Dabigatran etexilate for the prevention of venous thromboembolism in patients undergoing elective hip and knee surgery: a single technology appraisal

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Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of dabigatran etexilate (DBG) for the prevention of venous thromboembolism (VTE) in patients undergoing elective hip and knee surgery based upon a review of the manufacturer's submission to the NICE as part of the single technology appraisal (STA) process. The submission's evidence came from three reasonable-quality trials comparing DBG with enoxaparin, and a comparison of DBG with fondaparinux based on the relative efficacy and safety as derived from a mixed treatment comparison (MTC) meta-analysis. DBG (220 mg and 150 mg once daily) is not inferior to enoxaparin (40 mg once daily and 30 mg twice daily) in terms of major VTE or VTE-related events (secondary outcome). Meta-analysis shows that 220 mg DBG is not inferior to enoxaparin (40 mg once daily or 30 mg twice daily) in reducing total VTE and all-cause mortality (primary outcome) in total hip or knee replacement, whereas there is uncertainty around the clinical effectiveness of 150 mg DBG for this outcome. In the MTC analysis DBG compared favourably with the other interventions, with the exception of extended enoxaparin and fondaparinux. The adverse event profile was not significantly different in those receiving DBG and those receiving enoxaparin.

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The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

The submitted two-phase economic model compares DBG with enoxaparin and fondaparinux in total hip and knee replacement. The model structure is appropriate and the model assumptions are reasonable. The health states, costs, utilities and recurrence rates used are considered to be appropriate for the required analysis. The model estimated that at the licensed dose of 220 mg once daily DBG dominates enoxaparin in both total hip replacement and total knee replacement and that at the lower dose of 150 mg once daily DBG dominates enoxaparin in total hip replacement and enoxaparin dominates DBG in total knee replacement. DBG is less cost-effective than fondaparinux in total hip replacement at both doses; the cost per quality-adjusted life-year of fondaparinux versus DBG is £11,111 and £6857 for the higher and lower doses of DBG respectively. In total knee replacement, both DBG doses are dominated by fondaparinux. For DBG versus all comparators in all cases the cost-effectiveness results are based on small incremental cost and health benefits. Weaknesses of the submitted evidence include that methods used for screening studies, data extraction and applying quality assessment criteria to included studies, as well as key details of trials included in the MTC, were not adequately described. In addition, some input parameters into the modelling process are incorrect. The ERG was unable to correct all of these mistakes and the impact on the model results is therefore unknown. The National Institute for Health and Clinical Excellence guidance issued as a result of the STA states that DBG is recommended as an option for the primary prevention of VTE events in adults who have undergone elective total hip or knee replacement surgery.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, for which most of the relevant evidence lies with one manufacturer or sponsor.[1] Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA of dabigatran etexilate for the prevention of venous thromboembolism in patients undergoing elective hip and knee surgery.[2]

Description of the underlying health problem

Venous thromboembolism (VTE) is the formation of a blood clot (thrombus) in a vein, which may dislodge from its site of origin to cause an embolism. Most thrombi occur in the deep veins of the legs; this is called deep vein thrombosis (DVT). Dislodged thrombi may travel to the lungs; this is called a pulmonary embolism (PE) and can be fatal. Thrombi can also cause long-term morbidity due to venous insufficiency and post-thrombotic syndrome, potentially leading to venous ulceration.

Recurrence of DVT is common. Studies have shown that up to 30% of patients who have experienced an acute DVT will experience one or more recurrences over the following 10–15 years.[3–5]

Total hip or knee replacement surgery is a strong risk factor for VTE. In the absence of thromboprophylaxis the risk of developing a DVT after a primary total hip replacement and after a primary total knee replacement is 50% and 60% respectively.[6]

Mortality due to VTE is significant. Long-term follow-up of patients who have experienced an episode of VTE (usually acute DVT) has shown that there is a high mortality rate over the subsequent 10–15 years.[3,5,7,8]

PE has a high mortality rate with 13% proving fatal in elderly patients 1 month after onset[9] and 17.5% within 3 months.[10]

The National Joint Registry for England and Wales recorded 61,456 hip replacement procedures, of which 10% were revisions or reoperations, and 60,986 knee replacement procedures, of which 8% were revisions or reoperations, undertaken between 1 January and 31 December 2006.[11]

Scope of the ERG report

The objective of the appraisal is to evaluate the clinical effectiveness and cost-effectiveness of dabigatran etexilate (DBG) within its licensed indication for the prevention of VTE after elective hip or knee replacement surgery in adults. The comparators are enoxaparin (a low-molecular-weight heparin) and fondaparinux.

