

Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults

Technology appraisal guidance

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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

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1 Guidance

- 1.1 Dabigatran etexilate, within its marketing authorisation, is recommended as an option for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery.

2 The technology

- 2.1 Dabigatran etexilate (Pradaxa, Boehringer Ingelheim) is a direct inhibitor of the enzyme thrombin. Thrombin is a key enzyme in blood clot (thrombus) formation because it enables the conversion of fibrinogen to fibrin during the coagulation cascade. Inhibition of thrombin prevents further development of clot formation. Clot formation may be associated with inactivity and some surgical procedures. Dabigatran etexilate holds a marketing authorisation for the primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or elective total knee replacement surgery. Dabigatran is taken orally.
- 2.2 The summary of product characteristics (SPC) states that dabigatran etexilate treatment should be started within 1–4 hours of surgery with a half dose of 110 mg. Thereafter, treatment is continued with a standard dose of 220 mg once daily for 10 days after knee replacement and for 28–35 days after hip replacement. The SPC states that for special patient populations (including people with moderate renal impairment, those over 75 years and people receiving amiodarone), a reduced dose of 150 mg (75 mg starting dose, 150 mg continuing dose) once daily is recommended.
- 2.3 According to data reported in the SPC, around one in seven people undergoing hip or knee surgery and treated with dabigatran etexilate experienced a bleeding event (13.8% of those receiving daily doses of 220 mg or 150 mg). Major bleeds were common and were experienced by 1.8% and 1.3% of people treated with 220 mg or 150 mg dabigatran etexilate, respectively. Other common adverse effects (those occurring in at least 1%, but less than 10% of patients) include gastrointestinal haemorrhage, wound secretion, anaemia and haematoma. For full details of side effects and contraindications, see the SPC.
- 2.4 Dabigatran etexilate costs £21.00 for a pack of ten 75-mg or 110-mg capsules (£126.00 for 60 capsules), excluding VAT (NHS list price as reported by the manufacturer). The cost of treatment is estimated to be £39.90 (based on the use of 19 capsules) for knee replacement and to

range from £115.50 to £144.90 for hip replacement (based on the use of 55–69 capsules, respectively). Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee ([appendix A](#)) considered evidence submitted by the manufacturer of dabigatran etexilate for the prevention of venous thromboembolism (VTE) after hip or knee replacement surgery in adults and a review of this submission by the Evidence Review Group (ERG; [appendix B](#)).

- 3.1 The manufacturer's submission compared dabigatran etexilate (at 150 mg and 220 mg daily doses) with enoxaparin, a low molecular weight heparin (LMWH), using direct evidence from randomised controlled trials (RCTs), and with fondaparinux, using RCT evidence which had been incorporated into a mixed-treatment comparison. Outcomes analysed included: mortality; incidence of deep vein thrombosis (DVT); incidence of pulmonary embolism (PE); adverse effects of treatment including bleeding events; post-DVT complications including post-thrombotic syndrome; length of hospital stay; and health-related quality of life. All of these outcomes were specified in the decision problem for this appraisal. The manufacturer's submission (MS) did not include analysis of outcomes at the site of the orthopaedic intervention, such as joint infection.
- 3.2 The manufacturer conducted a systematic review which included three randomised, active-controlled parallel-group, non-inferiority trials of dabigatran etexilate (each including two dosing regimes) versus enoxaparin. These trials were:
- RE-NOVATE: a pivotal phase III, double-blind RCT of elective total hip replacement patients where dabigatran etexilate 150 mg or 220 mg once daily (started 1–4 hours after surgery with a half dose of 75 mg or 110 mg, respectively) was compared with 40 mg enoxaparin once daily (started the day before surgery). Both treatments were continued for 28–35 days (n = 3494 randomised)

- RE-MODEL: a pivotal phase III, double-blind RCT of elective total knee replacement patients where dabigatran etexilate 150 mg or 220 mg once daily (started 1–4 hours after surgery with a half dose of 75 mg or 110 mg, respectively) was compared with 40 mg enoxaparin once daily (started the day before surgery). Both treatments were continued for 6–10 days (n = 2101 randomised).
- RE-MOBILIZE: described in the manufacturer's submission as a supporting North American, phase III, double-blind RCT of elective total knee replacement patients where dabigatran etexilate 150 mg or 220 mg once daily (started 6–12 hours after surgery with a half dose of 75 mg or 110 mg, respectively) was compared with 30 mg enoxaparin twice daily (started 12–24 hours after surgery). Both treatments were continued for 12–15 days (n = 2615 randomised).

