NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Apixaban for the prevention of venous thromboembolism after hip and knee replacement in adults

This briefing presents the key issues arising from the manufacturer's submission, Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that this briefing is a summary of the information available and should be read with the full supporting documents.

The manufacturer was asked to provide:

- For total hip replacement and total knee replacement, an overview of the studies used in the indirect comparison and, separately, in the mixed treatment comparison.
- An explanation of why the results for the mixed treatment comparison are different from the results of the indirect comparison for apixaban with dabigatran and rivaroxaban.
- An explanation of why the model structure does not seem to allow for transition between mild to moderate post thrombotic syndrome in year 1 to severe post thrombotic syndrome in year 2 and beyond.
- An explanation of why the model does not distinguish between types of bleed and types of venous thromboembolic events for each comparator individually.
- A model that could be used to perform an incremental analysis and a probabilistic sensitivity analysis for all comparators simultaneously.

Indicative licensed indication

In March 2011 the Committee for Medicinal Products for Human Use recommended that apixaban (Eliquis, BMS and Pfizer) is indicated for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery.

Key issues for consideration

Clinical effectiveness

- What is current anticoagulation practice for people having total hip replacement and total knee replacement surgery?
- Are the LMWHs routinely given before surgery and continued on discharge?
- Is enoxaparin the most widely and commonly used LMWH?
- What are the potential advantages and disadvantages of apixaban compared with other anticoagulant treatments available?
- The manufacturer considered that enoxaparin was an appropriate reflection of all LMWHs and therefore only incorporated enoxaparin in cost-effectiveness analyses. Does the Committee agree that all appropriate comparators were included and does it agree with the manufacturer's assumption?
- The results of the indirect comparisons for apixaban with dabigatran and rivaroxaban are different from the mixed treatment comparison results. Does the Committee agree that it is appropriate for the manufacturer to focus on the indirect comparison analyses alone?

Cost effectiveness

- The manufacturer stated that the economic model submitted was based on the economic model submitted for NICE technology appraisal guidance 157 ('Dabigatran etexilate for the prevention of venous

thromboembolism after hip or knee replacement surgery in adults'). Does the Committee think that this is appropriate?

- The following assumptions in the model were made:
  - During the prophylactic phase, other and pulmonary embolism (PE) deaths are assumed to occur at 35 days for total hip replacement and 14 days for total knee replacement for each treatment arm.
  - During the post-prophylactic phase, PE deaths are assumed to occur at 63 days for total hip replacement and 52 days for total knee replacement, which are the mid points of the post-prophylactic phase for each indication.
  - Major bleed deaths are assumed to occur at 35 days for total hip replacement and 14 days for total knee replacement, regardless of whether the bleeding rates are based on the prophylactic duration or 90 days.
  - There is no transition between mild to moderate post thrombotic syndrome in year 1 to severe post thrombotic syndrome in year 2 and beyond.

  Does the Committee accept these assumptions?

- In the manufacturer's economic model structure, there is no transition between mild to moderate post thrombotic syndrome in year 1 to severe post thrombotic syndrome in year 2 and beyond. Does the Committee accept the manufacturer's model structure?
- What weight does the Committee place on the full incremental analysis that indicated that rivaroxaban dominated apixaban in total knee replacement, albeit with small differences in QALYs?

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	People having elective hip or knee replacement surgery
Intervention	Apixaban
Comparators	Pharmacological methods of prophylaxis using one of the following methods: • low molecular weight heparin (LMWH) • fondaparinux • rivaroxaban • dabigatran etexilate.
Outcomes	Mortality, incidence of VTE and adverse events are addressed in the clinical evidence. Post-deep vein thrombosis (DVT) complications and health-related quality of life are addressed in the economic evaluation.
Economic evaluation	Cost effectiveness of treatments is expressed in terms of incremental cost per quality-adjusted life year (QALY). The time horizon for estimating clinical and cost effectiveness is long enough to reflect any differences in costs or outcomes between the technologies being compared. Costs are considered from an NHS and personal social services perspective.

1.2 Evidence Review Group comments

1.2.1 Population

The ERG considered that the manufacturer's statement of the decision problem appropriately defines the population as adults having 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 apixaban.

1.2.3 Comparators

The ERG noted the comparators included enoxaparin (which is taken to be representative of LMWH dabigatran, rivaroxaban and fondaparinux. The ERG noted a comment from the manufacturer that fondaparinux is used in less than one per cent of people having total knee replacement or total hip replacement, that it is given by injection, and needs similar administration resources as the LMWHs. The ERG had no concerns with these comparators.

