NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

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

Premeeting briefing

This briefing presents major issues arising from the manufacturer's submission (MS), Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that although condensed summary information is included for ease of reference, this briefing should be read in conjunction with the full supporting documents.

The manufacturer was asked to provide clarification in March 2008, including:

- **Further description of the methods used for systematic review, and the mixed treatment comparison meta analysis.**
- **Information on pricing variations and justification of differences in data inclusion between clinical- and cost-effectiveness sections.**
- **Further analysis using all available efficacy and safety data; meta analysis using random effects and fixed effect models; revised mixed treatment comparison and results of economic evaluation using these revised inputs.**

Licensed indication

Dabigatran etexilate (Pradaxa, Boehringer Ingelheim Ltd) is indicated for the primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

Key issues for consideration

- Is the evidence base on clinical effectiveness of dabigatran etexilate sufficient for hip and knee indications? Particularly with respect to:
  - robustness of the evidence of non-inferiority of 220 mg relative to low molecular weight heparin (LMWH) (when also considering data from RE-MOBILIZE)
  - RCT data suggesting lower efficacy and similar safety of the 150-mg dose relative to LMWH
  - robustness of the evidence for superior effectiveness of fondaparinux (based on results of mixed treatment comparison) presented in the MS.
- What are the Committee's considerations on the relevance of data from RE-MOBILIZE to the clinical and cost effectiveness of dabigatran etexilate in the NHS?
- Noting that the cost effectiveness of dabigatran etexilate is highly sensitive to small changes in assumptions for clinical effectiveness does the Committee consider that there is sufficient evidence for dabigatran etexilate to be a treatment option for use in the NHS?
- The results of the manufacturer's economic evaluation include ICERs indicating dabigatran etexilate to be potentially cost saving, but less effective compared to fondaparinux; how might the Committee consider these results?

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	Adults undergoing elective hip or knee replacement surgery
Intervention	Dabigatran etexilate: • Hip replacement: 220 mg once daily (half dose on day 1). • Knee replacement: 220 mg once daily (half dose on day 1). • Special populations (people with renal impairment, the elderly and people using amiodarone): 150 mg once daily (half dose on day 1).
Comparators	• LMWH – direct evidence. • Fondaparinux – indirect comparison (mixed treatment comparison).
Outcomes	• Mortality. • Incidence of deep vein thrombosis (DVT). • Incidence of pulmonary embolism (PE). • Adverse effects of treatment including bleeding events (minor and major). • Post-DVT complications including post-thrombotic syndrome. • Length of hospital stay. • Health-related quality of life. • Joint outcomes (medium and long term), including joint infection. Bleeding complications (either fatal or non-fatal) are assumed to resolve within the acute phase, with the exception of intracranial haemorrhage, which will have long-term impacts on costs and quality of life. Joint outcomes were not presented in the MS.
Economic evaluation	Cost-utility analysis results as incremental cost per quality-adjusted life year (QALY). Time horizon – lifetime (due to chronic nature of some of the complications of venous thromboembolism [VTE]). Perspective – NHS and Personal Social Services.
Other issues	Separate analysis presented of cost effectiveness for patients undergoing elective hip or knee surgery.

1.2 Evidence Review Group comments

1.2.1 Population

The ERG indicated that the manufacturer's decision problem appropriately defined the population as adults undergoing elective total hip replacement or total knee replacement surgery.

1.2.2 Intervention

The ERG considered that the decision problem matches the marketing authorisation for dabigatran etexilate (an orally administered direct thrombin inhibitor). The group noted that there is limited clinical experience of using dabigatran etexilate in special populations.

1.2.3 Comparators

The ERG acknowledged that LMWH and fondaparinux are appropriate comparators for dabigatran etexilate. Both are administered by subcutaneous injection.

1.2.4 Outcomes

Consideration of joint outcomes (medium and long-term, including joint infection) was omitted from the MS. The manufacturer stated that this was because the pivotal clinical trials did not routinely report this particular outcome. The ERG confirmed this.

