National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Apixaban for the prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation

Response to consultee and commentator comments on the draft scope

Comment 1: the draft scope

Section	Consultees	Comments	Action
Background information	Arrhythmia Alliance, The Heart Rhythm Charity	It is worth mentioning that the most severe or debilitating strokes are caused by AF	Comment noted. The background section is only intended to be a very brief overview of the disease area.
	Atrial Fibrillation Association	Yes, we believe this to be accurate and appropriate	Comment noted.
	Boehringer Ingelheim Ltd	The NICE guidance for dabigatran etexilate in this indication (TA249) should be noted in the last paragraph of this section.	Comment noted. Reference to TA249 has been added to the background information.
	Bristol-Myers Squibb and Pfizer Ltd.	None.	Comment noted.
	Clinical Leaders of Thrombosis (CLOT)	Complete and accurate	Comment noted.
	CSAS	This is appropriate	Comment noted.
	Royal College of Pathologists and BSH	Yes	Comment noted.

Section	Consultees	Comments	Action
The technology/ intervention	Arrhythmia Alliance, The Heart Rhythm Charity	Yes it seems to be	Comment noted.
	Atrial Fibrillation Association	Yes, we believe it is	Comment noted.
	Bristol-Myers Squibb and Pfizer Ltd.	None.	Comment noted.
	Clinical Leaders of Thrombosis (CLOT)	Yes	Comment noted.
	CSAS	This is accurate	Comment noted.
	Royal College of Pathologists and BSH	Yes	Comment noted.
Population	Anticoagulation Europe (ACE)	Appropriate	Comment noted.
	Arrhythmia Alliance, The Heart Rhythm Charity	Yes it seems to be	Comment noted.
	Atrial Fibrillation Association	Appropriate	Comment noted.

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	Boehringer Ingelheim Ltd	The population should more closely reflect the likely licensed indication for apixaban. Currently it states: "*Adults with non-valvular atrial fibrillation who are at risk of stroke or systemic embolism*." This is not sufficiently specific. All atrial fibrillation patients are "at risk" of stroke and systemic embolism, however anticoagulation is aimed at those at elevated risk, howsoever defined. In general, eligibility for anticoagulation requires the presence of one or more specified risk factors; often those used as inclusion criteria into the phase-III clinical trial program. The likely required risk factors in the proposed licensed indication for apixaban should be incorporated into this definition.	This was discussed in the scoping workshop. Workshop attendees expressed the preference not to define the level of risk of stroke or systemic embolism in the population. The appraisal will consider apixaban within its licensed indications.
	Bristol-Myers Squibb and Pfizer Ltd.	The population definition (patients with NVAF at risk of stroke or systemic embolism) is appropriate and relevant to this technology appraisal. Warfarin-suitable and warfarin-unsuitable patient populations are clearly distinct, and it is important to consider direct evidence of efficacy in each of these populations.	Comment noted. The comparator section of the scope states that warfarin is a comparator in people for whom warfarin is suitable.
	Clinical Leaders of Thrombosis (CLOT)	Yes	Comment noted.
	CSAS	The population defined in the draft scope is similar to that defined in the two phase III clinical trials of the drug for this indication.	Comment noted.
	Royal College of Pathologists and BSH	Yes	Comment noted.
Comparators	Anticoagulation Europe (ACE)	Dabigatran Etexilate– NICE Guidelines now in place	Comment noted. The scope has been updated following the publication of NICE Technology Appraisal 249 (dabigatran etexilate).

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	Arrhythmia Alliance, The Heart Rhythm Charity	Yes, but as stated in the related NICE recommendations section, not all comparators are currently available with NICE Guidance	Comment noted. The scope has been updated following the publication of NICE Technology Appraisals 249 (dabigatran etexilate) and 256 (rivaroxaban).
	Atrial Fibrillation Association	Yes, however neither dabigatran nor rivaroxaban currently have NICE guidance	Comment noted. The scope has been updated following the publication of NICE Technology Appraisals 249 (dabigatran etexilate) and 256 (rivaroxaban).

