RIVAROXABAN FOR THE PREVENTION OF VENOUS THROMBOEMBOLISM

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[redacted]

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[redacted]

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1 SUMMARY

1.1 Scope of the submission

The Manufacturer's Submission (MS) generally reflects the scope of the appraisal issued by NICE, and is appropriate to the NHS. The MS reports on the use of rivaroxaban (Xarelto ®) for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery. The MS considered enoxaparin, a low molecular-weight heparin (LMWH), as the most relevant comparator, as reflected in the scope. A weighted comparison against all LMWHs was presented as a sensitivity analysis assuming equal efficacy between all LMWHs. Indirect comparisons with dabigatran (which NICE has recommended as an option for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip surgery or elective total knee replacement surgery) were undertaken. Fondaparinux was not considered in the submission as it does not reflect routine clinical practice, as agreed during the scoping phase. The outcome measures identified in the scope were all relevant and the majority of these efficacy outcomes (mortality, incidence of symptomatic and asymptomatic VTE, pulmonary embolism (PE)), and safety outcomes (bleeding events), were reported. However, outcomes relating to knee and hip joints, although identified in the scope, were not reported.

1.2 Summary of submitted clinical effectiveness evidence

- The main clinical evidence in the submission is derived from four head-to-head, phase III, two-arm, randomised, double blind, controlled trials. RECORD 1 and RECORD 2 were in a population undergoing total hip replacement (THR) whilst RECORD 3 and RECORD 4 were in a population undergoing total knee replacement (TKR). The duration of treatment and dosage varied across trials. RECORD 1 compared 10mg once daily (od) of rivaroxaban for 35 days with 40mg od of enoxaparin for 35 days; RECORD 2 compared 10mg od of rivaroxaban for 35 days with 40mg of enoxaparin od for 13 days; RECORD 3 compared 10mg od of rivaroxaban for 12 days with 40mg od of enoxaparin od for 12 days trials for 14 days, whilst RECORD 4 compared 10mg od of rivaroxaban for 12 days with enoxaparin 30mg twice daily (bid). Follow-up was 30 (+5) days after last treatment with study drug.

- Analysing total VTE (a primary outcome measure of the RCTs) it was seen that in each of the four trials rivaroxaban produced [redacted]. When all four RCTs were meta-analysed a [redacted] using a random effects model. Note we present results from fixed effects model where heterogeneity was not statistically significant and from random effects models otherwise.

- When the effect on symptomatic VTEs only were analysed, [redacted] When all four trial were meta-analysed using a fixed effect model a [redacted] between rivaroxaban and enoxaparin was obtained.

- Analysing non-fatal PE (a primary outcome measure of the RCTs) it was seen that in [redacted] This result remained when all trials were meta-analysed using a random effects model [redacted] The point estimate [redacted] Data on fatal PE showed that in all RCTs there were [redacted] The relative difference point estimate [redacted]

- Data on a final primary outcome measure (all cause mortality) was not presented, or meta-analysed. Commercial-in-confidence data on fatal PE was provided. The ERG has inferred that there were no other deaths bar those from PE.

- Data on major bleeding was presented for each RCT. Individually there was no statistically significant difference in major bleed rates between patients receiving rivaroxaban and enoxaparin, although all point estimates favoured enoxaparin treatment. On meta-analysing all four RCTs, the results [redacted] An

indirect comparison of rivaroxaban against dabigatran was undertaken, using the four rivaroxaban versus enoxaparin RCTs and the three RCTs of dabigatran versus enoxaparin. (RENOVATE, RE-MODEL and RE-MOBILIZE) RENOVATE was conducted in a population undergoing THR whilst RE-MODEL and RE-MOBILIZE were conducted in patients undergoing TKR. All comparisons between rivaroxaban and dabigatran used random effects models.

- Analysing trials of THR only (RECORD1, RECORD2 and RENOVATE) rivaroxaban was shown [redacted] compared with dabigatran. There was [redacted] major bleeding [redacted] although the point estimate [redacted]

- [redacted].

- The safety profile of rivaroxaban is comparable to that of enoxaparin, with no significant difference in any adverse event found. On meta-analysing all four RCTs there was a trend towards [redacted] Compared with dabigatran, [redacted]

1.3 Summary of submitted cost effectiveness evidence

- The manufacturer submitted a model in Microsoft Excel. The model was divided into a prophylaxis stage (a period of 35 days for THR and 12 days for TKR), a

post-prophylaxis stage (until 3 months after surgery) and a long-term complication stage (assumed to end when a patient died or became 101 years of age). The initial two stages were assessed using a decision tree, whereas the third phase was divided into a five year period, where VTE, PTS or death could occur, followed by a duration where only transitions to death were allowed

- The model was designed to facilitate cost-effectiveness analyses between rivaroxaban and a comparator (either enoxaparin or dabigatran) under a number of scenarios, which were using individual trial data, pooling data based on the population (THR or TKR) or pooling all data.

- The base case in the MS assumed that only those parameters that were statistically significantly different would be varied between rivaroxaban and the comparator. Using a comparator of enoxaparin, a reduction in total VTE was assumed for all analyses, whereas symptomatic VTE was reduced or not dependent on the scenario chosen. The rates of non-fatal PE and major bleeding episodes were set equivalent for both interventions. [redacted] Using a comparator of dabigatran, only the rates of total VTE were assumed to vary between treatment, with rivaroxaban having a reduced rate of total VTE.

- In the base case analyses rivaroxaban was shown to dominate (i.e. produce more QALYs at a lower cost) than both enoxaparin and dabigatran. The incremental costs saved and QALYs gained were small (typically below £200 and 0.005 respectively per person).

- Further results were presented, following a request by the ERG to conduct analyses sampling the distributions of efficacy observed from the RCTs (or indirect comparison with dabigatran) regardless of statistical significance. In such circumstances the results were firmly driven by the assumed impact on fatal PE. Unfortunately this parameter was not correctly included in the probabilistic sensitivity analyses, which rendered the uncertainty generated in the remaining parameters as largely redundant. The PSA results using the actual data produced different results than those when only parameters with a statistically significant difference were used. Rivaroxaban still dominated enoxaparin in all scenarios, except those using data from RECORD 4 alone (TKR), and when the results of RECORD 3 and 4 (both TKR) were pooled. Using RECORD 4 alone, enoxaparin produces more QALYs than rivaroxaban and has a incremental cost

per QALY of approximately £5,000; using the pooled results this value becomes approximately £8,000. These results imply that enoxaparin was more cost-effective than rivaroxaban in both of these scenarios using current recommended thresholds.
(http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf)

- When dabigatran is used as the comparator, rivaroxaban dominates dabigatran when RECORD 1 individually, RECORD 2 individually, or the pooled results from RECORD 1 and RECORD 2 are compared with RENOVATE and all when all four rivaroxaban RCTs are pooled compared with all three dabigabtran RCTs. Dabigatran dominates rivaroxaban using RECORD 4 compared with RE-MODEL and RE-MOBILIZE, and is more cost-effective than rivaroxaban using RECORD 3 compared with RE-MODEL and RE-MOBILIZE (an incremental cost per QALY of rivaroxaban compared with dabigatran of approximately £123,000) and when RECORD 3 and RECORD 4 are pooled and compared with RE-MODEL and RE-MIBOLIZE (an incremental cost per QALY of dabigatran compared with rivaroxaban of approximately £400).

