not appropriate. If evidence allows, the analysis should consider people for whom the need for long-term anticoagulation is uncertain and aspirin or no preventative treatment might be considered. Dabigatran is not currently established practice in the NHS for this indication, so is not included in the current scope. In light of the feedback received at the scoping workshop, the 'other considerations' section has been amended to include people with cancer as a subgroup.
	British Society	Yes	Thank you for your comment.

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	for Haemostasis and Thrombosis		No action required.
	Clinical Leaders of Thrombosis	Yes	Thank you for your comment. No action required.
	Leo Pharma	The comparator list is appropriate, however with respect to the "Low molecular weight heparins" (LMWHs) please note: LMWHs have a variety of licenses for the management of DVT/PE, in particular there are differences with respect to using LMWHs in cancer patients. The differences are driven not only by the available efficacy data but also by differences in pharmacokinetic and biological activity. In the UK, many LMWHs are used off-label in cancer patients. For example, enoxaparin, the comparator in the pivotal BMS randomised controlled trial of apixaban, is not licensed for use in cancer patients in the UK. Tinzaparin is expected to gain a UK license for the treatment of cancer patients in 2014. The LMWHs have different packaging and strengths/sizes, meaning that the calculation of an 'average' treatment cost for LMWHs may require extra consultation to establish current UK usage patterns.	Thank you for your comments. In light of the feedback received at the scoping workshop, the 'other considerations' section has been amended to include people with cancer as a subgroup.
	RCPath and BSH	Appropriate comparators are listed. Occasionally patients with non cancer related VTE are treated with LMWH rather than a VKA. Although recent trials suggest that aspirin may have a role in reducing VTE recurrence, it is far less effective than oral anticoagulants and is not currently recommended in any guidelines	Low molecular weight heparin alone is included as a comparator in people for whom a vitamin K antagonist is unsuitable.
Outcomes	AntiCoagulation Europe (ACE)	agree	Thank you for your comment. No action required.
	Bristol-Myers Squibb and Pfizer	None	Noted.
	British Society for Haemostasis	Cardiac failure is not a common outcome of VTE	Heart failure has been

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	and Thrombosis	It may be useful to expand on markers of health-related quality of life	removed from the outcomes.
	Clinical Leaders of Thrombosis	Yes	Thank you for your comment. No action required.
	Leo Pharma	The outcomes are appropriate.	Thank you for your comment. No action required.
	RCPath and BSH	Yes	Thank you for your comment. No action required.
Economic analysis	Bristol-Myers Squibb and Pfizer	None	Noted.
	British Society for Haemostasis and Thrombosis	What is the time period suggested Please provide measures included in the Personal Social Services perspective	Thank you for your comments. The NICE reference case states that the time horizon should be long enough to reflect any differences in costs or outcomes between the technologies being compared, and that the costs should be considered from an NHS and Personal Social Services perspective. This may be explored in more detail at the appraisal stage.
	Clinical Leaders of Thrombosis	No comments	Noted.
	Leo Pharma	The optimal time horizon for analysing cancer patients may be different to that required to analyse the general population. The most appropriate time horizon for analysing the cost-effectiveness of longer-term treatment with apixaban could be different to the time horizon required to assess shorter-term treatment.	Thank you for your comments. The time horizon may be explored in more detail at the appraisal stage.

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		Several models may thus be required.	
	RCPath and BSH	Short term (3-6 months) treatment and long term prevention of VTE should be considered in comparison to using either a VKA or Rivaroxaban. In long term prophylaxis, the cost benefit of the 2 dose regimes may need to be considered separately as there is a small absolute difference in bleeding rates in the AMPLIFY-EXT study	Thank you for your comments. The 'other considerations' section states that the appraisal should consider both those who require a limited period of anticoagulation (3–6 months) and those who require long-term anticoagulation (usually lifelong). The doses of apixaban may be considered in more detail at the appraisal stage.
Equality and Diversity	Bristol-Myers Squibb and Pfizer	None	Noted.
	British Society for Haemostasis and Thrombosis	None	Noted.
	Clinical Leaders of Thrombosis	No comments	Noted.
	Leo Pharma	No comment.	Noted.
	RCPath and BSH	Patients who have limited mobility or require medicines to be given in dosette box may benefit from this technology in comparison to use of a VKA	Thank you for your comment. Equalities issues were discussed at the scoping workshop. No changes to the scope were considered necessary.
	Royal College of	This part of the scope could be elaborated upon and is something that the	Thank you for your comment.

