National Institute for Health and Clinical Excellence
Health Technology Appraisal

Rivaroxaban for the prevention of venous thromboembolism after elective orthopaedic surgery of the lower limbs

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Bayer	Each year there are over 25,000 deaths due to venous thromboembolism (VTE) in England (1).Current guidelines recommend that in addition to mechanical prophylaxis, patients at increased risk of VTE and those undergoing orthopaedic surgery should be offered low molecular weight heparin (LMWH) or fondaparinux, and patients undergoing hip fracture surgery or hip replacement with one or more risk factors for VTE should have their LMWH or fondaparinux therapy continued for 4 weeks after surgery (2). Rivaroxaban is an oral, once-daily direct Factor Xa inhibitor. Phase III trials have shown that rivaroxaban significantly reduces the risk of VTE in patients undergoing total knee replacement surgery and total hip replacement surgery compared with enoxaparin (3-5). As an effective and convenient, once-daily oral treatment rivaroxaban offers a convenient treatment option that would aid the implementation of the current NICE guidelines as it is anticipated that the oral route of administration for rivaroxaban will be more acceptable than currently available subcutaneous injections of LMWH or fondaparinux. (1) House of Commons Select Committee 2005. The prevention of VTE in hospitalised patients. London (2) NICE Clinical Guideline No. 46 (3) Blood 110 (11); November 16th 2007, abstract #6 (4) Blood 110 (11); November 16th 2007, abstract #307 (5) Blood 110 (11); November 16th 2007, abstract #308	Comments noted
	GSK	GSK agree that it would be appropriate for this topic to be referred to NICE	Comments noted
	Anticoagulation Europe	Yes – it is in the interests of the general public to have new options for treatment to prevent DVTs and post lower limb surgery.	Comments noted
	RCN	It is very appropriate to refer this topic to NICE for appraisal.	Comments noted

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	sanofi-aventis	Sanofi-aventis believe that it is appropriate that NICE consider rivaroxaban; however we would like to query whether an STA is the appropriate method of review. Clinical Guideline 46 was published in 2007 and provides recent guidelines for healthcare professionals to reduce VTE for patients undergoing surgery, including orthopaedic surgery. Publication of separate STA guidance for rivaroxaban and for dabigatran will potentially confuse healthcare professionals. Given the imminent launch of these two oral compounds in the UK, sanofi-aventis consider that an MTA might be more appropriate given that both compounds will be licensed for exactly the same indication. This was not a consideration during the dabigatran scoping as final results for rivaroxaban were not available at that time. An alternative scenario may be a short clinical guideline update such as that initiated for Type II diabetes. This could focus on the two new oral compounds which will compliment the current guidelines, leaving no potential for confusion.	Dabigatran received its licence before rivaroxaban and is already being appraised via the STA process
Wording	GSK	The wording of the remit reflects the issues that NICE should consider.	Comments noted
Timing Issues	Bayer	Phase III trials have shown that rivaroxaban significantly reduces the risk of VTE in patients undergoing total knee replacement surgery and total hip replacement surgery compared with enoxaparin (3-5). As an oral, once-daily direct Factor Xa inhibitor it offers an effective and convenient treatment option that would aid the implementation of current NICE guidelines. Dabigatran etexilate is an oral direct thrombin inhibitor that is anticipated to be launched up to six months before rivaroxaban. This is being appraised by NICE as part of the 15th wave and therefore it would be in the interest of the NHS and general public for recommendations for these products to be available as close together as possible.	Comments noted Dabigatran received its licence before rivaroxaban and is already being appraised via the STA process
	GSK	No comment.	
	Anticoagulation Europe	Need to explore benefits of a new anticoagulation option which could reduce DVT and PE post lower limb surgery	Comments noted
	RCN	There is an urgent need to develop alternative anticoagulation in place of warfarin and this drug may well be sued in future.	Comments noted

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	sanofi-aventis	Given that rivaroxaban will be the second oral alternative in the VTE prophylaxis market to be launched in the UK it will help healthcare professionals to get recommendations. However, we feel that separate STA guidance for rivaroxaban and for dabigatran will merely confuse the current CG46. While the STA guidance may coincide with product launch it will not necessarily support healthcare professionals as intended given the fact they will be faced with multiple recommendations.	Comments noted Dabigatran received its licence before rivaroxaban and is already being appraised via the STA process
Additional comments on the draft remit			