1.4 Commentary on the robustness of submitted evidence

1.4.1 Strengths

- The searches were good, demonstrating use of relevant keywords and MeSH/thesaurus terms to describe the main elements of the question (intervention, population, comparison and outcome) along with appropriate filters to identify high quality evidence e.g. systematic reviews and randomised controlled trials.

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

- The meta-analyses demonstrated the non-inferiority of rivaroxaban versus enoxaparin in terms of all efficacy and safety endpoints, and the superiority of rivaroxaban for total VTE and symptomatic VTE.

- Following dialogue iterations with the ERG team, the resultant Excel file is a reasonable model of patients receiving prophylaxis for THR or TKR.

1.4.2 Weaknesses

- One of the trials used in the clinical effectiveness section is published only as an abstract (RECORD 4). However, the ERG have no reason to doubt the validity of the results presented.

- The probabilistic sensitivity analyses did not capture all the uncertainty present within the decision. The number of total VTE for rivaroxaban is assumed to equal the rates observed in the appropriate RCT(s). The number of total VTEs in the comparator arm are appropriately calculated by sampling from the relative risk of total VTE compared with rivaroxaban. For both rivaroxaban and the comparator the proportion of total VTEs that are symptomatic, non-fatal and fatal are fixed at the rates observed in the appropriate RCTs. These are relatively small numbers. For example, in RECORD 1 there were 18 VTE of which 4 were non-fatal PE. Fixing the proportion of non-fatal PE to 0.22 (4/18) of total VTE will result in considerable uncertainty being excluded compared with a more appropriate approach of sampling this value from a Beta distribution

- The long-term effects of major bleeding, in particular those that are intracranial, have been excluded from the model. In response to this criticism the manufacturer conducted an external calculation that showed that were 5% of patients who bleed to immediately die from an intracranial haemorrhage that rivaroxaban would still produce more QALYs than enoxaparin. The ERG has conducted a similar calculation for comparison with dabigatran, with similar conclusions.

- Following the post-prophylaxis stage of the model all VTE events are assumed to be DVT. This is conservative and will be unfavourable to the intervention that has the lowest number of VTEs, which is generally rivaroxaban.

- The utility of a patient is set to that of a 50-year old, and does not decline as the simulated patient ages. This will favour the intervention that has the greater estimated number of patients alive following the post-prophylaxis stage. The manufacturer conducted additional analyses to assess the impact of altering the underlying utility: with only a minor reduction in the incremental QALYs gained associated with rivaroxaban. The manufacturer's conclude that the inaccuracy introduced by not altering the utility will be small. The ERG agree with this conclusion.

- The initial model had a number of internal consistencies. These have been corrected to the satisfaction of the ERG.

1.4.3 Areas of uncertainty

- The ERG note that the rates of fatal PE have a considerable effect on the results which are much greater than those associated with other parameters. This is shown in Table 1, where the results from univariate sensitivity analyses are reported using the results from RECORD 4 alone. For each parameter the middle value is the midpoint estimate. The alternative estimates are the 95% confidence intervals reported in the MS.

Table 1. Univariate Sensitivity analyses on the results for RECORD 4.

Record 4: Adjusting bleed (RR)

value	0.78	2.47	7.86
Delta C	-56.95	-50.62	-48.62
Delta Q	-0.0093	-0.0097	-0.0096

Record 4: Adjusting VTE (RR)

value	0.51	0.69	0.92
Delta C	-54.83	-50.62	-47.53
Delta Q	-0.0095	-0.0097	-0.0099

Record 4: Adjusting symptomatic VTE (RR)

value	0.29	0.6	1.27
Delta C	-81.58	-50.62	-35.59
Delta Q	-0.0081	-0.0097	-0.0106

Record 4: Adjusting non-fatal PE (RD)

value	-0.01	-0.003	0.004
Delta C	-56.58	-50.62	-44.38
Delta Q	-0.0099	-0.0097	-0.0096

Record 4: Adjusting Fatal PE (RD)

- [redacted]

[redacted]

- It is unclear how the inclusion of PE events (both fatal and non-fatal) beyond the post-prophylaxis stage of the model would affect the results. The ERG note that the exclusion of future PE events is likely to be unfavourable to rivaroxaban.

1.5 Key issues

- The ERG believes that the MS represents a reasonable estimation of the cost-effectiveness of rivaroxaban against enoxaparin and dabigatran. The exclusion of intracranial bleeds is likely to be favourable to rivaroxaban; however the exclusion of secondary PEs will be favourable to the comparators. It is unclear which of these excluded parameters would have most impact on the results. The manufacturer has subsequently shown that the incorporation of intracranial bleed is not likely to markedly influence the results.

- A number of scenarios are reported, which are associated with different conclusions on the cost-effectiveness of rivaroxaban in TKR. Which scenario is most appropriate will depend on whether those parameters where there is not statistically significant differences are set equal for both rivaroxaban and the comparator and whether outcomes can be appropriately pooled across all studies. It is seen that the rate of fatal PE is the main driver of results in the model, however the ERG does not believe there is evidence to allow differential rates across interventions to be assumed. [redacted]

[redacted]

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

- The manufacturer's description of the underlying health problem is adequate and generally relevant to the submission. It is stated that there are approximately 25,000 deaths each year due to venous thromboembolism in England.[1] It is further stated that this figure includes not only those undergoing surgery but those admitted to hospital for the medical care of serious illnesses. Therefore, the reported 25,000 deaths each year may be misleading when describing the extent of the health problem associated with only total hip replacement and total knee replacement surgery. No indication of the number of deaths due to VTE associated only with elective hip and knee replacement surgery is provided. The MS also indicates that there is increasing evidence that extended prophylaxis (up to 35 days) significantly reduces VTE in total hip replacement procedures.[2,3,4] The MS uses four clinical trials, collectively known as the RECORD trials: RECORD 1,[5,] RECORD 2,[6] RECORD 3 [7] and RECORD 4 [8] to examine the effectiveness of rivaroxaban against enoxaparin. Due to the design of the RECORD RCTs the MS has compared rivaroxaban treatment of 35 days duration in THR and 14 days in TKR, with enoxaparin durations of at least 14 days. The decision problem compares the use of rivaroxaban compared with either 35 days or 14 days of enoxaparin. The ERG's clinical advisors have indicated that due to the intravenous method of delivery enoxaparin is generally discontinued after discharge from hospital (approximately 6 days). However the MS reports sensitivity analyses on this variable, analysing a scenario that is extremely unfavourable to rivaroxaban, which assumes that the efficacy of enoxaparin remains constant, whilst the intervention costs decrease. The ERG believes that this approach is sufficient to address the shorter duration of enoxaparin seen in current UK practice.

2.2 Critique of manufacturer's overview of current service provision

- The manufacturer's overview of current service provision is adequate although further detail is required. In particular the submission acknowledges a number of reasons for a disparity between clinical guidelines for the use of chemical prophylaxis and actual practice, such as safety issues around bleeding, and a

trade off between safety and efficacy, and the use of agents that are not recommended such as aspirin. The numbers of individuals currently using enoxaparin, or dabigatran is not given.

- There is no discussion in this section surrounding the disparity between recommended duration of chemical prophylaxis and current clinical practice. Although, this issue is acknowledged in later sections.

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF THE DECISION PROBLEM

- The ERG has no major concerns with the manufacturer's definition of the decision problem.

3.1 Population

- The manufacturer's statement of the decision problem appropriately defines the population as adults undergoing elective total hip replacement (THR) or total knee replacement (TKR) surgery.