1.2.4 Outcomes

The ERG noted that a majority of the key clinical outcomes were considered within the model both in the short term and long term.

1.2.5 Economic evaluation

The ERG considered that the time horizon of the model of 35 years is appropriate for this decision problem given the mean age of the population of 65 or 68 years (depending on gender and whether having total hip replacement or total knee replacement); this makes the final age of the population at least 100 years, which is approximately a lifetime.

1.3 Statements from professional/patient groups and nominated experts

Patient experts agreed that a treatment taken orally such as apixaban was preferable to injection of LMWH. Apixaban had the advantage of being used at home. This could shorten hospital inpatient times and also avoid the cost of providing training to people to self-inject enoxaparin. Patient experts commented that an oral technology was particularly advantageous for continued protection post surgery and discharge during a high risk period. Clinical specialists agreed that taking apixaban would not involve any anticoagulant monitoring. Clinical specialists commented that there was no difference between apixaban and other similar anticoagulants available such as rivaroxaban and dabigatran and were therefore unsure of what added benefit apixaban would give. Patient experts commented that apixaban twice

daily would be a disadvantage to people as compared with once daily preparations such as rivaroxaban and dabigatran.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

The manufacturer identified four randomised controlled trials comparing apixaban with enoxaparin for the prevention of VTE. ADVANCE1 ('Apixaban dosed orally versus anticoagulation with enoxaparin'), ADVANCE2, and APROPOS ('Apixaban prophylaxis in patients undergoing total knee replacement surgery') recruited people having total knee replacement surgery. ADVANCE 3 recruited people having total hip replacement surgery.

ADVANCE 1 and ADVANCE 2 were phase III multicentre parallel-group randomised controlled trials comparing apixaban with enoxaparin for the prevention of VTE after total knee replacement surgery. ADVANCE 1 was conducted in 14 countries including 6 European centres, none of which were in the UK. In ADVANCE 1, apixaban was given at a dosage of 2.5 mg twice daily, enoxaparin was given at a dosage of 2.5 mg twice daily and enoxaparin was given at a dosage of 30 mg twice daily. Both apixaban and enoxaparin were given for 12 days and started 12–24 hours after surgery. ADVANCE 2 was conducted in 27 countries including 15 European centres, two of which were in the UK. In ADVANCE 2 apixaban was given at a dosage of 2.5 mg twice daily and enoxaparin was given at a dosage of 40 mg once daily. Both apixaban and enoxaparin were given for 11 days. Apixaban was started 12–24 hours after surgery, and enoxaparin was started 9–15 hours before surgery. APROPOS was a phase II dose-finding study in which people were randomised to receive one of several doses of apixaban (5 mg, 10 mg, 20 mg, once or twice daily), enoxaparin 30 mg twice daily or warfarin. The manufacturer considered ADVANCE 2 to be the most relevant study in the manufacturer's submission for the prevention of VTE after total knee

replacement surgery as it was the only study that compared apixaban with the UK licensed dose of enoxaparin (40 mg once daily).

ADVANCE 3 was a phase III, multicentre parallel-group randomised controlled trial comparing apixaban with enoxaparin for the prevention of VTE after total hip replacement surgery. It was conducted in 21 countries and included 13 European centres, of which 3 were in the UK. Apixaban was given at a dosage of 2.5mg twice daily and enoxaparin was given at a dosage of 40 mg once daily. Both apixaban and enoxaparin were given for 32–38 days. Apixaban was started 12–24 hours after surgery and enoxaparin was started 9–15 hours before surgery.

The primary efficacy end point for the ADVANCE 1 and ADVANCE 2 studies was the composite of all adjudicated VTE (PE, symptomatic DVT and asymptomatic DVT), and all-cause death during the intended treatment period. The primary safety end point of the two studies was bleeding and included confirmed adjudicated major bleeding events, composite of confirmed adjudicated major bleeding events, confirmed adjudicated clinically non-major bleeding events, and all bleeding end points. The primary efficacy end point for ADVANCE 3 was the composite of adjudicated symptomatic or asymptomatic DVT, non-fatal PE and death from any cause during the intended treatment period. The primary safety end point was bleeding during treatment or within 2 days of the last dose of study medication.