1.2.5 Economic evaluation

The ERG noted that the MS included modelling in the acute phase (10 weeks) and longer term (up to 60 years after surgery). The ERG observed that this time horizon may not be justified given that the starting age of patients in the model was 69 years. Sensitivity analyses were performed for shorter time periods.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

2.1.1 Trials of dabigatran etexilate

The systematic review included three randomised, active-controlled parallel-group, non-inferiority trials of dabigatran etexilate (each including two dosing regimes) versus LMWH (enoxaparin). These trials were RE-NOVATE, RE-MODEL and RE-MOBILIZE.

Elective total hip replacement indication was studied in:

- **RE-NOVATE**: pivotal; multicentre; dabigatran etexilate 150 mg or 220 mg once daily (started 1–4 hours after surgery) versus 40 mg LMWH once daily (started the day before surgery) continued for 28–35 days; n = 3613.

Elective total knee replacement indication was studied in:

- **RE-MODEL**: pivotal; multicentre; dabigatran etexilate 150 mg or 220 mg once daily (started 1–4 hours after surgery) versus 40 mg LMWH once daily (started the day before surgery) continued for 6–10 days; n = 2183
- **RE-MOBILIZE**: described as 'supporting North American'; multicentre; dabigatran etexilate 150 mg or 220 mg once daily (started 6–12 hours after surgery) versus 30 mg LMWH twice daily (started 12–24 hours after surgery) continued for 12–15 days; n = 3016.

The primary efficacy outcome for all three trails was a composite of total incidence of VTE (proximal and distal DVT based on venogram[1] 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.

[1] Venography scheduled on days 28–35 (RE-NOVATE), 6–10 (RE-MODEL) and 12–15 (RE-MOBILIZE) and assessed by adjudication committees masked (blinded) to treatment allocation.

In the pivotal trials (RE-NOVATE and RE-MODEL), at 150- or 220-mg doses, the primary outcome demonstrated non-inferiority to LMWH (40 mg). In RE-MOBILIZE dabigatran etexilate was found to be inferior to LMWH (30 mg twice daily). The MS stated that the primary outcome was 'uncharacteristically low' in the LMWH comparator group, resulting in outcomes favouring the comparator.

The 150-mg dose has a UK marketing authorisation for use in special populations such as elderly people and those with moderate renal impairment. Subgroup analyses indicated that the 150-mg dose may be less effective than the 220 mg dose in these groups, in terms of primary efficacy outcome. Safety outcomes were not reported for subgroups.

Adverse events were not significantly different between those receiving dabigatran etexilate and those receiving LMWH. The MS reported that incidence of liver toxicity was similar in dabigatran etexilate and LMWH groups in the three included studies. There were no cases of severe liver toxicity considered to be associated with dabigatran etexilate use.

2.1.2 Meta-analysis

The MS included a series of meta-analyses (relative risk [RR] and absolute risk difference [RD], using fixed effect and random effects models). The MS also included analysis of a secondary efficacy endpoint (major VTE or VTE-related events, including VTE-related mortality). It stated that this endpoint may be more clinically relevant.

Below, the terms 'reduced' and 'higher' are used to describe the direction of effect calculated in the meta-analysis (quoted from the MS), but none are statistically significant.

Results of random effects meta-analysis indicated that for:

- Dabigatran etexilate at a 220-mg dose (RE-NOVATE, RE-MODEL), rates of VTE or all-cause mortality were reduced (RR 0.95, 95% confidence interval [CI] 0.82 to 1.10; RD –0.01, 95% CI –0.03 to 0.01) compared with

LMWH (40 mg). Secondary efficacy endpoints were also reduced for dabigatran etexilate (RR 0.70, 95% CI 0.51 to 1.14; RD –0.01, 95% CI –0.02 to 0.00). These results indicate dabigatran etexilate is not inferior to LMWH.