3.2 Intervention

- Rivaroxaban (Xarelto ®) manufactured by Bayer Schering Pharma is an oral, direct factor Xa inhibitor, which is marketed as an intervention to prevent thromboembolism in patients undergoing THR or TKR. The recommended dose is one10 mg tablet taken once daily, with a duration of 5 weeks for patients undergoing THR and for 2 weeks in patients undergoing TKR. It is anticipated that rivaroxaban will be prescribed and initiated whilst the patient is in hospital and the course of treatment will be completed post discharge.

3.3 Comparators

- The chosen parameters are enoxaparin, which is taken to be indicative of low molecular weight heparin, and dabigatran a direct inhibitor of the enzyme thrombin that has been recommended for use in patients undergoing THR or TKR. (http://www.nice.org.uk/nicemedia/pdf/DabigatranFAD.pdf) The ERG has no concerns with these choices of comparators.

3.4 Outcomes

- The majority of the key clinical outcomes are considered within the model. These are VTEs, PTS, mortality and bleeds. The ERG comments that intracranial bleeds have been omitted from the model and that all VTEs beyond the post-prophylaxis period are assumed to be DVTs, which will underestimate the morbidity associated with future PEs.

3.5 Time frame

- The ERG considers that the time horizon of the model (until either a patient is dead or reaches 101 years) is appropriate for this decision problem.

3.6 Other relevant factors

- The ERG has listed all concerns in the previous and in the following sections.

4 CLINICAL EFFECTIVENESS

4.1 Critique of manufacturer's approach

4.1.1 Description of manufacturers search strategy and comment on whether the search strategy was appropriate.

The searches undertaken by the manufacturer to identify all relevant randomised controlled trials (RCTs) were conducted in April 2008. The manufacturer followed the same search strategy used by the National Institute of Clinical Excellence (NICE) in their publication of guidelines for VTE prophylaxis.[9] The search strategy utilises terms to identify the patient group (Age 18 and above, undergoing elective hip or knee replacement, hip fracture), the intervention and comparators (rivaroxaban, enoxaparin, dabigatran), and type of study (Phase III, single or double blind RCT). Phase II studies, open-label studies, dose-ranging studies and non-English language references were excluded.

The search strategy was judged to be effective in identifying relevant literature relating to the question and showed use of relevant search techniques for systematic review and appraisal.

Searches were only conducted from 2006 onwards as NICE guidelines had covered previous years and this was an appropriate strategy to adopt. Also, the earliest papers (looking at rivaroxaban) from the Medline database are from 2006.

Five databases were searched (Medline, Embase, Cinahl, The Cochrane Library including NHS EED, and Health Economic and Evaluations Database (HEED)). This was adequate to identify the majority of the literature relating to the question.

Hand searches were also conducted of abstracts from key orthopaedic surgery / haematology conferences (American Society of Hematology (ASH) (http://www.hematology.org); British Orthopaedic Associated (BOA) (http://www.boa.ac.uk); http://www.clinicaltrials.gov) and from the reference lists of relevant articles identified in the database searches. No search strategies were supplied regarding the above. However, given that the search engines of these databases/websites only allow for very simple searching this was not a cause for concern.

4.1.2 Statement of the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

Details of the inclusion and exclusion criteria, as reported in the MS, are reproduced in Table 2. (Appendix 10.2, table 10.2.6, p.17, MS).

Table 2. Study Inclusion and Exclusion Criteria

	Inclusion criteria*	Exclusion criteria
Patient Group	Patients; • Aged 18+ • Undergoing elective hip or knee replacement, hip fracture.	Patients; • undergoing bilateral joint surgery in same procedure or within 2 weeks.** • with active bleeding, acute bacterial endocarditis, congenital or acquired bleeding, ulceration or angiodysplastic gastrointestinal disease, haemorrhagic stroke, brain, or spinal, ophthalmic surgery in past 3 months, catheter (indwelling, epidural or intrathecal) during treatment period, more than 2 attempts in achieving spinal epidural anaesthesia** • with sensitivity to heparin, LMWH, porcine products or iodinated contrast medium, contraindication to anticoagulant therapy, addictive disorders, serum creatinine above 180 mmol/L and platelet count below 100 x 10^9 /L.** • with anticoagulant therapy for other co-morbid disorders.**
Design / Method	Phase III studies. Single or Double blind RCT. Two groups differ only in terms of thrombophylactic method.	Failure in concealment of group allocation, non-random method of allocation, Use of historical controls, confounding by another factor e.g. co-morbidity
Intervention	enoxaparin, , rivaroxaban, dabigatran. Differences in duration of intervention not a reason for exclusion so long as follow up is same for both groups.	Phase I or II Dose ranging study, VTE prophylactic intervention combined with another intervention, e.g. other anti-coagulant. However intervention allowed to be combined with compression stockings and physiotherapy.
Outcomes	Primary outcomes: DVT and PE objectively determined (e.g. venography, fibrinogen labelled iodine, plethysmography, duplex ultrasound scanning,	DVT identified only through clinical signs ands symptoms

	thermography, or labelled plasmin. PE determined by lung scans, angiography or post mortem) and counted if occurred during treatment period. Secondary outcomes: Safety	

*Same as with the NICE guideline (NICE 2007) **Standard exclusion criteria; source Turpie et al. 2002[10]

The inclusion/exclusion criteria appear to be appropriate, they include appropriate detail and a rationale for the inclusion and exclusion criteria is provided as a footnote to the table.

4.1.3 Table of identified studies. What studies were included in the submission and what were excluded.

The MS identifies four direct head-to-head, phase III, randomised, blinded, trials (RECORD 1,[5] RECORD 2,[6] RECORD 3,[7] RECORD 4[8]). RECORD 1 and RECORD 2 were conducted in patients undergoing THR, whilst RECORD 3 and RECORD 4 were conducted in patients undergoing TKR. RECORD 1, RECORD 2 and RECORD 3 used the U.K dosing of the comparator enoxaparin, whilst RECORD 4 utilised the U.S dosing of enoxaparin. RECORD 4 is only published as an abstract, however summarised data from this trial was provided to the ERG.

A total of six individual RCTs comparing rivaroxaban with other therapies as a prophylaxis for VTE were identified from the systematic review. Of these six citations, two were correctly excluded as they were phase II, dose-ranging studies. The remaining four studies, the RECORD trials, were included. Details of the study design and patient characteristics of the RECORD trials are summarised in Table 3.

For the purposes of the indirect comparison analyses three trials comparing dabigatran at two different doses (150mg od, 220mg od) with enoxaparin were included in the MS. The 220mg od dose was used for the indirect comparisons. These trials were, RENOVATE,[11] which was conducted in a population undergoing THR and RE-MODEL[12] and RE-MOBILIZE[13] which were conducted in patients undergoing TKR. The search term dabigatran was included and the three trials were identified from the systematic review. A description of the dabigatran trials is provided in section 4.2.

The ERG does not believe that the exclusion criteria for the RECORD trials and the RENOVATE, RE-MODEL and RE-MOBILIZE trials are sufficiently different to prohibit comparison.

Table 3. Design and Patient Characteristics of the RECORD trials.