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	Boehringer Ingelheim Ltd	1) It is inappropriate to stratify the comparators by risk of stroke and suitability for warfarin. Currently the draft scope states: "*In people who are at moderate to high risk of stroke or systemic embolism and for whom warfarin is suitable:* • *Warfarin* • *dabigatran etexilate (subject to NICE guidance)* • *rivaroxaban (subject to NICE guidance)* *In people who are at low to moderate risk of stroke or systemic embolism for whom warfarin would not be considered and in people at moderate to high risk for whom warfarin is unsuitable:* • *aspirin* • *dabigatran etexilate (subject to NICE guidance)* • *rivaroxaban (subject to NICE guidance).*" "Suitability" for warfarin (as intended here) is not dependent on the patient's baseline stroke risk If a patient is eligible but deemed clinically "unsuitable" for warfarin (e.g. warfarin intolerant), then this is independent of their stroke risk. Accordingly, the comparators should be defined as a single set across the full licensed indication. It is unnecessary to have one set for "moderate to high risk" and another for "low to moderate risk", especially as the groups are not mutually exclusive (i.e. moderate stroke risk is contained in both groups). Further, care must be taken with the definition of "suitability" for warfarin, as this is often subjective. The AVERROES trial comparing apixaban with aspirin in patients "unsuitable" for warfarin permitted no less than twenty separate reasons for unsuitability of VKA (warfarin) treatment. The most common reason (38% of randomised patients) for unsuitability was "patient's refusal to take VKA". Given the clear superiority of warfarin compared to aspirin in this indication, the clinical merit of this reason for unsuitability is open to debate. In our view, a patient can only be considered truly unsuitable for warfarin if they are absolutely contraindicated due to established clinical criteria.	TA 249 recommends dabigatran etexilate and TA 256 recommends rivaroxaban as alternative anticoagulants to warfarin. This guidance was published after the draft scope for this appraisal was sent out for consultation and after NICE guidelines on the management of atrial fibrillation were published. Since the publication of TA 249 and TA 256 people who are unsuitable for warfarin may receive dabigatran etexilate or rivaroxaban. Prior to this recommendation the only alternative for people who were unsuitable for warfarin was aspirin. The consultees comments on the appropriateness of aspirin as a comparator were noted. It was determined that the population who would receive apixaban are likely to be clinically indicated for anticoagulation rather than antiplatelet therapy (having one or more risk factors for stroke). As there is now more than one alternative anticoagulant for people

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		Finally, the trend towards the marginalisation of the use of aspirin in this indication in international clinical guidelines and consensus should be noted. That is, aspirin, irrespective of suitability for warfarin could only ever be considered appropriate in a small cohort of patients, if any. See, for example, Olesen et al. (*Thromb Haemost* 2011; 106: 739-749) which concluded "*Acetylsalicylic acid should not be used for thromboprophylaxis in any patient with atrial fibrillation*." Indeed the relevance of the aspirin comparison in the published STA of dabigatran etexilate (TA249) and in the ongoing STA for rivaroxaban for this indication were/are extremely limited. Both appraisals have concentrated on demonstration of cost-effectiveness versus anticoagulation only, with very little attention paid by the Appraisal Committee to the aspirin comparison in either case. Dabigatran etexilate has been shown elsewhere to be cost-effective versus aspirin in the UK setting (Kansal *et al*. 2012). In summary: • Warfarin is an appropriate comparator irrespective of stroke risk within the licensed indication • Dabigatran etexilate is an appropriate comparator irrespective of stroke risk within the licensed indication • Aspirin could only be an appropriate comparator in the limited number of patients where it can be clinically justified (e.g. by NICE Clinical Guideline 36) AND where patients are truly clinically "unsuitable" for warfarin or any other anticoagulant. Therefore this comparator could be justifiably excluded from the scope altogether. 2) Dabigatran etexilate has now been recommended by NICE (TA249) and is therefore an appropriate comparator, i.e. the statement "(*subject to NICE guidance)"* in the draft scope can be deleted for dabigatran etexilate.	unsuitable for warfarin it was decided that aspirin would rarely be used in people requiring anticoagulation and should not be included as a comparator. The scope has been amended so that the comparators are: warfarin (for people who are suitable), dabigatran etexilate and rivaroxaban. Stratification of comparators by stroke risk has been removed from the scope. The consultee's comment that there are a wide range of reasons why a person may be unsuitable for warfarin was noted. There is uncertainty within clinical practice as to how to define unsuitability for warfarin. Current NICE guidelines suggest that the decision to treat with warfarin should be made on an individual basis by assessing the risks and benefits of treatment for each person. It was decided that owing to this uncertainty a definition of warfarin suitability should not be made in the scope. The scope has been updated