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Bayer	The current NICE guidelines on venous thromboembolism in patients undergoing surgery make specific recommendations for patients undergoing orthopaedic surgery. These recommend that patients having elective orthopaedic surgery should be offered mechanical prophylaxis and either LMWH or fondaparinux. Patients having hip replacement surgery with one or more risk factors should have their LMWH or fondaparinux continued for 4 weeks after surgery. LMWH or fondaparinux should be continued for 4 weeks after hip fracture surgery.	Scope amended
	National Collaborating Centre for Acute Care	Page 1: The 4th paragraph provides different figures for the incidence of DVT after hip and knee replacements compared with the dabigatran scope. Page 1: Last paragraph, NICE guideline 46 also recommends extended heparin or fondaparinux prophylaxis for 4 weeks for patient undergoing hip replacement or hip fracture surgery.	Scope amended
	RCN	DVT also occurs in the arm. Symptoms of PE also include haemoptysis Large PE can also cause right sided heart failure	Comments noted. Scope amended. The scope provides a brief, rather than comprehensive, summary of relevant background information.
The technology/ intervention	Bayer	Rivaroxaban (Xarelto, Bayer Schering Pharma) is a fixed dose oral anticoagulant which acts by direct inhibition of activated factor X (factor Xa) and has no requirements for monitoring. Data from the phase III RECORD studies suggest that daily oral rivaroxaban 10mg is statistically significantly more effective than subcutaneous (s.c.) enoxaparin 40mg for short term thromboprophylaxis in patients undergoing total knee replacement and extended thromboprophylaxis for total hip replacement.	Comments Noted
	RCN	The description of the technology seems accurate.	Comments noted

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Population	GSK	GSK suggest that the age is defined more clearly i.e. 'Adults *aged 18 and over* undergoing major orthopaedic surgery…..'	Population defined as adults undergoing elective hip or knee replacement surgery.
	RCN	Perhaps consider other groups of orthopaedic operations that put patients at risk of VTE. We understand that the trials have taken place with this group of patients.	Relevant sub groups will be considered in this appraisal where evidence allows.
	sanofi-aventis	Major orthopaedic surgery of the lower limbs would by definition also include hip fracture surgery. There is no clinical data on the use of rivaroxaban in this group of patients which have an extremely high rate of DVT. Administration of an oral drug in an emergency situation where absorption and administration of an oral compound have not been evaluated may not be appropriate as this is very different to an elective situation. Given the above we recommend that the final scoping document take this into consideration.	The updated scope now reflects the fact that rivaroxaban is likely to be indicated for elective hip or knee replacement surgery.
Comparators	Bayer	Enoxaparin is the most widely prescribed low molecular weight heparin in orthopaedic departments (6). (6) IMS Health, HPAI data, MAT to December 2007.	This suggestion is covered under LWMH
	Boehringer	Dabigatran etexilate is likely to be an appropriate comparator. It has received positive CHMP opinion (Jan 24th 2008) and will have been available in the UK for several months prior to the initiation of a potential STA for rivaroxaban. It is also likely that the NICE STA for dabigatran will be concluded prior to the launch of rivaroxaban.	Dabigatran has been included in the comparators.

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	GSK	GSK suggest consideration is given to the following therapies as comparators in this appraisal: - aspirin; - warfarin; - other direct thrombin inhibitors e.g. ximelagatran; mechanical prophylaxis e.g. compression stockings.	The clinical guideline for venous thromboembolism (CG 046) recommends low-molecular-weight heparin, and fondaparinux as an alternative, as pharmacological methods of prophylaxis (in addition to mechanical prophylaxis which should be offered to all patients having major surgery), and comparators should be consistent with that guidance.
	RCN	Warfarin has been used as prophylaxis in some instances.	The clinical guideline for venous thromboembolism (CG 046) recommends low-molecular-weight heparin, and fondaparinux as an alternative, as pharmacological methods of prophylaxis (in addition to mechanical prophylaxis which should be offered to all patients having major surgery), and comparators should be consistent with that guidance.
	sanofi-aventis	Given that dabigatran is also to be licensed and launched in the UK in the same indication we would suggest that this is also an appropriate comparator as both compounds will likely be considered for the same patient population.	Dabigatran has been included in the comparators.

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Outcomes	Boehringer	When comparing the absolute rates of events (and the pooled estimates) of different thromboprophylactic regimens via indirect comparison, it is important that differences in the methods for assessing outcomes between trials are examined. For example: • Differences in trial populations (hip replacement, hip fracture etc) • Differences in adjudication committees • Differences in definition of bleeding events and other safety endpoints Differences in duration of treatment and double blind periods	Comment noted
	GSK	GSK suggest that the outcomes of interest also include: - treatment related bleeding; - recurrent VTE. In addition whilst mortality and incidence of PE form the focus of clinical attention, consideration should be given to the 'contribution' of sub-clinical i.e. silent DVTs.	Outcomes amended in the scope.
	RCN	Yes	Noted
	sanofi-aventis	Sanofi-aventis consider that the adverse effects should include: • All clinically relevant bleeding • Liver toxicity The bleeding definitions in clinical trials in VTE differ significantly. All clinically relevant bleeding should be included in the evaluation as this is vital in assessing the risk/benefit balance of anticoagulants. This should include surgical site bleeding which was excluded in the overall bleed rates in the Phase III trial for Rivaroxaban. Inclusion of this data might have a significant impact on the risk/benefit assessment as the bleeding rates for the comparator product using this definition were lower than those seen in other trials.	Comments incorporated into the updated scope.
Economic analysis	National Collaborating Centre for Acute Care	In this area the convention is to compare results using both a 1-3-month and a 5-year timeline.	The time horizon will be appropriate for the nature of the condition.