- Dabigatran etexilate at a 150-mg dose (RE-NOVATE, RE-MODEL), rates of VTE or all-cause mortality were higher (RR 1.11, 95% CI 0.97 to 1.27; RD 0.02, 95% CI 0.00 to 0.04) compared with LMWH (40 mg). Secondary efficacy endpoints were higher for dabigatran etexilate (RR 1.09, 95% CI 0.76 to 1.56) or indistinguishable (RD 0.00, 95% CI –0.01 to 0.02) depending on statistic used. These results are within the margin for dabigatran etexilate to be considered non-inferior to LMWH.

Bleeding outcomes were not statistically different between dabigatran etexilate (at either 220 mg or 150 mg) and LMWH. Differences in rates between dabigatran etexilate at either dose and between dabigatran etexilate LMWH were numerically very small.

Results of random effects meta-analysis indicated that for:

- Dabigatran etexilate at a 220-mg dose (RE-NOVATE, RE-MODEL), rates of major bleeds were higher (RR 1.24, 95% CI 0.75 to 2.05) or indistinguishable (RD 0.00, 95% CI 0.00 to 0.01) compared with LMWH (40 mg). For clinically relevant or minor bleeds, rates were indistinguishable (RR 1.00, 95% CI 0.84 to 1.20; RD 0.00, 95% –0.02 to 0.02).
- Dabigatran etexilate at a 150-mg dose (RE-NOVATE, RE-MODEL), rates of major bleeds were higher (RR 0.88, 95% CI 0.51 to 1.52) or indistinguishable (RD 0.00, 95% CI -0.01 to 0.01) compared with LMWH (40 mg). For clinically relevant or minor bleed rates were higher (RR 1.05, 95% CI 0.89 to 1.25; RD 0.01, 95% CI –0.01 to 0.03) compared with LMWH (40 mg).

2.1.3 Mixed treatment comparison

In a mixed-treatment comparison, dabigatran etexilate compared favourably with other interventions (such as aspirin and mechanical treatments) in people

undergoing surgery and at risk of DVT. Exceptions were extended duration LMWH and fondaparinux. Some comparisons presented in the MS were not within the scope of decision problem. The manufacturer presented these as further evidence of the comparative efficacy and safety of dabigatran etexilate. Data for fondaparinux appeared to be based on one study. In the MS, it was suggested that the design of the study resulted in very low VTE rates for fondaparinux.

2.2 Evidence Review Group comments

Clinical evidence included in the MS was limited to the two pivotal trials, but according to the ERG was of reasonable methodological quality and was appropriate to UK clinical practice. Data from a third trial (RE-MOBILIZE), using an alternative regime for the comparator, was analysed at the request of the ERG. Dabigatran etexilate appeared comparatively less effective in this third study. The ERG noted, however, that the RE-MOBILZE study may not be comparable to UK clinical practice.

The ERG criticised the quality assessment methods employed in the MS and presented their own assessment using a tool for non-inferiority studies (ERG report, table 6).

The ERG noted that the mixed treatment comparisons appeared to use data directly from a recent meta-analysis (conducted by the National Collaborating Centre for Acute Care). The ERG commented that the efficacy and safety of dabigatran etexilate were comparable with those of LMWH (enoxaparin) and that dabigatran etexilate (220- or 150-mg dose) could be less effective than fondaparinux. The ERG commented that the reporting of the mixed treatment comparison was unclear. It also noted that it was not possible to determine the relative efficacies of fondaparinux and dabigatran etexilate from the results presented (ERG report, section 4.2.2, page 51).

2.3 Statements from professional/patient groups and nominated experts

Patient experts agreed that convenience of oral therapy, limited interactions with food and reduced need to attend healthcare centres were key advantages of dabigatran etexilate.

Clinical specialists identified that the choice between VTE prevention strategies was subject to debate. Specialists stated pharmaceutical prevention strategies carry the risk of bleeding and therefore a balance with VTE prevention should be maintained. It was suggested that even a low volume bleed could have very serious implications, as could joint infections. Specialists agreed that no (or minimal) additional inputs from healthcare professionals would be necessary for people taking dabigatran etexilate, as there is no need for assistance with administration (in contrast to LMWH, at least initially), nor for monitoring (in contrast to warfarin or heparin). It was suggested that oral administration (without professional input) was particularly advantageous for continued treatment post discharge and may support compliance with treatment compared with other methods.