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			following the publication of NICE Technology Appraisal 249 (dabigatran etexilate) and Technology Appraisal 256 (rivaroxaban).
	Bristol-Myers Squibb and Pfizer Ltd.	The comparators are appropriate and reflect UK clinical practice; they are also consistent with the existing NICE clinical guideline for the management of atrial fibrillation (CG36).	Comment noted. Aspirin is no longer listed as a comparator in the scope as there are alternative anticoagulant treatments available for people who require anticoagulation but who are unsuitable for warfarin. Dabigatran etexilate was approved for use in the NHS in Technology Appraisal 249 and rivaroxaban in Technology Appraisal 256.
	Clinical Leaders of Thrombosis (CLOT)	Comparators standard at the moment but aspirin is now contra-indicated in most guidance.	Comment noted. Aspirin is no longer listed as a comparator in the scope as there are alternative anticoagulant treatments available for people who require anticoagulation but who are unsuitable for warfarin.

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	CSAS	Warfarin and aspirin are the two main comparators defined in two phase III clinical trials of the drug for this indication. Dabigatran etexilate and rivaroxaban are both being considered under single technology assessments by NICE so their use is subject to NICE guidance. NICE CG36 states the appropriate use of warfarin and aspirin in people with atrial fibrillation depends on the stroke risk of the patient and contraindications to warfarin. These issues are captured in the comparators listed.	Comment noted. The scope has been updated following the publication of NICE Technology Appraisal 249 (dabigatran etexilate) and Technology Appraisal 256 (rivaroxaban). Aspirin is no longer listed as a comparator in the scope as there are alternative anticoagulant treatments available for people who require anticoagulation but who are unsuitable for warfarin.
	Royal College of Pathologists and BSH	Yes, nicoumalone and phenindione are also used but not as widely as warfarin and are sufficiently similar to warfarin not to need to be considered separately. There are other anti platelet agents such as dipyridamole and clopidogrel but as far as I'm aware they are not as effective as warfarin in Af.	Comment noted. Comments received during consultation indicated that warfarin is the most common vitamin K antagonist used in UK clinical practice.
Outcomes	Anticoagulation Europe (ACE)	Appropriate	Comment noted.
	Arrhythmia Alliance, The Heart Rhythm Charity	Yes, it seems to	Comment noted.
	Atrial Fibrillation Association	Yes	Comment noted.

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	Bristol-Myers Squibb and Pfizer Ltd.	None.	Comment noted.
	Clinical Leaders of Thrombosis (CLOT)	Yes	Comment noted.
	CSAS	The primary outcomes from the two clinical trials identified were ischemic stroke, haemorrhagic stroke or systemic embolism. Secondary outcomes included all of the above plus myocardial infarction, vascular death and death from any cause. Adverse events (including major bleeding) and impact on quality of life are important patient orientated outcomes.	Comment noted. These outcomes are included in the scope.
	Royal College of Pathologists and BSH	Yes	Comment noted.
Economic analysis	Anticoagulation Europe (ACE)	Does 'Personal Social Services perspective' extend to the associated financial burden to patients and carers attending primary and secondary care settings for regular blood tests to monitor warfarin – a comparator?	The NICE 'Guide to the methods to technology appraisals' states that the perspective on costs should be that of the NHS and Personal Social Services. The objective is to offer guidance that represents an efficient use of available NHS and PSS resources. For these reasons financial burden to patients and carers is generally not included in NICE appraisals.