The primary efficacy outcome for all three trials was a composite of total incidence of VTE (proximal and distal DVT based on venogram or objectively confirmed symptomatic DVT and PE) and all-cause mortality. Follow-up in all trials was 12–14 weeks after surgery. Participants were randomised to 150 or 220 mg doses irrespective of renal function status.

3.3 A range of meta-analyses were conducted which combined the two pivotal (RE-NOVATE, RE-MODEL), two knee (RE-MODEL, RE-MOBILIZE) and all three trials. Two phase II trials were excluded from meta-analysis. One trial was excluded because the dosing regimen was different to that specified in the marketing authorisation, and the other was excluded because only preliminary data were reported for dabigatran etexilate compared with placebo.

3.4 The results of primary efficacy and bleeding outcomes reported in individual RCTs are detailed below.

The total incidence of the composite outcome of VTE and all-cause mortality at 12–14 weeks after surgery in:

- RE-NOVATE was 6% (n = 880), 8.6% (n = 874) and 6.7% (n = 897) for dabigatran etexilate 220 mg, dabigatran etexilate 150 mg and enoxaparin, respectively. Absolute risk differences were -0.7% (95% confidence interval [CI] -2.9 to 1.6) and 1.9% (95% CI -0.6 to 4.4) for 220 mg and 150 mg respectively compared with enoxaparin. Relative risks were 0.9 (95% CI 0.63 to 1.29) and 1.28 (95% CI 0.93 to 1.78) for 220 mg and 150 mg respectively compared with enoxaparin.
- RE-MODEL was 36.4% (n = 503), 40.5% (n = 526) and 37.7% (n = 512) for dabigatran etexilate 220 mg, dabigatran etexilate 150 mg and enoxaparin, respectively. Absolute risk differences were -1.3% (95% CI -7.3 to 4.6) and 2.8% (95% CI -3.1 to 8.7) for 220 mg and 150 mg respectively compared with enoxaparin. Relative risks were 0.97 (95% CI 0.82 to 1.13) and 1.07 (95% CI 0.92 to 1.25) for 220 mg and 150 mg respectively compared with enoxaparin.
- RE-MOBILIZE was 33.1% (n = 604), 33.7% (n = 649) and 25.3% (n = 643) for dabigatran etexilate 220 mg, dabigatran etexilate 150 mg and enoxaparin (30 mg twice daily), respectively. Absolute risk differences were 5.8% (95% CI 0.8 to 10.8) and 8.4% (95% CI 3.4 to 13.3) for 220 mg and 150 mg respectively compared with enoxaparin. Relative risks were 1.23 (95% CI 1.03 to 1.47) and 1.33 (95% CI 1.12 to 1.58) for 220 mg and 150 mg respectively compared with enoxaparin (30 mg twice daily).

3.5 The incidence of the composite outcome of major bleeding and clinically relevant bleeding in:

- RE-NOVATE was 6.2% (n = 1146), 6.0% (n = 1163) and 5.0% (n = 1154) for dabigatran etexilate 220 mg, dabigatran etexilate 150 mg and enoxaparin, respectively. Absolute risk differences were 1.2% (95% CI -0.7 to 3.1) and 1.0% (95% CI -0.9 to 2.9) for dabigatran etexilate 220 mg and dabigatran etexilate 150 mg respectively compared with enoxaparin.
- RE-MODEL was 7.4% (n = 679), 8.1% (n = 703) and 6.6% (n = 694) for dabigatran etexilate 220 mg, dabigatran etexilate 150 mg and enoxaparin, respectively. Absolute risk differences were 0.7% (95% CI -2.0 to 3.4) and 1.5% (95% CI -1.3 to 4.2) for 220 mg and 150 mg respectively compared with enoxaparin.

- RE-MOBILIZE was 3.3% (n = 857), 3.1% (n = 871) and 3.8% (n = 868) for dabigatran etexilate 220 mg, dabigatran etexilate 150 mg and enoxaparin (30 mg twice daily), respectively. Absolute risk differences were –0.5% (95% CI –2.3 to 1.2) and –0.7% (95% CI –2.4 to 1.0) for 220 mg and 150 mg respectively compared with enoxaparin (30 mg twice daily).