Specialists noted that asymptomatic VTE was a surrogate outcome and the clinical relevance of this may be open to challenge and that all cause death was of primary relevance. One specialist referred to evidence from the National Joint Register suggesting higher rates of death from non-VTE causes associated with pharmacological treatment compared with other treatments. These included death due to gastrointestinal bleed or effects of withdrawal of contradicted drugs. It was also suggested that with pharmacological prophylaxis surgeons my change practice; potentially minimising bleeds, but extending operation time, delaying patient mobilisation and so increasing underlying VTE risk.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

The economic evaluation comprised an acute-phase decision-tree model to 10 weeks post-surgery and a chronic-phase Markov model with a lifetime (60-year) time horizon. The models compared dabigatran etexilate with LMWH and fondaparinux for both hip and knee replacements.

The acute-phase model predicted health states based on evidence from phase III trials for dabigatran etexilate compared with LMWH and a mixed treatment comparison for dabigatran etexilate compared with fondaparinux. At 10 weeks, patients entered a 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 VTE recurrence rates obtained from the literature.

The health states in the long-term model were: well; asymptomatic untreated VTE states (proximal DVT, distal DVT and PE); treated VTE states for patients 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 (due to intracranial bleed); or dead.

The acquisition cost of dabigatran etexilate was quoted in the MS (proposed NHS list prices) as £21.00 (for 10 capsules) and £126.00 (for 60 capsules); pack prices are identical for 75-mg and 110-mg capsules. The cost per dose quoted in the MS was £4.20. Based on these data, for knee replacement the drug acquisition cost was calculated to be £42.00 (based on treatment duration of 10 days). The acquisition cost for hip replacement was £117.60–£147.00 (based on treatment duration of 28–35 days). The MS calculated the average cost per dose of LMWH as £4.03 and fondaparinux as £6.66. A zero cost of 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 in hip or knee indications, respectively.

The economic evaluation estimated that at 220 mg, dabigatran etexilate economically dominated LMWH for both hip and knee indications; at the lower dose of 150 mg, dabigatran etexilate dominated LMWH for the hip indication, but was dominated by LMWH for the knee indications. In sensitivity analyses none of the univariate parameters resulted in a significant difference to the base-case results.

The economic evaluation estimated that at both doses, dabigatran etexilate is less cost effective than fondaparinux in hip replacement. The costs per QALY gained are £11,111 and £6,857 for both doses of dabigatran etexilate (the ERG points out 'these ICERs are in the south/west quadrant of the cost-effectiveness plane'). In knee replacement dabigatran etexilate at both doses is dominated by fondaparinux. In sensitivity analysis, increasing the RR of VTE for fondaparinux resulted in dabigatran etexilate dominating in hip replacement and being less costly, but less effective in knee replacement. Increasing the RR of major bleed for fondaparinux resulted in dabigatran etexilate being less costly and less effective. Reducing the duration of fondaparinux therapy (from 33 to 7 days; see table 50, ERG Report) resulted in an ICER of £9,088 for dabigatran etexilate.

Results of deterministic and probabilistic analyses using base case assumptions (summarised by the ERG) are presented in table 1, appendix B of this briefing. Probabilistic sensitivity analysis and examination of cost-effectiveness acceptability curves suggested high probabilities of dabigatran etexilate being cost effective compared with LMWH (at a willingness to pay threshold range of £20,000–30,000), except for the 150-mg dose in knee replacement. Points appear in the 'south west' quadrant of the probabilistic sensitivity analysis scatter plots for the 150-mg dose in hip replacement, indicating that there is a chance that dabigatran etexilate may be less

effective, but cost saving. Compared with fondaparinux, there appeared to be a low probability of dabigatran etexilate being cost effective.