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	Nursing	workshop meeting will probably tease out. This might also include patient scenarios when Apixaban is not indicated (thinking about suitability for intravenous drug users/pregnancy/breast feeding/renal dysfunction/liver dysfunction/bleeding history/thrombolysis for VTE etc).	Equalities issues were discussed at the scoping workshop. No changes to the scope were considered necessary.
Innovation	AntiCoagulation Europe (ACE)	Current treatment - Low molecular heparin is given by subcutaneous injection and can cause pain and discomfort to the individual. Warfarin requires dose adjustments and regular monitoring with blood tests to check if INR levels are in range to prevent further clotting or a bleeding event. Apixaban is an oral NOAC which does not require monitoring and is indicated for use to prevent blood clots in Knee and Hip Replacement Surgery.	Thank you for your comments. The innovative nature of apixaban may be considered by the Appraisal Committee at the appraisal stage.
	Bristol-Myers Squibb and Pfizer	Apixaban offers a step change in the management of patients with DVTs and/or PEs by offering a simpler treatment regimen, compared to LMWH/warfarin, without the need of an initial parenteral therapy with UFH or LMWH. It allows patients to be managed as an out-patients with no requirement for INR monitoring or dose adjustments, and has fewer food and drug restrictions. Patients are also more likely to adhere to treatment, due to the lower risk of bleeding and better tolerability compared to warfarin. In addition, apixaban addresses an unmet medical need as an option in patients whose risk of a bleed outweighs their risk of a recurrent DVT and/or PE and who would normally not receive preventative therapy with warfarin. A prophylactic low dose of apixaban (2.5 mg) in these patients not only reduced the risk of a further DVT and/or PE, but also had no increased risk of bleeds compared to patients who did not receive preventative therapy with an anticoagulant. Therefore, in addition to meeting the requirements for VTE treatment, apixaban is also an option for the long-term prevention of recurrent DVTs and PEs. Over time, the availability of apixaban will allow the NHS to consider changing the significant infrastructure required to treat and monitor patients being treated	Thank you for your comments. The innovative nature of apixaban may be considered by the Appraisal Committee at the appraisal stage.

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		with LMWH/warfarin for DVTs and PEs to a simpler treatment pathway. Apixaban will also prevent further DVTs and PEs which will have an impact on both the health services and the patient's quality of life.	
	British Society for Haemostasis and Thrombosis	Yes	Thank you for your comments. The innovative nature of apixaban may be considered by the Appraisal Committee at the appraisal stage.
	Clinical Leaders of Thrombosis	Eliminating the need for parenteral injections and clinic visits will be a potential benefit.	Thank you for your comments. The innovative nature of apixaban may be considered by the Appraisal Committee at the appraisal stage.
	Leo Pharma	No comment.	Noted.
	RCPath and BSH	The innovation is similar to that of Rivaroxaban in that it avoids the need to use LMWH while loading with a VKA at diagnosis and the need for INR monitoring and is favourable in terms of dietary and drug interactions. The trial data (AMPLIFY) suggests that the major bleeding risk is lower than with a VKA and the lower dose of Apixaban used for prevention of VTE recurrence (AMPLIFY-EXT) had a similar bleeding risk to placebo but appeared similarly effective to the treatment dose in terms of VTE prevention. This could result in a different approach to management of VTE with an initial 3 month treatment phase dose followed by a lower dose for longer term prevention in appropriate cases (eg. unprovoked or recurrent VTE)	Thank you for your comments. The innovative nature of apixaban may be considered by the Appraisal Committee at the appraisal stage.
Other considerations	Bristol-Myers Squibb and Pfizer	As commented under 'Comparators' above, we propose that consideration of the active cancer subgroup is specified here, alongside the existing description of the 'type of venous thromboembolism' subgroup, where evidence permits.	The 'other considerations' section has been amended to include people with cancer as a subgroup.
	British Society for Haemostasis	Any other unexpected adverse events like GI side effects not limited to bleeding, allergic reactions or anything previously not reported	Thank you for your comment. Adverse events are included

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	and Thrombosis	In patients with cancer, any impact on cancer or its treatment	in the outcomes.
	Clinical Leaders of Thrombosis	The lack of an antidote to Apixaban is a major concern.	Thank you for your comment. No changes to the scope are required.
	Leo Pharma	No comment.	Noted.
	RCPath and BSH	There are similar issues to those identified in the Rivaroxaban TA's for treatment and long term prevention of VTE. For example the issue of assessing cost effectiveness of long term prevention of VTE when published trials of extended treatment are of 6-12 months duration (thus any assumptions about therapy beyond 12 months must be extrapolated from this). There is also the issue of treating cancer related VTE where the comparator is LMWH. It would clearly be attractive to have an oral treatment option but only a small % of patients had cancer within the AMPLIFY trial and the comparator is a VKA rather than LMWH (which is more effective than a VKA in cancer patients)	Thank you for your comments. These issues may be explored by the manufacturer at the Appraisal Committee at the appraisal stage.
Questions for consultation	Bristol-Myers Squibb and Pfizer	None.	Noted.
	British Society for Haemostasis and Thrombosis	The technology is expected to be more clinically effective and cost effective in patients who were to receive the drug long-term due to the monitoring involved with warfarin Apixaban will have to be compared with another oral agent, rivaroxaban and prove superior, if not, non-inferior	Thank you for your comment. The 'other considerations' section states that the appraisal should consider both those who require a limited period of anticoagulation (3–6 months) and those who require long-term anticoagulation (usually lifelong).
	Leo Pharma	No comment.	Noted.
	RCPath and BSH	It may be worth asking BMS/Pfizer if they have any data on quality of life experience for patients on Apixaban vs traditional VKA treatment (although	Thank you for your comments. No changes to the scope are

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		clearly not possible from blinded trials). Also any data on relative efficacy and adverse events with apixaban in comparison to a VKA according to time in therapeutic range. Data on subanalysis of vulnerable patients (elderly, underweight, renal disease) should be requested if available. Although laboratory monitoring of Apixaban is not routinely recommended within current licensed indications, any data on drug levels within the treated trial population and any relationship with efficacy and bleeding would be relevant.	required.
Additional comments on the draft scope.	Bristol-Myers Squibb and Pfizer	None.	Noted.
	British Society for Haemostasis and Thrombosis	None	Noted.

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

Department of Health
Healthcare Improvement Scotland
Lifeblood: The Thrombosis Charity
Medicines and Healthcare products Regulatory Agency