- 3.6 In the absence of direct evidence comparing dabigatran etexilate with fondaparinux, the manufacturer presented results of a mixed-treatment comparison based on a recent meta-analysis performed for the NICE clinical guideline 'Venous thromboembolism' (NICE clinical guideline 46 [Replaced by [NICE clinical guideline 92](#)]). Results were expressed as relative risks for each intervention versus no intervention. The analysis included trial data for dabigatran etexilate and fondaparinux as well as for other VTE prevention strategies (such as aspirin and non-pharmacological prevention), although this was not part of the decision problem specified in the scope. The manufacturer reported that fondaparinux and LMWH (given for an 'extended duration' of more than 14 days) were associated with lower relative risk for DVT than other existing interventions (compared to no intervention). The manufacturer also reported that fondaparinux had the highest relative risk for bleeding, but noted that confidence intervals for all the interventions overlapped. The manufacturer stated that dabigatran compared favourably with existing alternatives in terms of both efficacy and safety.
- 3.7 The manufacturer submitted an economic model assessing the impact of dabigatran etexilate for VTE prevention after hip and knee replacement compared with LMWH and fondaparinux. The model included an acute-phase decision-tree model to 10 weeks after surgery and a chronic-phase Markov model with a lifetime (60-year) time horizon.
- 3.8 The acute-phase model predicted transition between health states based on evidence from the two pivotal phase III trials of dabigatran etexilate (RE-NOVATE and RE-MODEL) compared with enoxaparin and the mixed-treatment comparison for dabigatran etexilate and fondaparinux. At 10 weeks, patients entered the chronic-phase Markov model in the same health state in which they ended the decision-tree model. No further treatment effect was applied in the chronic-phase model. Transitions between states in the chronic-phase model were dependent on recurrence rates for VTE from the literature. The health

states in the chronic-phase model were: well; asymptomatic untreated VTE (proximal DVT, distal DVT and PE); treated VTE for people surviving after symptomatic VTE (proximal DVT, distal DVT and PE); recurrent DVT or PE; mild to moderate post-thrombotic syndrome; severe post-thrombotic syndrome; disabled (owing to an intracranial bleed); or dead.

- 3.9 Key assumptions in the economic evaluation are detailed in the manufacturer's submission. Among these, the manufacturer assumed that all LMWHs are bioequivalent, because literature on dalteparin, tinzaparin and enoxaparin and the NICE clinical guideline 'Venous thromboembolism' (NICE clinical guideline 46 [Replaced by [NICE clinical guideline 92](#)]) recommendations did not distinguish between LMWHs. Furthermore, a zero cost for administration was assumed for dabigatran etexilate, whereas LMWH and fondaparinux were assumed to require resources for administration (including provision for a proportion of people who were unable or unwilling to self-inject). These administration costs were determined to be £100.00 and £6.00 for LMWH and £83.00 and £6.00 for fondaparinux after hip or knee replacement, respectively.
- 3.10 The base-case analysis estimated that at 220 mg dabigatran etexilate was less costly and more effective than LMWH for both hip and knee replacement surgery. At the lower dose of 150 mg, dabigatran etexilate was less costly and more effective than LMWH for hip replacement surgery, but was more costly and less effective than LMWH for knee replacement surgery. In univariate sensitivity analyses none of the parameters were associated with a significant difference in the base-case results.
- 3.11 The economic evaluation estimated that at both doses dabigatran etexilate is less costly but also less effective than fondaparinux after hip replacement (ICERs were in the 'southwest' quadrant of the cost-effectiveness plane). After knee replacement, dabigatran etexilate at both doses was dominated by fondaparinux (that is, it was more costly and less effective than fondaparinux). In sensitivity analysis, increasing the relative risk of VTE for fondaparinux was associated with dabigatran etexilate dominating for hip replacement and being less costly, but being less effective in knee replacement.

