National Institute for Health and Clinical Excellence

Dabigatran for the prevention of deep vein thrombosis after hip and knee replacement surgery in adults

Comment 1: the draft remit

Section	Consultees	Comments	Response
Appropriateness	Boehringer Ingelheim Ltd	The recently published NICE clinical guidelines (number 46, Prevention of Venous Thromboembolism (VTE)) highlighted that VTE is a major problem for hospital inpatients, especially those undergoing high-risk surgical procedures such as major orthopaedic surgery. Coupled with the report from the House of Commons Select Committee in 2005 and the recent letter from the Chief Medical Officer, this topic is highly relevant, timely and addresses a key area of NHS priority.	Comment noted.
	GlaxoSmithKline	We agree that this appraisal would be suitable for a single technology appraisal.	Comment noted.
	Lifeblood: the thrombosis charity	Dabigatran is the first of a series of new oral anticoagulants coming into use. It would be appropriate to look at its use. However rivaroxaban another new oral anticoagulant (Bayer) has also completed clinical trials and should also be considered.	Rivaroxaban is due to go through the topic selection process in November 2007.
Wording	Boehringer Ingelheim Ltd	The wording of the remit should be adjusted to [redacted] as follows: "To appraise the clinical and cost effectiveness of dabigatran etexilate in the prevention of venous thromboembolism after elective total hip and total knee replacement surgery in adults".	The remit has been reworded.
Timing Issues	Boehringer Ingelheim Ltd	Dabigatran etexilate is planned for launch in [redacted], therefore this guidance will be required in a timely fashion in order to keep the clinical guidelines referred to above up-to-date.	Comment noted.
	Lifeblood: the thrombosis charity	Good timing	Comment noted.

Comment 2: the draft scope

Section	Consultees	Comments	Response
Background information	Boehringer Ingelheim Ltd	We consider the background information to be accurate and complete.	Comment noted.
	GlaxoSmithKline	*Background - Paragraph 3 (Page 1)* *We suggest this is clarified as follows:* DVT occurs in over 30% of surgical patients 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). *Paragraph 5 (Page 1)* We suggest that current standard treatment should include: …pharmacological prophylaxis such as heparin *and fondaparinux* …… (as recommended by NICE guidelines)	Wording amended. Draft scope amended to include fondaparinux.
	National Collaborating Centre for Acute Care	The incidence of fatal pulmonary embolism in these patient groups is much lower than suggested here – perhaps around 0.2-0.3%	Scope amended.
The technology/ intervention	Boehringer Ingelheim Ltd	As per previous correspondence, the brand name for dabigatran etexilate remains unconfirmed. [redacted] The technology should be referred to as dabigatran etexilate throughout. The population under consideration is those undergoing *elective* total hip and knee replacement therapy.	The confirmed brand name has been included in the scope. The technology is referred to as dabigatran etexilate throughout. The population has been amended to "adults undergoing elective hip or knee replacement".
Population	Boehringer Ingelheim Ltd	It is important to emphasise that the population will be those patients undergoing *elective* total hip and knee replacement surgery. It is appropriate that the two indications (hip and knee) should be considered separately within the single appraisal.	The population has been amended to "adults undergoing elective hip or knee replacement".

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	GlaxoSmithKline	We suggest that the scope clarifies whether the population is limited to patients > 18 years old.	The population has been amended to "adults undergoing elective hip or knee replacement".
Comparators	Boehringer Ingelheim Ltd	Pharmacological thromboprophylaxis may not always be used in combination with physical methods, where such physical methods are contraindicated. The pharmacological comparators listed are the most appropriate in terms of the evidence, in line with the recently published NICE clinical guidelines. According to data from the National Joint Registry, it would be reasonable to consider low-molecular weight heparin (LMWH) to be the current standard of care. Almost 2/3 of patients (in both total hip and knee replacement) who receive pharmacological thromboprophylaxis, receive LMWH.	Comment noted.
	GlaxoSmithKline	Other potential oral interventions for this patient group are aspirin and warfarin and as such, consideration should be given to these as potential comparators.	The clinical guideline for venous thromboembolism (CG 046) recommends low-molecular-weight heparin and Fondaparinux as an alternative as the pharmacological method of prophylaxis and comparators should be consistent with that guidance.
	National Collaborating Centre for Acute Care	Physical methods alone should also be considered.	The clinical specialists at the scoping workshop advised consultees that physical methods alone would not be an appropriate comparator due to the lack of clinical effectiveness data in this area.
Outcomes	Boehringer Ingelheim Ltd	Whilst the list of outcomes presented is complete, it is important to note that the various types of DVT (symptomatic, asymptomatic, proximal, distal) can vary in their clinical relevancy and impact on costs and outcomes.	Comment noted.

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Economic analysis	Boehringer Ingelheim Ltd	The suggestions relating to the economic analysis are appropriate. Whilst the surgical procedure is an acute event, the consequences of suffering VTE can be life-long in terms of complications associated with the event and risk of recurrence.	Comment noted.
	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. There is not direct evidence that prophylaxis prevents post-thrombotic syndrome and therefore the 5-year model is a more tentative one.	The time horizon will be appropriate for the nature of the condition.
Other considerations	Boehringer Ingelheim Ltd	The suggested duration of treatments do not accurately reflect the proposed marketing authorisation. In total knee replacement, the duration of treatment should be [redacted] days. In hip replacement surgery, the duration of treatment should be 28-35 days.	Scope amended.
Questions for consultation	Boehringer Ingelheim Ltd	We believe that this appraisal is suitable for the single technology appraisal process. No relevant comparators have been omitted.	Comment noted.
Additional comments on the draft scope.	Boehringer Ingelheim Ltd	As per previous correspondence, the brand name for dabigatran etexilate remains unconfirmed. [redacted]	The confirmed brand name has been included in the scope.
	National Collaborating Centre for Acute Care	Related NICE guidance also includes the clinical guideline for the prevention of venous thromboembolism in all patients admitted to hospital which is currently in development and due to be published in September 2009. This guideline will incorporate the published NICE clinical guideline for prevention of venous thromboembolism in surgical inpatients (http://guidance.nice.org.uk/page.aspx?o=429276). In addition if this HTA were to go ahead, the timing of the appraisal in relation to this guideline will need to be carefully considered.	Scope amended.

Comment 4: Regulatory issues

Section	Consultees	Comments	Action
Remit	Boehringer Ingelheim Ltd	The wording of the remit should be adjusted [redacted] as follows: "To appraise the clinical and cost effectiveness of dabigatran etexilate in the prevention of venous thromboembolism after elective total hip and total knee replacement surgery in adults".	The remit has been reworded.
Current or proposed marketing authorisation	Boehringer Ingelheim Ltd	Planned indications: 1) Prevention of venous thromboembolism after elective total hip and total knee replacement surgery in adults. 2) [redacted] Target date for regulatory submission 1) [redacted] Regulatory process: 1) [redacted] Anticipated date for CHMP: 1) [redacted]	Comment noted.