In total hip replacement, the recommended standard dose of DBG is 110 mg within 1–4 hours of surgery, continuing with 220 mg daily thereafter for a total of 28–35 days. In total knee replacement, the recommended standard dose is 110 mg within 1–4 hours of surgery, continuing with 220 mg daily thereafter for a total of 10 days. A reduced dose of 150 mg once a day is recommended for special populations: those aged 75 years and older, those with moderate renal impairment and those taking amiodarone.

The outcomes measured are mortality, incidence of DVT, incidence of PE, post DVT complications including post-thrombotic syndrome, length of hospital stay, health-related quality of life and adverse effects of treatment including bleeding events (minor and major).

The comparison with enoxaparin is based on the evidence from two pivotal head-to-head DBG phase III clinical trials: RE-NOVATE[12] in a total hip replacement population and RE-MODEL[13] in a total knee replacement population. There are no head-to-head trials comparing DBG with fondaparinux. This comparison is based on the relative efficacy and safety as derived from a mixed treatment comparison (MTC) meta-analysis.

The economic evaluation presented a cost–utility analysis with cost-effectiveness expressed in terms of incremental cost per quality-adjusted life-years (QALYs). Given the potential chronic nature of some complications arising from VTE, the time horizon of the model was lifetime. Costs were considered from an NHS and personal social services perspective.

Methods

The ERG report comprised a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process.

The only additional work undertaken by the ERG was a series of meta-analyses on the primary safety outcomes. There was no difference between DBG and enoxaparin in any of these outcomes.

The ERG requested the manufacturers to repeat the cost-effectiveness analysis with the inclusion of the RE-MOBILIZE study,[14] a second trial in a total knee replacement population. The inclusion of the RE-MOBILIZE study reverses the results, from DBG dominating to DBG being dominated for both dosages. However, the manufacturers do not believe that the RE-MOBILIZE study is generalisable to the England and Wales setting. It is their opinion that these analyses are therefore inappropriate for this submission. The ERG's clinical advisors agree with this opinion.

Results

Summary of submitted clinical evidence

The main evidence in the submission is derived from three head-to-head, phase III, multi-arm, randomised, double-blind, controlled, non-inferiority trials (RE-NOVATE, RE-MODEL and RE-MOBILIZE). These trials compared the efficacy and safety of DBG at doses of 220 mg and 150 mg once daily with that of enoxaparin [40 mg once daily in RE-NOVATE and RE-MODEL, 30 mg twice daily in RE-MOBILIZE] in patients undergoing total knee replacement (RE-MODEL and RE-MOBILIZE) or total hip replacement (RE-NOVATE). Follow-up was 12–14 weeks.

DBG (at both 220 mg once daily and 150 mg once daily) does not appear to be inferior to enoxaparin (40 mg once daily and 30 mg twice daily) in terms of the secondary efficacy outcome of major VTE or VTE-related events.

The meta-analysis of the primary efficacy outcome across all three trials, and across combinations of these trials, appears to show that the intervention DBG at a dose of 220 mg once daily was not inferior to the comparator enoxaparin (at either 40 mg once daily or 30 mg twice daily) in reducing levels of total VTE and all-cause mortality among patients undergoing total hip replacement and total knee replacement.

Evidence from post hoc subgroup analyses of the included trials indicates that the 150-mg once daily dose may be less effective in terms of incidence of total VTE and all-cause mortality than the 220-mg

once daily dose in the special populations indicated for this lower dose and for whom the lower dose is specifically licensed. Safety outcomes were not reported for these subgroups.

The meta-analysis of the RE-MODEL and RE-NOVATE trials appears to show that the 150-mg once daily dose of DBG is not inferior to the comparator enoxaparin (at either 40 mg once daily or 30 mg twice daily) in reducing levels of total VTE and all-cause mortality among patients undergoing total hip replacement and total knee replacement.

The meta-analyses of the two total knee replacement trials combined (RE-MODEL and RE-MOBILIZE) and the three total knee replacement and total hip replacement trials combined (RE-NOVATE, RE-MODEL and RE-MOBILIZE) appear to show that the 150-mg once daily dose of DBG is inferior to the comparator enoxaparin (at both 40 mg once daily and 30 mg twice daily) in reducing levels of total VTE and all-cause mortality among patients undergoing total hip replacement and total knee replacement.

An MTC analysis compared the results of these trials of DBG with results for all other available interventions for patients undergoing surgery and at risk of DVT and found that DBG compared favourably with the other interventions, with the exception of extended enoxaparin and fondaparinux, which appear to be relatively more effective (level of statistical significance of difference not reported).

The adverse event profile was not significantly different in those receiving DBG compared with those receiving enoxaparin. The primary safety end point was major bleeding. Clinically relevant bleeding, any bleeding and liver function were also measured (secondary end points).

