National Institute for Health and Clinical Excellence

Single Health Technology Appraisal (STA)

Apixaban for the prevention of venous thromboembolism in people undergoing elective knee and hip replacement surgery

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	Bristol-Myers Squibb and Pfizer	It is appropriate to refer this topic to NICE for appraisal	Comment noted. No action required
	Commissioning Support Unit (CSU): appraisals	This is an appropriate appraisal topic given application by the manufacturers for marketing authorisation and pending NICE guidance on preventing VTE in patients admitted to hospital	Comment noted. No action required
	GlaxoSmithKline	GlaxoSmithkline believes this is an appropriate topic for referral to NICE.	Comment noted. No action required

Section	Consultees	Comments	Action
	NHS Warwickshire (Warwickshire PCT)	The topic seems appropriate given that elective hip and knee replacement surgery are now common orthopaedic surgical procedures, and it is useful to assess new treatment options to prevent VTE following this type of surgery. It is hoped that a NICE appraisal will offer an independent review of the comparative clinical- and cost-effectiveness of apixaban relative to other anticoagulant agents in current use in elective orthopaedic surgery. We note that single technology appraisals have already been undertaken on two other oral anticoagulants - dabigatran etexilate (TA 157) and rivaroxaban (TA 170) - for the same indication (prevention of VTE after hip or knee replacement surgery in adults). As these agents have become available at different times, it was presumably not possible to approach their assessment through a 'multiple technology appraisal', but this would be preferable when these technology appraisals reach the time for review in the future. This would have the advantage of bringing recommendations on similar agents for the same indications into a single piece of guidance. (However, this may be addressed to some extent by the anticipated revised NICE 'Clinical Guideline' on reducing the risk of VTE in patients admitted to hospital.)	Comment noted. The appraisal will compare apixaban with current standard care. The appraisal has been referred as an STA to allow timely guidance to the NHS close to marketing authorisation.
	Royal College of Nursing	yes	Comment noted. No action required
	RCPath, BSH	NICE has recently approved two new antithrombotic agents for the same indication so this is an appropriate referral, although not yet licensed. Venous thrombosis continues to be a major focus for hospitals but appropriate use in orthopaedic surgery remains contentious.	Comment noted. No action required
Wording	Bristol-Myers Squibb and Pfizer	The wording is suitable	Comment noted. No action required
	CSU: appraisals	Wording is appropriate	Comment noted. No action required
	GlaxoSmithKline	No comment.	Comment noted. No action required

Section	Consultees	Comments	Action
	NHS Warwickshire	The wording seems appropriate.	Comment noted. No action required
	RCPath, BSH	Yes	Comment noted. No action required
Timing Issues	Bristol-Myers Squibb and Pfizer	The appraisal timelines should be aligned with the revised regulatory timelines [redacted]	Comment noted. Following referral the appraisal will be scheduled into the work programme to enable timely guidance to the NHS close to marketing authorisation.
	CSU: appraisals	Marketing authorisation submission expected [redacted]; authorisation due [redacted]. NICE guideline "Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital" is currently out to consultation. It may need revision based on the recommendations from this STA.	Comment noted. Following referral the appraisal will be scheduled into the work programme to enable timely guidance to the NHS close to marketing authorisation.
	GlaxoSmithKline	No comment.	Comment noted. No action required

Section	Consultees	Comments	Action
	NHS Warwickshire	We understand that apixaban does not yet have a UK marketing authorisation for the prevention of VTE events in people undergoing elective hip or knee surgery. With any TA guidance, we would suggest that it is most helpful if it is issued as close as possible to the granting of a marketing authorisation. To some extent, the degree of urgency of the proposed appraisal to the NHS depends on the emerging clinical effectiveness data and likely cost of apixaban. (If it is demonstrated to be non-inferior to other alternative thromboprophylactic agents, then the urgency is perhaps less than if trials suggest superiority. If RCT data showed clinical effectiveness of apixaban to be superior to alternative agents currently in use, then a cost-effectiveness appraisal from NICE might be more urgently required - i.e. to help in answering the question “is the additional cost (if any) justified by the additional benefit?”)	Comment noted. Following referral the appraisal will be scheduled into the work programme to enable timely guidance to the NHS close to marketing authorisation. The appraisal will take into account all available clinical effectiveness data.
	RCPath, BSH	Urgency is low in that other agents are available and published data on this agent is limited.	Comment noted. No action required
Additional comments on the draft remit		None received	