Study	Design	Participants	Interventions (n=randomised)	Outcomes	Duration (planned)
RECORD 1[5]	Phase III, Multicentre (n=NR), 27 countries worldwide, randomised, double-blind, active comparator controlled, parallel group, double-dummy, trial (n=4541) in Europe, Australia, South America, North America, South Africa.	▪ Patients scheduled to undergo elective total hip arthroplasty. ▪ Male and female patients of 18 years or older. ▪ Patients who provided written informed consent for study participation.	T1: rivaroxaban 10mg tablet o.d., 6-8 hours after wound closure, every 24 hours until day 35 (n=2266). T2: enoxaparin sodium 40mg subcutaneous injection o.d, 12 hours before surgery and restarted 6-8 hours after would closure then every 24 hours until day 35. (n=2275)	Primary efficacy endpoint: ▪ Composite of any deep-vein thrombosis (proximal or distal), nonfatal pulmonary embolism, or death from any cause. Secondary endpoints: ▪ Major VTE (incidence of the composite endpoint comprising proximal DVT, non-fatal PE and VTE-related death). ▪ Incidence of symptomatic VTE (DVT, PE) during treatment and follow-up (at 65 days). ▪ Incidence of DVT (total, proximal,	35 days of treatment then follow-up 30-35 days after the last does of the study drug.

Study	Design	Participants	Interventions (n=randomised)	Outcomes	Duration (planned)
				distal) ▪ Incidence of treatment-emergent bleeding observed not later than 2 days after last intake of study drug.	
RECORD 2[6]	Phase III, Multicentre (n=123), 21 countries worldwide, randomised, double-blind, active comparator controlled, parallel group, double-dummy, trial (n=2509) in Europe, Australia, New Zealand, South America, North America, Asia, South Africa.	As RECORD 1	T1: rivaroxaban 10mg tablet o.d., 6-8 hours after wound closure, every 24 hours until day 31-39 (n=1252). T2: enoxaparin sodium 40mg subcutaneous injection o.d, 12 hours before surgery and restarted 6-8 hours after would closure then every 24 hours until day 10-14 (n=1257)	As RECORD 1	31-39 days of treatment in T1, 10-14 days of treatment in T2. Then follow-up 30-35 days after the last does of the study drug.
RECORD 3[7]	Phase III, Multicentre (n=147), 19 countries worldwide, randomised, double-blind, active comparator controlled,	▪ Patients scheduled to undergo elective total knee	T1: rivaroxaban 10mg tablet o.d., 6-8 hours after wound closure, every 24 hours until day	As RECORD 1.	10-14 days of treatment. Then follow-up 30-35 days after the last does of

Study	Design	Participants	Interventions (n=randomised)	Outcomes	Duration (planned)
	parallel group, double-dummy, trial (n=2531) in Europe, South America, North America, Asia, South Africa.	arthroplasty. ▪ Male and female patients of 18 years or older. ▪ Patients who provided written informed consent for study participation.	10-14 (n=1254). T2: enoxaparin sodium 40mg subcutaneous injection o.d, 12 hours before surgery and restarted 6-8 hours after would closure then every 24 hours until day 10-14 (n=1277)		the study drug.
RECORD 4 (abstract)[8]	[redacted]	[redacted]	[redacted]	As RECORD 1	[redacted]

4.1.4 Details of any relevant studies that were not included in the submission

Repeat searches were performed by the ERG using the Manufacturer's search terms, no additional relevant trials were identified.

The searches performed by the manufacturer were examined by the ERG and found to be satisfactory. The ERG is confident that all relevant studies were included in the MS and details of ongoing trials that are likely to be reporting additional evidence within 12 months were reported.

4.1.5 Description and critique of manufacturers approach to validity assessment

The reasons provided for excluding studies were all justified.

The critical appraisal of the trials included in the MS appears to be based on the full details of the trials, rather than the published details, therefore, it is difficult for the ERG to verify all details. The RECORD 4[8] trial is currently published only as an abstract. The trials details and full results are those reported in the MS, rather than an independently peer-reviewed paper. The validity assessment of the RECORD 4 trial performed by the ERG is therefore based on the trial as it is reported in the MS.

The MS reports on efforts to ensure blinding, but does not report if any of these studies assessed the success of blinding, as required by point 11 on the CONSORT checklist (http://www.consort-statement.org/). The assessment of the ERG is that such assessments were not undertaken.

The majority of participants included in the four RECORD trials are not from the U.K. However, the ERG are satisfied that the data can be generalised to a U.K population.

The ERG considered the validity assessment performed by the manufacturer and found that the MS had answered the questions suggested by NICE for validity assessment. The ERG then assessed the validity of the three published trials (RECORD 1,[5] RECORD 2,[6] and RECORD 3[7]) and the trial information for RECORD 4,[8] contained in the MS. The validity of the trials was found to be satisfactory, and of adequate methodological quality.

4.1.6 Description and critique of manufacturers outcome selection

The main outcome measures selected by the manufacturer were the primary efficacy endpoint (total VTE and all-cause mortality), symptomatic VTE, non-fatal PE, Fatal

PE and major bleeding. Joint outcomes were not measured as outcomes in any of the trials and were therefore not included in the MS, despite being included as an outcome measure in the final scope issued by NICE.

4.1.7 Describe and critique the statistical approach used

The MS used the Modified intention-to-treat (MITT) population in the analyses of the trials. The MITT was defined as the number of patients who were 1) valid for safety analysis; and 2) had the appropriate surgery; and 3) had an adequate assessment of thromboembolism. The ERG judged this to be an appropriate approach.

The MS contained a series of meta-analyses. The meta-analysis of all of the RECORD trials was performed on five outcomes; primary efficacy endpoint (total VTE and all-cause mortality), symptomatic VTE, non-fatal PE, and major bleeding. The measure of difference used was relative risk (RR) for VTE, symptomatic VTE and major bleeding, and risk difference (RD) for PE events. Each comparison was conducted using a fixed effects model, if heterogeneity was observed between studies, a random effects model was performed. This approach is not theoretically correct as a decision on whether a fixed or random effects model is most appropriate should be made prior to analysis, but this methodology does not materially affect the conclusions.

The main clinical evidence in the submission is derived from four head-to-head, phase III, two-arm, randomised, double blind, controlled trials (RECORD 1, RECORD 2, RECORD 3, and RECORD 4). RECORD 1 and RECORD 2 were in a population undergoing total hip replacement (THR) whilst RECORD 3 and RECORD 4 were in a population undergoing total knee replacement (TKR). The duration of treatment and dosage varied across trials. RECORD 1 compared 10mg once daily (od) of rivaroxaban for 35 days with 40mg od of enoxaparin for 35 days; RECORD 2 compared 10mg od of rivaroxaban for 35 days with 40mg of enoxaparin od for 13 days; RECORD 3 compared 10mg od of rivaroxaban for 12 days with 40mg od of enoxaparin od for 12 days trials for 14 days, whilst RECORD 4 compared 10mg od of rivaroxaban for 12 days with enoxaparin 30mg twice daily (bid). Follow-up was 30 (+5) days after last treatment with study drug.

Analysing total VTE (a primary outcome measure of the RCTs) it was seen that in all four trials (RECORD 1, RECORD 2, RECORD 3, and RECORD 4) rivaroxaban [redacted] compared with enoxaparin. Combining all four trials produced a

[redacted] when using a random effects model due to heterogeneity.

Analysing the effect on symptomatic VTEs, only RECORD 2 and RECORD 4 [redacted]. When all four RCTs were meta-analysed a [redacted] with rivaroxaban was obtained. This meta-analysis used a fixed effect model as no significant heterogeneity was observed.