Summary of submitted cost-effectiveness evidence

The model developed by Boehringer Ingelheim has an acute phase that starts at the time of surgery and ends at 10 weeks post surgery and a chronic phase with a lifetime horizon. The model compares DBG with enoxaparin and fondaparinux in both total hip replacement and total knee replacement. The acute phase model is a decision tree which predicts the health states that patients will be in at 10 weeks based on evidence from phase III trials of DBG compared with enoxaparin and from an MTC of DBG compared with fondaparinux. At 10 weeks patients enter a chronic phase Markov model in the same health state in which they terminated the decision tree model. No further treatment effect is applied in the chronic phase model. Transition between states in the chronic phase model is dependent on VTE recurrence rates obtained from the literature.

The health states, costs, utilities and recurrence rates used within the model are considered to be appropriate for the required analysis.

The Boehringer Ingelheim model estimated that:

- at the licensed dose of 220 mg once daily DBG dominates enoxaparin in both total hip replacement and total knee replacement
- at the lower dose of 150 mg once daily DBG dominates enoxaparin in total hip replacement and enoxaparin dominates DBG in total knee replacement
- DBG is less cost-effective than fondaparinux in total hip replacement at both doses of DBG. The cost/QALY of fondaparinux versus DBG is £11,111 and £6857, respectively, for the higher and lower doses of DBG.
- In total knee replacement, both DBG doses are dominated by fondaparinux.

Table 1 presents a summary of the cost-effectiveness results. For DBG versus all comparators it should be noted that in all cases the cost-effectiveness results are based on small incremental cost and health benefits.

Commentary on the robustness of submitted evidence

Strengths

The manufacturer conducted a limited, but systematic search for clinical and cost-effectiveness studies of DBG for the prevention of VTE in patients undergoing total knee replacement and total hip replacement. It appears unlikely that any additional trials would have met the inclusion criteria had the search been widened to include more free-text terms or to include other databases.

The three identified trials, which represent the main clinical efficacy evidence, were of reasonable methodological quality, with some limitations, and measured a range of outcomes that were appropriate and clinically relevant.

TABLE 1 *Summary of deterministic and probabilistic sensitivity analysis results*

		Probability cost-effective at threshold:	
	Deterministic	**£20,000/QALY**	**£30,000/QALY**
DBG compared with enoxaparin in THR patients			
DBG 220 mg			
Incremental cost	–£99	99%	98%
Incremental QALYs	0.010		
ICER	DBG dominant		
DBG 150 mg			
Incremental cost	–£83	76%	71%
Incremental QALYs	0.001		
ICER	DBG dominant		
DBG compared with enoxaparin in TKR patients			
DBG 220 mg			
Incremental cost	–£18	82%	82%
Incremental QALYs	0.011		
ICER	DBG dominant		
DBG 150 mg			
Incremental cost	£20	38%	39%
Incremental QALYs	–0.002		
ICER	DBG dominated		
DBG compared with fondaparinux in THR patients			
DBG 220mg			
Incremental cost	–£200	40%	35%
Incremental QALYs	–0.018		
ICER	£11,111[a]		
DBG 150mg			
Incremental cost	–£192	32%	27%
Incremental QALYs	–0.028		
ICER	£6857[a]		
DBG compared with fondaparinux in TKR patients			
DBG 220 mg			
Incremental cost	£16	0%	0%
Incremental QALYs	–0.016		
ICER	DBG dominated		
DBG 150 mg			
Incremental cost	£25	0%	0%
Incremental QALYs	–0.019		
ICER	DBG dominated		

DBG, dabigatran etexilate; ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life-year(s); THR, total hip replacement; TKR, total knee replacement.
a Note that this ICER is in the 'south/west' quadrant of the cost-effectiveness plane.

The meta-analyses demonstrated the non-inferiority of DBG 220 mg once daily versus enoxaparin in terms of the efficacy and safety end points, and acknowledged the apparent inferiority of the 150-mg once daily dose in terms of the primary efficacy outcome.

An MTC analysis compared DBG with all other available interventions for patients undergoing surgery and at risk of DVT and found that DBG compared favourably with the other interventions, with the exception of extended low-molecular-weight heparins and fondaparinux, which appear to be more effective.

The model structure is appropriate and allows sensitivity analysis to be carried out easily.

The model assumptions are reasonable.

The univariate sensitivity analysis is extensive and is performed on appropriate parameters.

The probabilistic sensitivity analysis is performed correctly.

Weaknesses

The processes undertaken by the manufacturer for screening studies, data extraction and applying quality assessment criteria to included studies were not made explicitly clear in the submission. These factors limit the robustness of the systematic review.