3.2 Evidence Review Group comments

The model structure was appropriate and assumptions were reasonable. Health states included were considered appropriate, although ERG noted that previously published models included progression from distal to proximal DVT, which the manufacturer's model did not. Alternative effectiveness data were incorporated into the model by the manufacturer as requested by the ERG. The univariate sensitivity analysis was extensive and performed with appropriate parameters. The probabilistic sensitivity analysis was performed correctly.

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 supplementary RE-MOBILIZE trial produced such a change in direction of results, where dabigatran etexilate became dominated by LMWH).

Some parameters used in the modelling process appear to be incorrect (for example, the RR for dabigatran etexilate versus fondaparinux in hip replacement; underlying risk of DVT was used incorrectly for VTE in the comparison with fondaparinux; recurrence rates for VTE events considered were incorrect). The impact of these errors was not assessed by the ERG.

3.3 Further considerations following premeeting briefing teleconference

- How might the Committee take account of variation in acquisition cost of the technologies due to locally negotiated procurement discounts?
- Results presented in the MS indicate dabigatran etexilate is less cost effective than fondaparinux in hip replacement and is dominated by

fondaparinux in knee replacement. Does the Committee consider that these estimates of cost effectiveness may change significantly if considering:

- different rates of bleeding associated with the comparator
- different patterns in locally negotiated procurement discounts
- different durations of treatment, given the difficulties in providing extended fondaparinux for the duration modeled (such as administration by subcutaneous injection and adherence).

4 Authors

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Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A The evidence review group (ERG) report for this appraisal was prepared by the School of Health and Related Research (ScHARR), at the University of Sheffield:

- Holmes M, Carroll C and 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 Submissions or statements from the following organisations:

I Manufacturer/sponsor

- Boehringer Ingelheim Ltd

II Professional/specialist, patient/carer and other groups:

- Anticoagulation Europe
- British Orthopaedic Association
- British Society for Haematology and Royal College of Pathologists
- British Society for Haemostasis and Thrombosis
- Royal College of Nursing

Appendix B: Cost effectiveness results

Results using manufacturer's base case assumptions	**Deterministic**	**Probability cost effective at threshold:**	
		£20,000/QALY	**£30,000/QALY**
Dabigatran etexilate compared with LMWH in total hip replacement patients			
Dabigatran etexilate 220 mg			
Incremental cost	–£99	99%	98%
Incremental QALYs	0.010		
ICER	Dabigatran etexilate dominant		
Dabigatran etexilate 150 mg			
Incremental cost	–£83	76%	71%
Incremental QALYs	0.001		
ICER	Dabigatran etexilate dominant		
Dabigatran etexilate compared to LMWH in total knee replacement patients			
Dabigatran etexilate 220 mg			
Incremental cost	–£18	82%	82%
Incremental QALYs	0.011		
ICER	Dabigatran etexilate dominant		
Dabigatran etexilate 150 mg			
Incremental cost	£20	38%	39%
Incremental QALYs	–0.002		
ICER	Dabigatran etexilate was dominated		
Dabigatran etexilate compared to fondaparinux in total hip replacement patients			
Dabigatran etexilate 220 mg			
Incremental cost	–£200	40%	35%
Incremental QALYs	–0.018		
ICER	Dabigatran etexilate lower costs, lower QALY gained		
Dabigatran etexilate 150 mg			
Incremental cost	–£192	32%	27%
Incremental QALYs	–0.028		
ICER	Dabigatran etexilate lower costs, lower QALY gained		

Results using manufacturer's base case assumptions	Deterministic	Probability cost effective at threshold:	
		£20,000/QALY	£30,000/QALY
Dabigatran etexilate compared to fondaparinux in total knee replacement patients			
Dabigatran etexilate 220 mg			
Incremental cost	£16	0%	0%
Incremental QALYs	–0.016		
ICER	Dabigatran etexilate dominated		
Dabigatran etexilate 150 mg			
Incremental cost	£25	0%	0%
Incremental QALYs	–0.019		
ICER	Dabigatran etexilate dominated		

ICER, incremental cost-effectiveness ratio; LMWH, low molecular weight heparin; QALY, quality-adjusted life year