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	Arrhythmia Alliance, The Heart Rhythm Charity	This seems appropriate	Comment noted.
	Atrial Fibrillation Association	Yes	Comment noted.
	Bristol-Myers Squibb and Pfizer Ltd.	None.	Comment noted.
	CSAS	The cost of apixaban is currently unknown. Both trials used a dose of 5mg twice daily for the majority of participants. The two clinical trials followed-up patients for an average of 1.1 and 1.8 years.	Comment noted.
	Royal College of Pathologists and BSH	Time horizon satisfactory but it is important to appreciate that the cost of controlling warfarin varies considerably according to how the local arrangements operate – the cost estimates in the NICE documents on Dabigatran failed to mention that with decentralised phlebotomy, centralised testing, computerised dosing and telemedicine the cost can be under £100 per year	Comment noted. No changes required to the scope.
Equality and Diversity	Anticoagulation Europe (ACE)	Ensure *that all* existing and newly diagnosed AF patients are advised of the new oral anticoagulant treatments available and with the support and guidance of their Healthcare Professionals be able to make an informed decision as to which therapy will provide the maximum protection to prevent a bloodclot/stroke.	Comment noted. NICE has an obligation to ensure that its guidance does not disadvantage people with protected characteristics as defined in the current UK equality and diversity legislation. Dissemination of information falls outside the equality legislation.

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	Arrhythmia Alliance, The Heart Rhythm Charity	We have no suggestions for this at the current stage	Comment noted.
	Atrial Fibrillation Association	We are not aware of any groups who may specifically be unlawfully discriminated against if this technology is appraised for all 'adults with non-valvular AF who are at risk of stroke or systemic embolism'	Comment noted.
	Bristol-Myers Squibb and Pfizer Ltd.	None.	Comment noted.
	CSAS	No issues identified	Comment noted.
	Royal College of Pathologists and BSH	These considerations do not apply here	Comment noted.
Other considerations	Anticoagulation Europe (ACE)	This treatment will be considered for newly diagnosed AF patients and those who may not be able to maintain TTR. Patients who are currently on warfarin and stay within TTR targets should not be excluded from converting to this treatment which will reduce the impact of regular monitoring, dietary restrictions and timely and costly trips for INR testing. Alternative a/c treatments may increase health and general well- being and in particular, reduce pain, discomfort and inconvenience of regular blood tests. Warfarin needs to be dose adjusted – Apixaban is one fixed daily dose.	Comment noted. No changes required to the scope.
	Arrhythmia Alliance, The Heart Rhythm Charity	We have no suggestions for this at the current stage	Comment noted.
	Bristol-Myers Squibb and Pfizer Ltd.	None.	Comment noted.

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	Clinical Leaders of Thrombosis (CLOT)	We have some concerns that a good TTR may be used to exclude patients from receiving Apixaban.	Comment noted.
	CSAS	NICE Clinical Guidance 36 stroke risk stratification algorithm defines stroke/thromboembolic risk in people with atrial fibrillation as low, moderate, and high risk. Alternative stroke risk algorithms are in use in clinical practice (e.g. CHADS2, CHA2DS2-VASc) and the relationship between the three schemes needs consideration. It is important that any additional benefits or harms in the sub-group of patients already well controlled on warfarin are described.	Comment noted. Scoping workshop attendees acknowledged that NICE Clinical Guideline 36 is currently under review and risk algorithms may therefore be subject to change. In view of this, attendees expressed the opinion that the definition of risk should not be defined in scope.
	Royal College of Pathologists and BSH	The comparison with warfarin needs to take into account the actual effectiveness of warfarin and the real time in range results currently being achieved – as at least one of the computer companies runs a benchmarking service this up to date information can easily be obtained	Comment noted.

Section	Consultees	Comments	Action
Questions for consultation	Anticoagulation Europe (ACE)	Yes – the treatment will provide protection to existing AF sufferers who are not currently receiving any form of A/C treatment, those who are unable to take warfarin and newly diagnosed patients who will benefit from a one daily dosage of medication that does not require the demands of monitoring, dietary adjustments and impact on lifestyle. Warfarin is a demanding treatment option. Patients who are prescribed this drug often feel that they will have to make significant adjustments to lifestyle and this can have a detrimental effect on general health and well-being. Warfarin can restrict travel for work and pleasure. The need for regular blood tests needs to be factored into day to day activities. With an older population, AF sufferers will be working longer, and therefore, employees may be disadvantaged if they need to take time off for frequent blood tests. Patients who are immobile will need carer/family support to get to appointments. The cost of travel and parking can be considerable.	Comments noted.
	Arrhythmia Alliance, The Heart Rhythm Charity	Yes, we believe that Apixaban offers a significant innovation to AF patients currently being managed with warfarin and aspirin. The quality of life for those who would be suitable for this therapy would be vastly improved. Often feedback that we receive from patients on warfarin is that they find it difficult to live and manage their treatment on warfarin, notably staying in their therapeutic range, coping with day to day commitments such as work and family, and feeling the impact upon their quality of life. Historically, warfarin has been the leading anticoagulation medication. Apixaban will offer a valuable alternative treatment option which could benefit thousands of patients and help improve their quality of life. Arrhythmia Alliance relies upon the information received through its patient helpline and surveys conducted with its patient, carer and clinical members.	Comments noted.