Analysing non-fatal PE (a primary outcome measure of the RCTs) it was seen that in none of the RCTs was the rate between rivaroxaban and enoxaparin significantly different. This result remained when all trials were meta-analysed in a random effects model. [redacted] The point estimate [redacted] Data on fatal PE showed that in all RCTs [redacted]

Additional analyses were presented to explore the heterogeneity across the four RECORD trials. The MS considered two sources of this heterogeneity; the duration of enoxaparin administration in RECORD 2 was not equal to the rivaroxaban administration, and the enoxaparin dose regimen (30mg bid) in RECORD 4 did not match that of the other three trials (40mg od). This was investigated in two ways, an influence analysis and a meta-regression. The influence analysis investigated the influence of a single study on the overall meta-analysis estimate by computing the pooled estimated without each study of interest in turn. The meta-regression extends a random effects meta-analysis to estimate the extent to which one or more covariates, with values defined for each study in the analysis explain heterogeneity in the treatment effects. These analyses demonstrated that the inclusion of RECORD 2 or RECORD 4 did not introduce a significant bias in the pooled meta-analysis of all RECORD trials.

Further additional analyses were employed pooling the studies by indication. RECORD 1 and RECORD 2 for total hip replacement (THR) and RECORD 3 and RECORD 4 for total knee replacement (TKR). Each meta-analysis was performed on the five outcomes used in the overall meta-analysis; primary efficacy endpoint

(total VTE and all-cause mortality), symptomatic VTE, non-fatal PE, and major bleeding. The measure of difference used was relative risk (RR) for VTE, symptomatic VTE and major bleeding, and risk difference (RD) for PE events. Each comparison consisted of one fixed effects model, if heterogeneity was observed between studies, a random effects model was performed.

The ERG are of the opinion that the use of meta-analysis followed by the additional analyses were appropriate, however the inclusion of forest plots within the submission would have eased interpretation.

An indirect comparison of rivaroxaban against dabigatran was undertaken, using the four rivaroxaban versus enoxaparin RCTs and the three RCTs of dabigatran versus enoxaparin. Meta-regression analysis was used for these indirect comparisons. The meta-regression approach extends a random-effects meta-analysis to estimate the degree to which one or more covariates account for differences between treatment effects. Type of treatment was considered a covariate and no other covariates were considered. The measure of difference used was relative risk (RR) for VTE, symptomatic VTE and major bleeding, and risk difference (RD) for PE events, as in previous analyses. The ERG did not deem that this methodology was inappropriate.

Analysing trials of THR only (RECORD1, RECORD2 and RENOVATE) [redacted].

It is the opinion of the ERG that the submitted evidence reflects satisfactorily the decision problem defined in the submission.

4.2 Summary of submitted evidence

Four relevant trials (RECORD 1, RECORD 2, RECORD 3, and RECORD 4) were identified in the effectiveness section of the MS. The RECORD 1 study (rivaroxaban n=2266; enoxaparin n=2275) was a phase III, two-arm, randomised, double-blind, multi-centre trial comparing the efficacy and safety of rivaroxaban (10mg od) with enoxaparin (40mg od) in patients undergoing elective THR. Duration of treatment was 31-39 days. The RECORD 2 trial (rivaroxaban n=1252; enoxaparin n=1257) was a phase III, two-arm, randomised, double-blind, multi-centre, trial comparing the efficacy and safety of rivaroxaban (10mg od) with enoxaparin (40mg od) in patients undergoing elective THR. Duration of treatment was 31-39 days. The RECORD 3 trial (rivaroxaban n=1254; enoxparin n=1277) was a phase III, two-arm, randomised, double-blind, multi-centre trial comparing the efficacy and safety of rivaroxaban (10mg od) with enoxaparin (40mg od) in patients undergoing elective TKR. Duration of treatment was 10-14 days. The RECORD 4 trial (rivaroxaban n=1584; enoxparin n=1564) was a phase III, two-arm, randomised, double-blind, multi-centre trial comparing the efficacy and safety of rivaroxaban (10mg od) with enoxaparin (30mg bid) in patients undergoing elective TKR. Duration of treatment was 10-14 days. Follow up was 30-35 days after last study drug for all trials.

For the indirect comparison analysis three relevant trials were identified. The RE-NOVATE study (dabigatran 150mg n=1174; dabigatran 220mg n=1157; enoxaparin n=1162) was a phase III, three-arm, randomised, double-blind, multi-centre trial comparing the efficacy and safety of dabigatran (220mg od), dabigatran (150mg od) with enoxaparin (40mg od) in patients undergoing elective THR. Duration of treatment was 28-35 days. The RE-MODEL trial (dabigatran 150mg n=708; dabigatran 220mg n=694; enoxaparin n=699) was a phase III, three-arm, randomised, double-blind, multi-centre, trial comparing the efficacy and safety of dabigatran (220mg od), dabigatran (150mg od), with enoxaparin (40mg od) in patients undergoing elective TKR. Duration of treatment was 6-10 days. The RE-MOBILIZE trial (dabigatran 150mg n=877; dabigatran 220mg n=862; enoxaparin n=876) was a phase III, three-arm, randomised, double-blind multi-centre trial comparing the efficacy and safety of dabigatran (220mg od), dabigatran (150mg od) with enoxaparin (30mg od) in patients undergoing elective TKR. Duration of treatment was 12-15 days.

4.2.1 Summary of results

This section presents the main clinical efficacy evidence, as reported in the MS.

Efficacy

The clinical evidence for the use of rivaroxaban in the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery is derived from four randomised controlled trials (RCTs), directly comparing rivaroxaban with enoxaparin, the main product currently used in the UK in the same indication.

In RECORD 1, 3, and 4, rivaroxaban was demonstrated to have superior efficacy over enoxaparin after total hip replacement and total knee replacement. RECORD 2 also demonstrated superiority comparing 35 days rivaroxaban versus 12-14 days enoxaparin. Based on the composite primary endpoint of any DVT, non-fatal PE and death from all causes the relative risk reductions were 70-79% in THR and 31-49% in TKR. Rivaroxaban was also demonstrated to have superior efficacy over enoxaparin in RECORD 1, 2 and 3 for the secondary endpoint major VTE. Superior efficacy was also shown for the symptomatic VTE endpoint in RECORD 2 and RECORD 3.

Critique of efficacy data reported

Appropriate analyses and comparisons are included in the MS. Data on the final primary outcome measure (all cause mortality) was not presented, or meta-analysed. The ERG have inferred that this was due to no additional deaths bar fatal PE, the data for which was presented as commercial in confidence.

Safety and tolerability

There were no adverse events that were significantly different between rivaroxaban and enoxaparin. Major bleeding occurred more frequently in patients on rivaroxaban. Individually there was no statistically significant difference in major bleed rates between patients receiving rivaroxaban and enoxaparin, although all point estimates favoured enoxaparin treatment. On meta-analysing all four RCTs, the results remained [redacted]).

[redacted]

([redacted]

Critique of safety data reported

The reporting and interpretation of the safety data is good.

4.2.2 Critique of submitted evidence syntheses

The MS reported the following meta-analyses for both the primary and secondary efficacy outcomes; random and fixed effects models for RR and RD. The ERG has no concerns with the methodology used for the evidence syntheses.

4.2.3 Summary

The manufacturer's search strategy was adequately reported and the submission appears to contain all of the relevant head-to-head RCTs. The outcomes selected were relevant and appropriate, although joint outcomes, included in the final scope issued by NICE, were excluded as none of the trials reported this outcome.

Processes and validation of study screening and data extraction appear to be appropriate. Statistical methods were explicitly described for the meta-analyses and indirect comparisons and all relevant analyses were performed, although reporting of the results of these analyses were limited due to the omission of conclusions or plots to aid interpretation.