Quality assessment of the included studies should have been undertaken using a checklist appropriate to the types of study included (non-inferiority randomised trials).

One of the trials used in the clinical effectiveness section is published only as an abstract (RE-MOBILIZE); much of the key data employed are unpublished.

A simple pooled analysis of the patient level data from the two pivotal trials, as well as all three head-to-head trials, was reported. However, the methods used for this data pooling were not described; the statistical approach for combining the data appears to be inappropriate as it fails to preserve randomisation and introduces bias and confounding. The resulting pooled data should therefore be treated with caution.

Elements of the MTC reported in the manufacturer's submission are reproduced from documents produced by organisations other than the manufacturer, rather than specifically in response to the scope. The key details of trials included in the MTC, and issues relating to heterogeneity of trials, are neither reported nor discussed. The resulting MTC should therefore be treated with caution.

The economic results for DBG compared with enoxaparin in total hip replacement and total knee replacement both rely on one trial each. These trials indicate that DBG is not inferior to enoxaparin. The small numerical difference seen in these trials is reproduced in the model in terms of both incremental costs and incremental health benefits (see *Table 1*). A small change in the direction of the trial results could significantly change the cost-effectiveness conclusions.

The economic results for DBG versus fondaparinux in total hip replacement are based on one study for which the manufacturer appears to have used an incorrect relative risk estimate. However, the difference is small and the impact on the results is likely to be small.

VTE recurrence rates, post-thrombotic syndrome rates and quality of life utilities used in the model are based on a literature review limited to economic studies. It is therefore possible that non-economic studies reporting these data in sources such as MEDLINE have not been identified.

Some input parameters into the modelling process are incorrect. These include using the underlying risk of DVT instead of the underlying risk of VTE for the comparison of DBG with fondaparinux, wrongly estimating the recurrence rates for VTE, wrongly estimating the probability of PE being severe, not including intensive care unit costs in PE post discharge and including the cost of informal care when it should be excluded. The ERG was unable to correct all of these mistakes and the impact on the model results is therefore unknown.

Conclusions

Key issues

The external validity of the evidence is limited. Only a single randomised controlled trial (RCT) using a comparator and dose applied in England and Wales has been conducted on each of the relevant total hip replacement and total knee replacement populations. The addition of evidence from any future RCTs may alter the results regarding the non-inferiority of DBG. Small changes in key parameters could markedly alter

the conclusions with respect to cost and clinical effectiveness.

The results of the RE-MOBILIZE total knee replacement trial indicate that both the 220-mg once daily and the 150-mg once daily dose of DBG are inferior to enoxaparin in terms of the primary efficacy outcome of total VTE and all-cause mortality. When the pivotal trials (RE-MODEL and RE-NOVATE) are combined with this trial in a meta-analysis the 150-mg once daily dose of DBG is found to be inferior to enoxaparin in terms of the primary efficacy outcome. The 150-mg once daily dose may therefore not be suitable for use in the special populations indicated. Post hoc subgroup analyses for total VTE and all-cause mortality conducted on the special populations indicated also suggest that this dose may be less effective than the 220-mg once daily dose in terms of the primary efficacy outcome.

The economic results for DBG compared with enoxaparin in total hip replacement and total knee replacement both rely on one trial each. These trials indicate that DBG is not inferior to enoxaparin. Although at the licensed dose of 220 mg once daily DBG dominates enoxaparin, a small change in the direction of the trial results could significantly alter the cost-effectiveness conclusions.

The cost-effectiveness analysis based on a meta-analysis of the RE-MODEL plus the RE-MOBILIZE trials reverses the direction of the results, that is, DBG is now dominated by enoxaparin for both doses. However, it is the manufacturer's opinion that the RE-MOBILIZE study is not generalisable to the England and Wales setting. This is also the opinion of the clinical advisors to the ERG.

Areas of uncertainty

There is uncertainty around the clinical effectiveness and cost-effectiveness of DBG compared with other relevant treatments included in the scope, especially fondaparinux and standard and extended low-molecular-weight heparins other than enoxaparin, especially with respect to the 150-mg once daily dose. The 150-mg once daily dose may be less effective than the 220-mg once daily dose for the special populations for whom this lower dose is licensed.

The economic results for DBG compared with enoxaparin in total hip replacement and total knee replacement both rely on one trial each. The small numerical difference seen in these trials is reproduced in the model in terms of both incremental costs and incremental health benefits. The conclusions of the cost-effectiveness analysis could be significantly changed with only a small change in the direction of the trial results.

Summary of NICE guidance issued as a result of the STA

At the time of writing, the final appraisal determination issued by NICE on 21 July 2008 states that:

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.

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