- 3.12 Probabilistic sensitivity analysis and cost-effectiveness acceptability curves suggested probabilities of dabigatran etexilate being cost effective compared with LMWH (at a willingness-to-pay threshold range of £20,000 per additional QALY gained) of 99% for the 220-mg dose after hip replacement, 82% for the 220-mg dose after knee replacement, 76% for the 150-mg dose after hip replacement, and 38% for the 150-mg dose after knee replacement). The corresponding results for dabigatran compared with fondaparinux were 40% for the 220-mg dose and 32% for the 150-mg dose after hip replacement, and zero for both doses after knee replacement).
- 3.13 Following a request for clarification from the ERG, the manufacturer provided cost-effectiveness analyses with inputs from meta-analysis which included data from the RE-MOBILIZE trial. The revised economic evaluation estimated that dabigatran etexilate was dominated by LMWH (that is, it was more costly and less effective than LMWH) for knee replacement at both 220-mg and 150-mg doses.
- 3.14 The ERG confirmed that the decision problem matched the marketing authorisation for dabigatran etexilate and that LMWH and fondaparinux were appropriate comparators. The ERG acknowledged that clinical trials did not routinely report hip or knee joint outcomes, such as joint infection. The ERG also noted that there was limited clinical experience of using dabigatran etexilate in the special populations (including people with moderate renal impairment, those over 75 years and people who are receiving amiodarone) defined in the SPC.
- 3.15 The ERG identified evidence of variation in the dosing regimen for LMWH. In the RE-NOVATE and RE-MODEL studies the protocol was for enoxaparin to be started before surgery, but in some countries treatment was started post-operatively to reflect local practice. It was not clear from reporting of the studies what proportion of patients received which regimen. In the RE-MOBILIZE study, enoxaparin was started post-operatively. The ERG stated that the trials may not completely reflect the practice of administering LMWH preoperatively in England and Wales. This variation in practice could introduce confounding because in these situations LMWH would not be administered to people with uncontrolled bleeding following joint replacement. 'Venous thromboembolism' (NICE

clinical guideline 46 [Replaced by [NICE clinical guideline 92](#)]) states that the currently available randomised evidence is too limited to determine whether giving LMWH can be safely delayed until after surgery, or whether it must be given preoperatively. The guideline identifies this as a major evidence gap and is therefore non-specific about timing.

- 3.16 The ERG commented that the mixed-treatment comparison did not provide indirect comparisons of fondaparinux and dabigatran etexilate, making it difficult to reach conclusions about their relative efficacy and safety. The ERG also noted that the outcome assessed in the mixed-treatment comparison was DVT (not the composite primary outcome of the dabigatran etexilate trials). It was also unclear how the trial data had been used to derive the mixed-treatment comparison of DVT outcome. The ERG suggested that results of the manufacturer's mixed-treatment comparison should be considered with caution.
- 3.17 The ERG commented that the model structure, health states and parameters were reasonable. The univariate sensitivity analysis was extensive and performed with appropriate parameters. The probabilistic sensitivity analysis was performed correctly. However, the ERG noted that previously published models included progression from distal to proximal DVT, which the manufacturer's model did not. The literature search for recurrence of VTE, rates of post-thrombotic syndrome and quality of life data used in the model was limited to published economic studies. The ERG suggested that it was therefore possible that the manufacturer had not considered all applicable data in the model.
- 3.18 The ERG highlighted that small numerical differences in data from pivotal trials were reproduced in the model in terms of small incremental costs and small incremental health benefits. A small change in the direction of these inputs resulted in a similar change in the direction of the model results. Inclusion of data from meta-analyses that included the RE-MOBILIZE trial produced such a change in direction of results, and dabigatran etexilate became dominated by LMWH (that is, it was more costly and less effective than LMWH).
- 3.19 Full details of all the evidence are in the [manufacturer's submission and the ERG report](#).

4 Consideration of the evidence

- 4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of dabigatran etexilate for the prevention of VTE after elective total hip or knee replacement surgery in adults having considered evidence on the nature of the condition and the value placed on the benefits of dabigatran by people with experience of VTE, those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources.
- 4.2 The Committee discussed the decision problem and agreed that this appraisal would focus on choice among pharmacological agents for VTE prevention. The Committee discussed the NICE clinical guideline 'Venous thromboembolism' (NICE clinical guideline 46 [Replaced by [NICE clinical guideline 92](#)]). It noted the recommendation that in addition to mechanical prophylaxis, people at increased risk of VTE and people undergoing orthopaedic surgery should be offered LMWH, and that fondaparinux, within its marketing authorisation, may be used as an alternative to LMWH. It also heard representations that drugs for the prevention of VTE are not used by all orthopaedic surgeons because some surgeons are concerned that they may increase the incidence, or worsen the consequences, of deep infection in the site of the orthopaedic surgery. The Committee was mindful of these concerns, but concluded that any recommendations made would be limited to situations where drugs for the prevention of VTE were already recommended in 'Venous thromboembolism' (NICE clinical guideline 46 [Replaced by [NICE clinical guideline 92](#)]).
- 4.3 The Committee discussed the clinical effectiveness of dabigatran etexilate compared with LMWH and fondaparinux in people undergoing elective hip or knee surgery, as well as the relative acceptability and ease of management conferred by oral as opposed to subcutaneous administration. It noted that LMWH is the key comparator for dabigatran etexilate because fondaparinux is used much less extensively, but concluded that both should be considered in this appraisal. It also noted that the available direct evidence was limited to a comparison of dabigatran etexilate and enoxaparin and that the manufacturer assumed