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Bristol-Myers Squibb and Pfizer	Higher rates of VTE have been reported in the literature where no anti-coagulant prophylaxis is used. This includes the 8th ACCP Guidelines for the prevention of VTE (Geerts et al, Chest 2008) which found that the prevelance of DVT following hip replacement surgery was 42 - 57 %, and 41 - 85 % following knee replacement surgery. The prevelance of PE was found to be between 0.9 - 28 % following hip replacement and 1.5 - 10 % following knee replacement surgery (Geerts et al, Chest 2008).	The text in the scope has been amended accordingly.
	CSU: appraisals	Background information is accurate and complete	Comment noted. No action required
	GlaxoSmithKline	For completeness, GlaxoSmithKline suggest the following is included in the first paragraph of this section: DVT can also cause long-term morbidity due to the development of post-thrombotic syndrome (chronic leg pain, swelling, dermatitis and ulcers resulting from the destruction of leg vein valves).	The text in the scope has been amended accordingly.
	NHS Warwickshire	No comments on accuracy. For completeness, it would be useful to have information about current usage (and trends in usage) and costs of existing alternatives for pharmacological prophylaxis of VTE after joint replacement surgery.	This level of detail is not required in the scope, but will be considered during the appraisal. No changes made to the scope.
	Royal College of Nursing	ok	Comment noted. No action required
	RCPath, BSH	OK	Comment noted. No action required
The technology/	Bristol-Myers Squibb and Pfizer	The description of the technology is accurate	Comment noted. No action required

Section	Consultees	Comments	Action
intervention	CSU: appraisals	Accurate description of technologies	Comment noted. No action required
	GlaxoSmithKline	No comment.	Comment noted. No action required
	NHS Warwickshire	The description appears to be accurate.	Comment noted. No action required
	Royal College of Nursing	Appears to be	Comment noted. No action required
	RCPath, BSH	yes	Comment noted. No action required
Population	Bristol-Myers Squibb and Pfizer	The population is defined appropriately	Comment noted. No action required
	CSU: appraisals	Could consider stratification by surgical patient risk profile (DVT risk, bleeding risk after hip or knee surgery may be different) or background anticoagulation or antiplatelet treatment	It was agreed at the scoping workshop that knees and hips will be analysed as different subgroups in the same appraisal.
	GlaxoSmithKline	GlaxoSmithKline suggest that the scope should clarify whether the population is limited to patients > 18 years old.	It was agreed that age will not be specified in the scope. NICE will appraise apixaban within its marketing authorisation.

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	NHS Warwickshire	The population appears to be defined adequately. (It is assumed that this will be equivalent to the population group and indications for which the drug will be licensed.) We are not aware of any evidence that would suggest that any particular population subgroups should be considered separately. However, if data is available to do so, it may be appropriate to consider people with known additional risk factors for VTE as separate subgroups. Our understanding is that clinical trials have considered the two indications (hip and knee) separately, so it would be appropriate to look at the evidence for these separately within the single appraisal.	Comments noted. NICE will appraise apixaban within its marketing authorisation. It was agreed at the scoping workshop that knees and hips will be analysed as different subgroups in the same appraisal.
	Royal College of Nursing	yes	Comment noted. No action required
	RCPath, BSH	this is well defined	Comment noted. No action required
Comparators	Bristol-Myers Squibb and Pfizer	These are standard treatments currently used in the NHS despite the low uptake of fondaparinux, rivaroxaban & dabigatran in the UK	It was agreed at the scoping workshop that fondaparinux, rivaroxaban and dabigatran are appropriate comparators.
	CSU: appraisals	These are appropriate	Comment noted. No action required
	GlaxoSmithKline	Other potential oral interventions for this patient group include aspirin and warfarin and hence consideration should be given to these as potential comparators.	It was agreed at the scoping workshop that aspirin and warfarin are not appropriate comparators

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	NHS Warwickshire	These comparators are appropriate, and include those that we understand are in current use in the NHS locally. The comparators listed include the pharmacological prophylactic agents identified in the current NICE Clinical Guideline 46 (April 2007) on 'Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients undergoing surgery' (i.e. Low molecular weight heparin and Fondaparinux); and also include the two new oral anticoagulant agents, dabigatran etexilate and rivaroxaban, that have recently been appraised by NICE in the Technology Appraisals 157 and 170 respectively. Guidance to aid choice between the various new oral anticoagulants that are available would appear to be particularly helpful. i.e. comparing apixaban to rivaroxaban and dabigatran etexilate.	It was agreed at the scoping workshop that these were appropriate comparators.
	Royal College of Nursing	Unfractionated heparin? (although it not used much it is still quoted in some text) Danaparoid (Although it is considered a LMWH, it works in a slightly different way)	It was agreed at the scoping workshop that danaparoid should not be listed as a separate comparator. Unfractionated heparin has not been included as a comparator for people with renal failure because it is not anticipated that apixaban will be approved for use in this population. NICE will appraise apixaban within its marketing authorisation.
	RCPath, BSH	yes	Comment noted. No action required
Outcomes	Bristol-Myers Squibb and Pfizer	These outcome measures will capture the most important health related benefits (and harms) of the technology	Comment noted. No action required