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	sanofi-aventis	While economic models are generally built to consider the lifetime of the patient we recommend that a variety of time horizons also be considered ranging from 30 days, 1 year, 3 years, 5 years and 10 years. Monitoring costs may be a key consideration within the economic analysis. In addition, the consideration of costs from the NHS and Personal Social Services perspective may overestimate the cost of current compounds in the market which are often subject to significant discounts at a hospital level. This may lead to an underestimation of the cost /QALY therefore we recommend some cost variation within considered sensitivity analysis.	Discounts can only be considered if they are consistently available across the NHS. The reference-case analysis should use the public list price. For further details, see the updated Guide to the Methods of Technology Appraisal: http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf
Other considerations	GSK	GSK suggest that consideration is also given to the route of administration of the different therapies as this impacts on the bioavailability of the drugs. Subcutaneously administered drugs have 100% bioavailability compared with orally administered drugs which are associated with reduced bioavailability. This has particular significance for patients with reduced mobility.	Comment noted. The appraisal will consider differences in health outcomes associated with the intervention and comparator technologies, and this is expected to include those related to mode of administration.

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	sanofi-aventis	Sanofi-aventis believe that specific subgroups should be considered: The relevance of oral treatment versus injectable in different patients groups should also be considered as well as the potential impact of treatment compliance on effectiveness. These aspects should be followed through within the sensitivity analysis in the economic analyses. Patients who are nil by mouth, vomiting or in pain may not be receiving an adequate dose. These are common post-operative problems and may affect absorption of an oral compound. Patients with liver disease or severe renal insufficiency are a special group as they were excluded from the RCT's. There is a large accumulation rate of rivaroxaban in patients with renal insufficiency and specific recommendations are necessary for this group of patients (*Halabi et al. Blood 2006:108(11) :Abstract 913*) Hip fracture surgery is an emergent situation, patients are generally older than those for elective Total Hip Replacement, and severe renal insufficiency prevalence is high. Groups of patients who are at high risk of bleeding due to co-morbidity or polypharmacy may need to have monitoring of their anticoagulation levels. There needs to be clear guidance on how to do this. In addition the issue of how to reverse the effects in the event of a major bleed needs to be addressed.	Certain sub groups were identified at the scoping workshop for consideration where evidence allows. These were: patients with high risk of VTE other than because of their surgery, patients having knee replacements versus those having hip replacements and patients having hip fracture surgery versus those having total elective hip replacements. Guidance will only be issued in accordance with the marketing authorisation and it is anticipated that this will only apply to elective hip or knee replacement surgery and not hip fracture.

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Questions for consultation	GSK	The following sub-groups of patients might be considered as being at a higher risk of DVT and/or PE and may require to be treated separately: - patients presenting with recurring clinical or sub-clinical VTE; - severely obese patients; - patients presenting with other circulatory problems; - long term disabled patients; - patients with a genetic disposition to VTE; patients who are prescribed oestrogens.	Certain sub groups were identified at the scoping workshop for consideration where evidence allows. . These were: patients with high risk of VTE other than because of their surgery, patients having knee replacements versus those having hip replacements and patients having hip fracture surgery versus those having total elective hip replacements. Guidance will only be issued in accordance with the marketing authorisation and it is anticipated that this will only apply to elective hip or knee replacement surgery and not hip fracture.
	sanofi-aventis	We do not feel that this product is suitable for an STA given the imminent launch of dabigatran plus the existence of the recently published clinical guidelines 46. Two alternative approaches seem more appropriate, either an MTA of both oral compounds to minimise confusion or a short clinical guidelines update to ensure healthcare professionals are able to position these new oral compounds within the already existing guidelines to optimise patient care.	Dabigatran received its licence before rivaroxaban and is already being appraised via the STA process

Section	Consultees	Comments	Action	
Additional comments on the draft scope.				
Comments on matrix of consultees & commentators				

Comment 4: Regulatory issues

Section	Consultees	Comments	Action
Remit			
Current or proposed marketing authorisation		Rivaroxaban does not have current marketing authorisation.	Comments noted
	What is the target date (mm/yyyy) for regulatory submission?	1. Prevention of VTE after major orthopaedic surgery of the lower limbs: Submitted Nov 2007 2. Treatment of VTE: [redacted] 3. Prevention of stroke in atrial fibrillation [redacted] Prevention of VTE in medically ill patients [redacted]	Comments noted
	Which regulatory process are you following?	Centralised for all indications	Comments noted
	What is the anticipated date (mm/yyyy) of CHMP positive opinion (if applicable) and regulatory approval?	1. Prevention of VTE after major orthopaedic surgery of the lower limbs: Submitted Nov 2007 [redacted] 2. Treatment of VTE: [redacted] 3. Prevention of stroke in atrial fibrillation [redacted] • Prevention of VTE in medically ill patients [redacted]	Comments noted

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

NHS Quality Improvement Scotland
The Research Institute for the Care of Older People
Welsh Assembly Government
Board of CHCs in Wales
Department of Health
RICE
NHS IQS