that all LMWHs were bioequivalent. The Committee agreed that LMWH types may be considered to have equivalent clinical effectiveness, as stated in the NICE clinical guideline 'Venous thromboembolism' (NICE clinical guideline 46).

- 4.4 The Committee first considered evidence on the clinical effectiveness of dabigatran etexilate compared with enoxaparin. It discussed the applicability of the trials to UK clinical practice, understanding that there is variation in prevention strategies. The Committee agreed that data from the RE-NOVATE and RE-MODEL RCTs, in which the patients in the control arm received 40 mg LMWH once daily, were applicable to UK clinical practice. It agreed that the RE-MOBILIZE study, which used an alternative dosing regimen of 30 mg LMWH twice daily, did not reflect the UK clinical setting, but agreed that it usefully contributes to the overall evidence base and that the results of RE-MOBILIZE were relevant for consideration.
- 4.5 The Committee discussed the outcome data from these trials. It heard from one clinical specialist that a major component of the composite primary outcome of the studies (DVT detected by venogram) was a surrogate outcome that was not universally recognised as a valid predictor of clinically relevant outcomes. However, the Committee considered that this outcome was objectively assessed and allowed comparison between prevention strategies. It noted that the Guideline Development Group for 'Venous thromboembolism' (NICE clinical guideline 46 [Replaced by NICE clinical guideline 92]) had accepted these outcomes after careful consideration.
- 4.6 The Committee discussed the results of the RE-NOVATE, RE-MODEL and RE-MOBILIZE studies. The Committee considered that the results of the trials overall indicated that dabigatran etexilate was not inferior to LMWH in preventing VTE despite some concerns about the statistical power of the studies and the RE-MOBILIZE study indicating that dabigatran was inferior to 30 mg LMWH twice daily. The Committee considered adverse events such as bleeding, noting that no statistically significant differences were observed between dabigatran etexilate and LMWH. The Committee was mindful of the absence of an antidote for dabigatran etexilate, and noted that antidotes were available for LMWH and

warfarin. Overall the Committee concluded that dabigatran etexilate could, on the evidence available, be considered broadly comparable to LMWH in preventing VTE events and in terms of short-term adverse effects.

- 4.7 The Committee considered evidence on the clinical effectiveness of dabigatran etexilate at the reduced 150-mg dose for special patient populations (see section 2.2). The Committee noted that the 150-mg dose for special populations was specified in the marketing authorisation. The Committee was mindful of the results of meta-analysis that indicated that 150 mg may be less effective in terms of the primary outcome than 220 mg, but that few differences were observed in safety outcomes. It also considered that in those special populations, 150 mg might have a similar pharmacokinetic profile to 220 mg, but there were no subgroup analyses from which this could be determined. It heard from clinical specialists and patient experts how important it was to balance the potential advantages of prevention of VTE with the potential consequences of adverse effects, especially for people for whom the lower dose is specified in the market authorisation.
- 4.8 The Committee considered evidence on the clinical effectiveness of dabigatran etexilate compared with fondaparinux. The Committee was aware of indirect evidence suggesting that fondaparinux was more effective at reducing VTE, but that it may be more likely to be associated with treatment-related bleeds than dabigatran etexilate. However, it agreed with the ERG that it was not possible to clearly determine from the mixed-treatment comparison whether fondaparinux was significantly more or less effective than dabigatran etexilate, or no different due to limitations of the data included in the analysis. It was mindful of the need to balance prevention of VTE with possible adverse effects.
- 4.9 The Committee discussed the use of oral compared with subcutaneous treatments. The Committee heard from clinical specialists and the patient expert about their experience of administration of LMWH and their opinions on an oral alternative such as dabigatran etexilate. The Committee discussed the implications of providing an option for oral administration for adherence to treatment and thus effectiveness of prevention of VTE after hospital discharge. The Committee heard that

adherence might be improved because people may find oral medication more acceptable. The once-daily dosing regimen of dabigatran etexilate might also encourage adherence. However, it also heard that people who are offered treatment for the prevention of thromboembolism may consider injected medications important (that is, clinically efficacious and necessary to adhere to). Therefore they may be highly motivated towards adhering to the treatment.