The MS appears to contain an unbiased estimate of the treatment effect of rivaroxaban in relation to the relevant outcomes and the comparator, enoxaparin. Overall the evidence from the four RECORD trials in the MS indicates that rivaroxaban 10mg od is not inferior to the comparator enoxaparin in terms of the total VTE and all-cause mortality, symptomatic VTE, non-fatal PE, and fatal PE. Rivaroxaban was also not inferior to the comparator on the safety outcomes of major bleeding.

5 ECONOMIC EVALUATION

5.1 Overview of manufacturer's economic evaluation

Including 1-page summary of structure, assumptions and sources, with signposting to tables with numerical inputs and their distributions where appropriate.

- The manufacturer submitted a model in Microsoft Excel. The model was divided into a prophylaxis stage (a period of 35 days for THR and 12 days for TKR), a post-prophylaxis stage (until 3 months after surgery) and a long-term complication stage (assumed to end when a patient died or became 101 years of age). The initial 2 stages were assessed using a decision tree, whereas the third phase was divided into a 5 year period, where DVT, PTS or death could occur, followed by a period where only transitions to death were allowed. In the basecase all parameters that were not statistically significantly different were set equivalent for rivaroxaban and the comparator. The parameters that were significantly different when pooling all trials when comparing rivaroxaban and enoxaparin were total VTE and symptomatic VTE; only total VTE was significantly different when comparing rivaroxaban and dabigatran. All statistically significant differences favoured rivaroxaban. A number of further scenarios are presented that divide studies into type (THR or TKR) or individual trials. Additional analyses were presented, following a request by the ERG, which incorporated all variables sampling from the relevant distribution regardless of whether statistical significance was achieved. Probabilistic sensitivity analyses were undertaken but initially did not include the probability of a fatal PE.

5.1.1 Natural history

- The experience of patients who receive current treatment (enoxaparin) has been derived from data from the RCTs. The event rates for major bleeds, total VTE, symptomatic VTE, non-fatal PE and fatal PE for rivaroxaban have been assumed, with certainty, to be those reported in the RCTs appropriate for the scenario. The RR of rivaroxaban compared with enoxaparin has been taken from meta-analyses appropriate to the scenario. The RR has been sampled from the relevant confidence interval and used in combination with the values for rivaroxaban to estimate event rates for those patients on enoxaparin or dabigatran. The ERG notes that there is no uncertainty considered in the event rates for rivaroxaban, which will underestimate the uncertainty in the results.

5.1.2 Treatment effectiveness within the submission

- As stated in 5.1.1 the MS does not follow a 'standard' approach of formulating a natural history model and then applying the relative efficacy of the intervention. Instead the MS uses the rates for rivaroxaban and then calculates the incremental changes in costs and QALYs that would occur were the relative risks associated with enoxaparin produced. Whilst ideally this would produce the same answer overall, such a methodology can be prone to bias were the rates of events within the RCT to differ significantly from those observed in a 'real world' setting. The ERG is uncertain regarding the consistency between enoxaparin results within the RECORD RCTs and in the 'real world'.

5.1.3 Health related quality of life

- The utilities used within the model have been taken from a systematic review of VTE related utilities. These are contained in Table 43 on page 96 of the MS. One limitation on the utilities used within the model is that the values used are not adjusted as the patient ages. The utility for people without VTE complications is assumed to be [redacted], which is referenced to Kind et al.[14] However this value is for a 50 year old, and [redacted] at 80 years of age. Within the model the value of [redacted] is assumed to remain constant which will overestimate the benefits of avoiding events. Following a request from the ERG additional analyses were conducted that showed that the reduction in incremental QALYs gained was not large when this problem was addressed.

- The ERG also comment that the state of intracranial haemorrhage, which is associated with a marked disutility, has not been included within the model. This exclusion is favourable to those interventions with a greater risk of major bleeding, which is generally rivaroxaban. Additional analyses were undertaken by the manufacturers that showed that the effect of including intracranial bleeds would not be large even when all patients with an intracranial bleed were assumed to immediately die. The ERG was satisfied that the exclusion of intracranial bleed did not markedly affect the results.

5.1.4 Resources and costs

- The resources and costs used within the model are provided in Table 45 on page 97 of the MS and has been influenced by an economic model produced by NICE.[15] The ERG has little concern with the methodology and sources used, although did ask for sensitivity analyses to be conducted on the cost of PTS; this

analysis was received and was shown to have little effect on the overall cost per QALY.

5.1.5 Discounting

- Both costs and benefits have been discounted at NICE's recommended rates of 3.5% per annum.

5.1.6 Sensitivity analyses

- The sensitivity analyses undertaken in the MS (Table 53 – 55, pages 113-119) for the basecase did not markedly change the results, primarily as variables where there was not a statistically significant difference in the rates were assumed to be equivalent for rivaroxaban and the comparator (enoxaparin). Assuming that enoxaparin prophylaxis was not continued post-discharge had most impact due to the reduction in costs of the comparator, but the cost-effectiveness of rivaroxaban compared with enoxaparin remained within standard thresholds. (http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf) When the observed data was used rather than setting those with non-significant rates to equivalence, there was still little change when the probabilistic sensitivity analyses were conducted. However the key driver of the results (the rate of fatal PE) was excluded from the sensitivity analyses without explanation.

5.1.7 Model validation

- The ERG noted internal errors within the model which were disclosed to the manufacturer. These included incorrect uses of standard error, probabilities becoming negative and some cells being incorrectly cleared. These errors were fixed to the satisfaction of the ERG.

- The ERG highlighted a number of issues regarding the structure of the model. The manufacturer provided evidence that these limitations would not be markedly favourable to rivaroxaban. The ERG were satisfied with these responses.

5.2 Critique of approach used

- The approach adopted appears to be reasonable and has followed the lead from previous models (including one produced by NICE) and taken into consideration guidance provided in the peer-reviewed literature.

5.3 Results included in manufacturer's submission

- The basecase results reported in the MS are provided in Table 56 (page 120) for the comparison with enoxaparin and Table 60 (page 121) for the comparison with dabigatran. In all of the presented scenarios rivaroxaban was shown to dominate the comparator; however the incremental costs were not large (savings of typically £200 per patient) with incremental QALYs gained particularly small (rarely greater than 0.005 per patient)

- On the request of the ERG further analyses were undertaken assuming that parameters with non-statistically significant differences were not set equivalent for rivaroxaban and dabigatran, the results were fundamentally driven by the assumed rates of fatal PE (which were not included in the probabilistic sensitivity analyses). For patients with THR, rivaroxaban still remained dominant but this was not true for patients undergoing TKR. In patients undergoing TKR enoxaparin appears to be more cost-effective when the results from RECORD 4 or the pooled results from RECORD 3 and RECORD 4 are used, as the incremental cost per QALY gained of enoxiparin compared with rivaroxabanis below £10,000. For the indirect comparison, dabigatran was shown to dominate rivaroxaban in RECORD 3. The MS did not present results on RECORD 4 nor the pooled results using RECORD 3 and RECORD 4.

- It is noted that when pooled data is used from all RECORD RCTs that rivaroxaban dominates enoxaparin. The MS does not provide corresponding data regarding dabigatran.

5.4 Comment on validity of results presented with reference to methodology used

- The ERG note that the results presented in the MS are from deterministic analyses. Using probabilistic sensitivity results it is seen that dabigatran rarely dominates rivaroxaban, but that the incremental cost per QALY gained of rivaroxaban compared with dabigatran is high (regularly greater than £100,000).