Section	Consultees	Comments	Action
	CSU: appraisals	Outcomes are appropriate, some studies may have composite end points, especially for bleeding and so the scope should specify those bleeding outcomes to be considered	This was discussed at the scoping workshop. No specific bleeding outcomes will be included in the scope. However, specific bleeding outcomes could be considered in the appraisal.
	GlaxoSmithKline	No comment.	Comment noted. No action required
	NHS Warwickshire	The outcome measures appear to be appropriate. (We assume that cause of mortality will be considered within overall mortality.)	Comment noted. No action required. Cause of mortality will be included in overall mortality.
	Royal College of Nursing	yes, we think so	Comment noted. No action required

Section	Consultees	Comments	Action
	RCPath, BSH	As before NICE will need to decide whether it is considering symptomatic thrombosis or all detected thromboses.	The text in the scope has been amended to include asymptomatic and symptomatic VTE
		Length of hospital stay should be considered alongside readmission rates.	Readmission rates have not been included as a specific outcome in the scope. However, these may be captured through length of hospital stay and can be included in the appraisal where they are relevant.
		Post thrombotic syndrome may be too long-term an event for evaluation.	It was agreed at the scoping workshop that post thrombotic syndrome would be important for the economic analysis and should be considered as an outcome.
Economic analysis	Bristol-Myers Squibb and Pfizer	No further comments	Comment noted
	CSU: appraisals	Scope does not provide a time horizon. Maximum follow up in a Phase III study of this drug after hip surgery was 35 days (5 weeks) of treatment. The economic analysis should consider issues of timing for benefits and bleeding and also model different doses and durations of therapy in the sensitivity analysis	The time horizon is specified in the scope as being the time over which differences in costs and benefits can be expected to accrue. No changes made to the scope.
	GlaxoSmithKline	No comment.	Comment noted. No action required

Section	Consultees	Comments	Action
	NHS Warwickshire	No comments.	Comment noted. No action required
	RCPath, BSH	OK	Comment noted. No action required
Equality and Diversity	Bristol-Myers Squibb and Pfizer	No further comments	Comment noted. No action required
	CSU: appraisals	None	Comment noted. No action required
	GlaxoSmithKline	No comment.	Comment noted. No action required
	NHS Warwickshire	We are not aware of any equality issues relating to this technology.	Comment noted. No action required
	Royal College of Nursing	not aware of any at this stage	Comment noted. No action required
	RCPath, BSH	none	Comment noted. No action required
Other considerations	Bristol-Myers Squibb and Pfizer	No further comments	Comment noted. No action required
	CSU: appraisals	None	Comment noted. No action required
	GlaxoSmithKline	No comment.	Comment noted. No action required
	NHS Warwickshire	No comments	Comment noted. No action required
	Royal College of Nursing	none	Comment noted. No action required

Section	Consultees	Comments	Action
	RCPath, BSH	route of administration and adjunctive tests or monitoring, effect of renal or hepatic impairment.	It was agreed at the scoping workshop that knees and hips will be analysed as different subgroups in the same appraisal.
Questions for consultation	Bristol-Myers Squibb and Pfizer	There are differences between knee surgery and hip surgery in terms of costs, duration of therapy etc. Therefore, it would be relevant to analyse these separately. The appraisal via the STA process is appropriate	It was agreed at the scoping workshop that knees and hips will be analysed as different subgroups in the same appraisal.
	CSU: appraisals	n/a	Comment noted. No action required
	GlaxoSmithKline	No comment.	Comment noted. No action required
	NHS Warwickshire	No comments	Comment noted. No action required
	Royal College of Nursing	none at this stage	Comment noted. No action required
Additional comments on the draft scope.	NHS Warwickshire	No	Comment noted. No action required
	Royal College of Nursing	The outlined PICO framework for evaluating the clinical efficacy and cost effectiveness of Apixaban in the prevention of VTE in knee and hip replacement surgery, seems appropriate to this Single Technology Appraisal.	Comment noted. No action required

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

Bayer Schering Pharma
Boehringer Ingelheim
The Research Institute for the Care of Older People (RICE)
NPHS Wales
NHS Quality Improvement Scotland