4.10 The Committee discussed the evidence submitted by the manufacturer on the cost effectiveness of dabigatran etexilate for the prevention of VTE in people undergoing hip or knee replacement, the ERG's critique of the manufacturer's submission, and the manufacturer's response to the clarification requested by the ERG.

4.11 The Committee considered the results of the economic evaluation and noted that because of the closeness of all the effectiveness and cost data, the ICERs were very sensitive to changes in assumptions. At the 220-mg once-daily dose dabigatran etexilate was less costly and more effective than LMWH for both hip and knee replacement. At the lower dose of 150 mg, dabigatran etexilate dominated LMWH for hip replacement, but was dominated by LMWH for knee replacement. It noted that results were not very sensitive to reduced drug acquisition costs reflecting the reduced purchase price available to some NHS trusts.

4.12 The Committee noted that in the base-case modelling dabigatran etexilate at either dose was less costly and less effective than fondaparinux in hip replacement and more costly and less effective than fondaparinux in knee replacement. However, the Committee was mindful of the small differences between interventions and noted the sensitivity of the model results to changes in clinical effectiveness inputs.

4.13 Furthermore, the Committee considered that the model had not attempted to incorporate the utility benefits (in the form of disutility avoided) of oral administration over injection, and that the potential benefit of greater adherence with oral as opposed to subcutaneous treatment had been modelled conservatively.

- 4.14 Overall, taking into account that the cost and effectiveness data of dabigatran etexilate are similar to those of LMWH and fondaparinux, and that some benefits of the availability of an oral formulation had not been captured in the modelling, the Committee concluded that dabigatran etexilate was as cost-effective a use of NHS resources as LMWH or fondaparinux.
- 4.15 The Committee concluded that although there was uncertainty in the evidence base, dabigatran etexilate was likely to be of equivalent clinical and cost effectiveness to LMWH or fondaparinux in the prevention of VTE. The Committee acknowledged that oral administration of dabigatran etexilate, without the need for monitoring, would reduce administration costs and may support adherence to treatment. The Committee therefore concluded that dabigatran etexilate should be recommended as an option in the circumstances in which LMWH (or fondaparinux as an alternative) may be offered.

5 Implementation

- 5.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.
- 5.2 'Healthcare standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 that requires local health boards and NHS trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.
- 5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has had hip or knee replacement surgery and the doctor responsible for their care thinks that dabigatran etexilate is the right treatment for the prevention of venous thromboembolism, it should be available for use, in line with NICE's recommendations.
- 5.4 NICE has developed tools to help organisations implement this guidance (listed below).
- A costing statement explaining the resource impact of this guidance.
 - Audit support for monitoring local practice.

6 Recommendations for further research

- 6.1 Further pragmatic trials of dabigatran etexilate compared with LMWH in both total hip replacement and total knee replacement would serve to lessen the uncertainty surrounding the effectiveness and cost effectiveness of these treatments and head-to-head trials of dabigatran etexilate versus fondaparinux would strengthen the evidence base for this comparison.

7 Related NICE guidance

- Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) (in patients admitted to hospital). NICE clinical guideline 92 (2010).
- Rivaroxaban for the prevention of venous thromboembolism. NICE technology appraisal guidance 170 (2009).

8 Review of guidance

- 8.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.
- 8.2 The guidance on this technology was considered for review in August 2011. Details are available on the [NICE website](#).

Andrew Dillon
Chief Executive
September 2008

Appendix A: Appraisal Committee members, guideline representatives and NICE project team

A Appraisal Committee members

The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, each with a chair and vice chair. Each branch considers its own list of technologies, and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the [NICE website](#).