- There is little comment on interpreting cost per QALY ratios calculated from points in the south-west quadrant of the cost-effectiveness plane. In this quadrant 'standard' criteria regarding meeting cost-effectiveness thresholds are reversed and the intervention must have a value greater than the threshold to be considered cost-effective. The MS fails to note that rivaroxaban is actually less

cost-effective than enoxaparin when using data from RECORD 4, or pooled data from RECORD 3 and 4.

5.5 Summary of uncertainties and issues

- The key driver of the results in the model provided to the ERG is the rates of fatal PE.

[redacted]

- The ERG note that potential events that could significantly effect the conclusions have been excluded from the model. These are the possibility of further VTE events that are not DVT (i.e. fatal and non-fatal PE) in the longer term complication model. The omission of these events will be unfavourable to rivaroxaban.

- The model also excludes the possibility of intracranial haemorrhage, which has a marked effect on utility. An estimate of the proportion of bleeds that are intracranial is 5%.[16] This source also reports a marked effect of intracranial haemorrhage on utility, which equates to a patient losing, on average 71% of their utility. This exclusion will be favourable to rivaroxaban in scenarios where the observed bleeding rates are used in preference to setting the rate of bleeding equal for rivaroxaban and the comparators due to there being no statistically significant difference. The effects of excluding these events on the results have not been quantified however, the manufacturers have provided further evidence that shows that the effect of including intracranial haemorrhage was likely to be limited.

- The conclusions on the cost-effectiveness of rivaroxaban is dependent on the assumptions made regarding parameters that are not statistically significant and on the appropriateness of pooling data. If all parameters where the p-value > 0.05 were set equivalent for rivaroxaban and the comparator, then assuming that all trials are pooled, rivaroxaban dominates the comparators. Where the observed data is used and THR and TKR are pooled separately, rivaroxaban is less cost-effective than dabigatran in TKR. The ERG does not believe that pooling of the data from all trials, or setting those parameters where there is no statistically significant difference to be equivalent, are unreasonable actions.

6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

The most recent model provided by the manufacturer was adapted by the ERG to calculate results from 24 scenarios. These were all combinations of the following:

Comparator: Enoxaparin or dabigatran

Setting: THR and TKR pooled, pooled THR, and pooled TKR

Method: Deterministic or probabilistic sensitivity analyses

Variables assumed to be different between rivaroxaban and comparator: Only those that have a p-value below 0.05 or all variables regardless of statistical significance.

The model structure was adapted so that the proportion of non-fatal PE and fatal PE were not fixed compared with the overall level of VTE but were instead sampled independently. Comparative rates of both non-fatal and fatal PE were expressed as risk differences, which were distributed normally, and combined with the numbers associated with rivaroxaban to estimate those for the comparator. On occasions this methodology would result in negative values associated with the comparator; where this occured the value was set to zero. As the normal distribution was not truncated when rivaroxaban is more efficacious than the comparator, the methodology will be favourable to rivaroxaban.

Note that in the pooled THR and TKR data comparing rivaroxaban with dabigatran the ERG believe there is a typographical error within the model. In the submitted model the midpoint value is [redacted] The ERG believe that the value for the pooled estimate [redacted] and have used this within the calculations.

Comparing rivaroxaban with enoxaparin.

Table 4. Deterministic Analyses – Only statistically significant variables assumed different between rivaroxaban and enoxaparin.

		Rivaroxaban	Enoxaparin (Clexane)	Incremental
THR and TKR	Cost	£160.29	£225.10	-£64.81
	QALY	10.33305	10.33120	0.0019
	ICER	Rivaroxaban dominates		

		Rivaroxaban	Enoxaparin (Clexane)	Incremental
THR	Cost	£195.83	£251.66	-£55.84
	QALY	10.36755	10.36580	0.0018
	ICER	Rivaroxaban dominates		

		Rivaroxaban	Enoxaparin (Clexane)	Incremental
TKR	Cost	£116.60	£180.80	-£64.20
	QALY	10.29811	10.29663	0.0015
	ICER	Rivaroxaban dominates		

In all scenarios rivaroxaban was shown to dominate enoxaparin

Table 5. Deterministic Analyses – All variables assumed different between rivaroxaban and enoxaparin.

		Rivaroxaban	Enoxaparin (Clexane)	Incremental
THR and TKR	Cost	£160.29	£224.69	-£64.40
	QALY	10.33305	10.32902	0.0040
	ICER	Rivaroxaban dominates		

		Rivaroxaban	Enoxaparin (Clexane)	Incremental
THR	Cost	£195.83	£250.19	-£54.36
	QALY	10.36755	10.35777	0.0098
	ICER	Rivaroxaban dominates		

		Rivaroxaban	Enoxaparin (Clexane)	Incremental
TKR	Cost	£116.60	£181.45	-£64.85
	QALY	10.29811	10.30240	-0.0043
	ICER	£15,096.05	per QALY lost	

Rivaroxaban is estimated to dominate enoxaparin when THR and TKR data are pooled, and using THR data only.

When TKR data only are used then enoxaparin is estimated to be more cost-effective (assuming a cost per QALY threshold of £20,000) as it has an incremental cost per QALY gained of £15,000 compared with rivaroxaban.

Table 6. Probabilistic Sensitivity Analyses – Only statistically significant variables assumed different between rivaroxaban and enoxaparin.

		Rivaroxaban	Enoxaparin (Clexane)	Incremental
THR and TKR	Cost	£161.16	£227.88	-£66.73
	QALY	10.33452	10.33257	0.0019
	ICER	Rivaroxaban dominates		

		Rivaroxaban	Enoxaparin (Clexane)	Incremental
THR	Cost	£196.47	£254.10	-£57.63
	QALY	10.36595	10.36411	0.0018
	ICER	Rivaroxaban dominates		

		Rivaroxaban	Enoxaparin (Clexane)	Incremental
TKR	Cost	£117.34	£183.26	-£65.93
	QALY	10.29662	10.29507	0.0016
	ICER	Rivaroxaban dominates		

In all scenarios rivaroxaban was shown to dominate enoxaparin

Assuming a £20,000 per QALY threshold, the estimated probability of rivaroxaban being more cost-effective than dabigatran were 1.000, 1.000 and 1.000 for pooled THR and TKR, THR alone and TKR alone respectively.

Table 7. Probabilistic Sensitivity Analyses – All variables assumed different between rivaroxaban and enoxaparin.

		Rivaroxaban	Enoxaparin (Clexane)	Incremental
THR and TKR	Cost	£161.10	£228.05	-£66.95
	QALY	10.33224	10.32776	0.0045
	ICER	Rivaroxaban dominates		

		Rivaroxaban	Enoxaparin (Clexane)	Incremental
THR	Cost	£196.26	£252.40	-£56.14
	QALY	10.36753	10.35670	0.0108
	ICER	Rivaroxaban dominates		

		Rivaroxaban	Enoxaparin (Clexane)	Incremental
TKR	Cost	£117.86	£184.85	-£66.99
	QALY	10.29687	10.29561	0.0013
	ICER	Rivaroxaban dominates		

Rivaroxaban is estimated to dominate enoxaparin in all scenarios. The TKR results differ from those produced by deterministic analyses, which will be due to the normal distribution associated with differences in fatal PEs being truncated to ensure that the numbers expected in the enoxaparin arm does not become lower than zero. As such the TKR results should be treated with caution.