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	Atrial Fibrillation Association	i) Yes, we believe it is innovative ii) Yes, we do believe the technology could result in potential, significant and substantial health-related benefits which may not be included in the QALY. These include: - Benefit to AF patients with mobility issues - Benefit to individuals with AF in care home settings and / or reliant on carers to manage their medication - Beneficial to those currently not prescribed appropriate OAC which optimise their reduction of risk of stroke - Benefit AF patients who are prescribed a large number of therapies which may interact with existing options making TTL challenging - Those whose work / family life is significantly restricted due to current monitoring requirements of existing therapy iii) Data in reports and papers: AF Report and Atrial Fibrillation, Anticoagulation, - Anecdotal evidence gathered via research based interviews, AFA surveys and case accounts	Comments noted.
	Boehringer Ingelheim Ltd	Please see comments in comparators sections above.	Comments noted.
	Clinical Leaders of Thrombosis (CLOT)	It is likely that Apixaban would remove some of the workload of testing and monitoring associated with warfarin use.	Comment noted.
	Bristol-Myers Squibb and Pfizer Ltd.	None.	Comment noted.
	CSAS	This technology may have a significant impact on the management of stroke prevention in people with atrial fibrillation.	Comment noted.

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	Royal College of Pathologists and BSH	Innovation: Yes – it is an Oral Xa inhibitor – one of only two (the other is Rivoroxaban) coming to the market at present. From the currently available information it appears to be more effective than warfarin for those patients who do not have the best level of warfarin control. Therefore it will be an advantage for those patients. Apixaban versus warfarin in patients with atrial fibrillation. ARISTOTLE New England Journal of Medicine. 365(11):981-92, 2011 Sep 15. Apixaban in patients with atrial fibrillation. AVERROES Steering Committee and Investigators. New England Journal of Medicine. 364(9):806-17, 2011 Mar 3. Apixaban for stroke prevention in atrial fibrillation: a review of the clinical trial evidence. [Review] Yates SW. Hospital practice (1995) Hospital practice. 39(4):7-16, 2011 Oct. Rationale and design of AVERROES: apixaban versus acetylsalicylic acid to prevent stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment. Eikelboom JW. O'Donnell M. Yusuf S. Diaz R. Flaker G. Hart R. Hohnloser S. Joyner C. Lawrence J. Pais P. Pogue J. Synhorst D. Connolly SJ. Safety and efficacy of the oral direct factor xa inhibitor apixaban in Japanese patients with non-valvular atrial fibrillation. -The ARISTOTLE-J study-.Circulation Journal. 75(8):1852-9, 2011 Jul 25Circulation Journal. 75(8):1852-9, 2011 Jul 25	Comments noted. The comparator section of the scope now states that warfarin is a comparator in people for whom warfarin is suitable. During the scoping workshop clinical specialists confirmed that aspirin was the antiplatelet agent used in the circumstances of this scope and agreed that aspirin should be the antiplatelet agent. However, aspirin is no longer listed as a comparator in the scope as there are alternative anticoagulant treatments available for people who require anticoagulation but who are unsuitable for warfarin.

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		Questions for consultation Is it appropriate to consider the groups for whom warfarin would and would not be suitable separately? Has the distinction been made appropriately (see under 'Comparators' in the table above)? - Yes Have the most appropriate comparators been included for each group?" – yes, but you may wish to review whether maximal antiplatelet therapy should be considered as well – some cardiologists advocate them	
Additional comments on the draft scope.	Arrhythmia Alliance, The Heart Rhythm Charity	None	Comment noted.
	Bristol-Myers Squibb and Pfizer Ltd.	None.	Comment noted.
	Clinical Leaders of Thrombosis (CLOT)	None	Comment noted.
	CSAS	None	Comment noted.

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

Bayer Plc
Department of Health
Royal College of Physicians
Royal College of Nursing