Professor David Barnett

Professor of Clinical Pharmacology, University of Leicester

Dr David W Black

Director of Public Health, Chesterfield PCT

Mr Brian Buckley

Chairman, Incontact

Dr Carol Campbell

Senior Lecturer, University of Teesside

Professor Mike Campbell

Professor of Medical Statistics, University of Sheffield

Professor David Chadwick

Professor of Neurology, University of Liverpool

Dr Christine Davey

Senior Researcher, North Yorkshire Alliance R & D Unit

Dr Mike Davies

Consultant Physician, Manchester Royal Infirmary

Mr Richard Devereaux-Phillips

Public Affairs Manager, Medtronic Ltd

Dr Rachel A Elliott

Lord Trent Professor of Medicines and Health, the University of Nottingham

Mrs Eleanor Grey

Lay member

Dr Dyfrig Hughes

Senior Research Fellow in Pharmacoeconomics, Centre for the Economics of Health and Policy in Health, University of Wales

Dr Peter Jackson

Clinical Pharmacologist, the University of Sheffield

Ms Rachel Lewis

Nurse Advisor to the Department of Health

Dr Damien Longson

Consultant in Liaison Psychiatry, North Manchester General Hospital

Professor Jonathan Michaels

Professor of Vascular Surgery, University of Sheffield

Dr Eugene Milne

Deputy Medical Director, North East Strategic Health Authority

Dr Simon Mitchell

Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

Dr Katherine Payne

Health Economics Research Fellow, The University of Manchester

Dr Philip Rutledge

Consultant in Medicines Management, NHS Lothian

Mr Miles Scott

Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust

Dr Surinder Sethi

Consultant in Public Health Medicine, North West Specialised Services Commissioning Team

Professor Andrew Stevens

Chair of Appraisal Committee C

Dr Cathryn Thomas

Senior Lecturer, Department of Primary Care & General Practice, University of Birmingham

Dr William Turner

Consultant Urologist, Addenbrooke's Hospital

B Guideline representatives

The following individual, representing the Guideline Development Group responsible for developing the Institute's clinical guideline related to this topic, was invited to attend the meeting to observe and to contribute as an adviser to the Committee.

- Professor Tom Treasure, VTE Guideline Development Group

C NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and

a project manager.

Dr Ruaraidh Hill and Prashanth Kandaswamy

Technical Leads

Dr Helen Chung

Technical Adviser

Chris Feinmann

Project Manager

Appendix B: Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by the School of Health and Related Research, University of Sheffield:

- Holmes M, Carroll C, Papaioannou D, Dabigatran etexilate for the prevention of venous thromboembolism in patients undergoing elective hip and knee surgery: A Single Technology Appraisal, May 2008.

B. The following organisations accepted the invitation to participate in this appraisal. They were invited to comment on the draft scope. Organisations listed in I were also invited to make written submissions. Organisations listed in II gave their expert views on dabigatran by providing a written statement to the Committee. Organisations listed in I and II have the opportunity to appeal against the final appraisal determination.

I) Manufacturer/sponsor:

- Boehringer Ingelheim (dabigatran)

II) Professional/specialist and patient/carers groups:

- Anticoagulation Europe
- British Association for Surgery of the Knee
- British Haematology Society
- British Orthopaedic Association
- British Society for Haemostasis and Thrombosis
- British Thoracic Society
- DVT Awareness Campaign
- Lifeblood: The Thrombosis Charity
- Royal College of Nursing

- Royal College of Pathologists
- Royal College of Physicians

III) Other consultees

- Department of Health
- Welsh Assembly Government

IV) Commentator organisations (did not provide written evidence and without the right of appeal)

- Department of Health, Social Services and Public Safety for Northern Ireland
- GlaxoSmithKline (fondaparinux sodium)
- National Collaborating Centre for Acute Care
- National Coordinating Centre for Health Technology Assessment
- NHS Quality Improvement Scotland
- Pfizer (dalteparin sodium)
- sanofi-aventis (enoxaparin sodium)
- School of Health & Related Research Sheffield (SchARR)

C. The following individuals were selected from clinical specialist and patient advocate nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on dabigatran by providing oral evidence to the Committee.

- Professor Roger Atkins, consultant orthopaedic surgeon, nominated by the British Orthopaedic Association – clinical specialist
- Mrs Diane Eaton, nominated by Anticoagulation Europe (ACE) – patient expert

Changes after publication

February 2014: implementation section updated to clarify that dabigatran etexilate is recommended as an option for the prevention of venous thromboembolism after hip or knee replacement surgery. Additional minor maintenance update also carried out.

March 2012: minor maintenance

About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

This guidance was developed using the NICE [single technology appraisal](#) process.

The recommendations from this guideline have been incorporated into a [NICE Pathway](#). We have produced a [summary of this guidance for patients and carers](#). Tools to help you put the guidance into practice and information about the evidence it is based on are also [available](#).

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

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