Assuming a £20,000 per QALY threshold, the estimated probability of rivaroxaban being more cost-effective than dabigatran were 1.000, 1.000 and 0.560 for pooled THR and TKR, THR alone and TKR alone respectively.

Comparing rivaroxaban with dabigatran.

Table 8. Deterministic Analyses – Only statistically significant variables assumed different between rivaroxaban and enoxaparin.

		Rivaroxaban	Dabigatran (Rendix)	Incremental
THR and TKR	Cost	£160.29	£168.44	-£8.14
	QALY	10.33305	10.33197	0.0011
	ICER	Rivaroxaban dominates		

		Rivaroxaban	Dabigatran (Rendix)	Incremental
THR	Cost	£195.83	£236.00	-£40.17
	QALY	10.36755	10.36436	0.0032
	ICER	Rivaroxaban dominates		

		Rivaroxaban	Dabigatran (Rendix)	Incremental
TKR	Cost	£116.60	£116.79	-£0.20
	QALY	10.29811	10.29768	0.0004
	ICER	Rivaroxaban dominates		

In all scenarios rivaroxaban was shown to dominate dabigatran

Table 9. Deterministic Analyses – All variables assumed different between rivaroxaban and dabigatran.

		Rivaroxaban	Dabigatran (Rendix)	Incremental
THR and TKR	Cost	£160.29	£186.33	-£26.04
	QALY	10.33305	10.33324	-0.0002
	ICER	£137,231.58	per QALY lost	

		Rivaroxaban	Dabigatran (Rendix)	Incremental
THR	Cost	£195.83	£236.76	-£40.93
	QALY	10.36755	10.36446	0.0031
	ICER	Rivaroxaban dominates		

		Rivaroxaban	Dabigatran (Rendix)	Incremental
TKR	Cost	£116.60	£117.33	-£0.73
	QALY	10.29811	10.30303	-0.0049
	ICER	£149.04	per QALY lost	

Rivaroxaban is estimated to dominate dabigatran when THR data only are used.

When TKR data only are used, dabigatran is estimated to be more cost-effective (assuming a cost per QALY threshold of £20,000) as it has an incremental cost per QALY gained of less than £1,000 compared with rivaroxaban.

When THR and TKR data are pooled, rivaroxaban is estimated to be more cost-effective (assuming a cost per QALY threshold of £20,000) as dabigatran has an incremental cost per QALY gained of over £130,000 compared with rivaroxaban.

Table 10. Probabilistic Sensitivity Analyses – Only statistically significant variables assumed different between rivaroxaban and dabigatran.

		Rivaroxaban	Dabigatran (Rendix)	Incremental
THR and TKR	Cost	£160.81	£191.40	-£30.58
	QALY	10.33502	10.33271	0.0023
	ICER	Rivaroxaban dominates		

		Rivaroxaban	Dabigatran (Rendix)	Incremental
THR	Cost	£196.61	£260.14	-£63.53
	QALY	10.36995	10.36546	0.0045
	ICER	Rivaroxaban dominates		

		Rivaroxaban	Dabigatran (Rendix)	Incremental
TKR	Cost	£117.38	£122.91	-£5.53
	QALY	10.29450	10.29377	0.0007
	ICER	Rivaroxaban dominates		

In all scenarios rivaroxaban was shown to dominate dabigatran

Assuming a £20,000 per QALY threshold, the estimated probability of rivaroxaban being more cost-effective than dabigatran were 0.990, 0.999 and 0.645 for pooled THR and TKR, THR alone and TKR alone respectively.

Table 11. Probabilistic Sensitivity Analyses – All variables assumed different between rivaroxaban and dabigatran.

		Rivaroxaban	Dabigatran (Rendix)	Incremental
THR and TKR	Cost	£160.73	£194.51	-£33.78
	QALY	10.33413	10.32776	0.0064
	ICER	Rivaroxaban dominates		

		Rivaroxaban	Dabigatran (Rendix)	Incremental
THR	Cost	£196.43	£260.62	-£64.18
	QALY	10.36842	10.36397	0.0044
	ICER	Rivaroxaban dominates		

		Rivaroxaban	Dabigatran (Rendix)	Incremental
TKR	Cost	£116.87	£123.40	-£6.53
	QALY	10.30000	10.29721	0.0028
	ICER	Rivaroxaban dominates		

Assuming a £20,000 per QALY threshold, the estimated probability of rivaroxaban being more cost-effective than dabigatran were 0.858, 0.999 and 0.446 for pooled THR and TKR, THR alone and TKR alone respectively.

As detailed earlier, the methodology used for the probabilistic sensitivity analysis is likely to overestimate the relative cost-effectiveness of rivaroxaban in circumstances where it has an estimated greater risk of fatal PE. [redacted]

7 DISCUSSION

7.1 Summary of clinical effectiveness issues

The review performed for the MS was adequate and there were relatively few issues with the report. The searches were good, demonstrating use of relevant keywords along with appropriate filters to identify high quality evidence. The submission appears to contain all of the relevant head-to-head RCTs, although one of the trials used is published only as an abstract (RECORD 4[8]). The outcomes selected were relevant and appropriate, although joint outcomes were not considered. Statistical methods were explicitly described for the meta-analyses and all required meta-analyses were performed.

7.2 Summary of cost effectiveness issues

The ERG believes that the MS represents an unbiased attempt to assess the cost-effectiveness of rivaroxaban for the prevention of VTE in people undergoing THR or TKR. The lack of future PEs being modelled is unfavourable whilst the lack of intracranial haemorrhage is favourable to rivaroxaban. It is unclear at present how the inclusion of these events would affect the cost-effectiveness of rivaroxaban; however the manufacturer has provided evidence that the impact of including intracranial haemorrhages are likely to be small.

The cost-effectiveness of rivaroxaban also depends on how variables where there are non-significant differences between the interventions are handled and whether the pooling of trials is appropriate. The ERG believe that setting the variables where the p-value is greater than >0.05 is a reasonable action given the point estimates and the confidence intervals. The ERG believes that the pooling of data across the trials is also an appropriate course of action.

The calculations undertaken by the ERG produce similar conclusions to those provided by the manufacturer; namely that rivaroxaban is highly likely to be more cost-effective than enoxaparin, and that rivaroxaban is likely to be more cost-effective than dabigatran. Mean results indicate that rivaroxaban [redacted]

[redacted] The methodology used for adapting the submitted model to undertake probabilistic sensitivity analyses that independently sampled RR for non-fatal and fatal PE is known to be favourable to rivaroxaban as detailed in section 6.

The ERG comment that the absolute incremental differences between rivaroxaban and the comparators are small. As such, were health providers to negotiate prices for interventions that were markedly different to those assumed within the analyses (rivaroxaban £4.50 per day, dabigatran £4.20 per day, enoxaparin £4.20 per day) then conclusions on the intervention that is most likely to be cost-effective may change.

7.3 Implications for research

The key parameter in terms of influencing the cost-effectiveness of rivaroxaban is the number of fatal PEs experienced. [redacted] A proxy for fatal PEs may be rates of VTE; rivaroxaban has shown to have significantly lower rates to total VTE than both enoxaparin or dabigatran and significantly lower rates of symptomatic VTE than enoxaparin. Observational databases should be used to record fatal VTE events for each intervention.

The rates of major bleeds for each intervention does not reach statistical significance. However rivaroxaban has been shown to have a greater point estimate than enoxaparin [redacted]. [redacted] Observational databases should be used to record major bleeding events for each intervention with particular focus on intracranial haemorrhage rates.

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