The primary efficacy analysis dataset included all randomised subjects who had an adjudicated and evaluable bilateral venogram, an adjudicated VTE, or died as a result of any cause. The manufacturer stated that intention-to-treat analysis assumes that no readable venogram represents no event, therefore potentially underestimating the number of VTE events occurring within the intention-to-treat population. The remaining efficacy and safety outcome analyses were conducted on the intention-to-treat population.

Results

ADVANCE 2 was the only trial comparing apixaban with enoxaparin 40 mg once daily in patients with total knee replacement. Apixaban was statistically superior to enoxaparin in terms of the primary composite end point of all VTE and all-cause death, as well as in terms of major VTE and all DVT. The available evidence for each outcome listed in the scope issued by NICE is summarised in table 1.

Table 1 Results for apixaban versus enoxaparin 40 mg once daily in total knee replacement (ADVANCE 2)

Outcome	ADVANCE-2		
	Apixaban (responders/ patients analysed) n = 1528[a]	**Enoxaparin (responders/ patients analysed) n = 1529[a]**	**Effect size (95% confidence interval)**
VTE/all-cause death	147/976	243/997	RR = 0.62 (0.51 to 0.74)
Death	2/1528	0/1529	RR = 5.0 (0.24 to 104.13)
Major VTE	13/1195	26/1199	RR = 0.5 (0.26 to 0.97)
All DVT	142/971	243/997	RR = 0.6 (0.50 to 0.72)
Post DVT complications:			
Pulmonary embolism (fatal or non-fatal)	4/1528	0/1529	RR = 9.01 (0.49 to 167.13)
Post-thrombotic syndrome	NR	NR	
Duration of hospital stay in days	NR	NR	
Joint outcomes including joint infection	NR	NR	
Adverse events:			
▪ all adverse events n (%)	786/1501[b] (52%)	836/1508[b] (55%)	RR = 0.94 (0.88 to 1.01)
▪ serious adverse events n (%)	72/1501[b] (5%)	88/1508[b] (6%)	RR = 0.82 (0.61 to 1.11)
▪ major bleeding events	9/1501[b] (0.6%)	14/1508[b] (0.9%)	RR = 0.65 (0.28 to 1.49)
• all bleeding events n (%)	104/1501[b] (6.9%)	126/1508[b] (8.4%)	RR = 0.83 (0.65 to 1.06)
Health related quality of life	NR	NR	

[a] randomised participants

[b] treated participants

Abbreviations: DVT, deep-vein thrombosis; NR, not reported; RR, relative risk; VTE, venous thromboembolism.

ADVANCE 3 was the only trial comparing apixaban with enoxaparin 40 mg once daily in patients with total hip replacement. Apixaban was statistically superior to enoxaparin in terms of the primary composite end point of all VTE and all-cause death, as well as in terms of major VTE and all DVT. The

available evidence for each outcome listed in the scope issued by NICE is summarised in the table 2.

Table 2 Results for apixaban versus enoxaparin 40 mg once daily in total hip replacement (ADVANCE 3)

Outcome	ADVANCE-3		
	Apixaban (Responders/ Patients analysed) n = 2708[a]	**Enoxaparin (Responders/ patients analysed) n = [2699a]**	**Effect size (95% CI)**
Venous thromboembolism /all-cause death	27/1949	74/1917	RR = 0.36 (0.23 to 0.56)
Death	3/2708	1/2699	RR = 2.99 (0.31 to 28.73)
Major venous thromboembolism	10/2199	25/2195	RR = 0.40 (0.19 to 0.83)
All deep-vein thrombosis	22/1944	68/1911	RR = 0.32 (0.20 to 0.51)
Post deep-vein thrombosis complications:			
• Pulmonary embolism (fatal or non-fatal)	3/2708	5/2699	RR = 0.60 (0.14 to 2.50)
• Post-thrombotic syndrome	Not reported	Not reported	
Duration of hospital stay in days	Not reported	Not reported	
Joint outcomes including joint infection	Not reported	Not reported	
Adverse events:			
▪ All adverse events n (%)	NR	NR	
▪ Serious adverse events n (%)	NR	NR	
▪ Major bleeding events	22/2673[b] (0.8%)	18/2659[b] (0.7%)	RR = 1.22 (0.65 to 2.26)
• All bleeding events n (%)	313/2673[b] (11.7%)	334/2659[b] (12.6%)	RR = 0.93 (0.81 to 1.08)
Health related quality of life	Not reported	Not reported	

[a] randomised participants; [b] treated participants

Abbreviations: CI, confidence interval; NR, not reported; RR, relative risk.

The ADVANCE 1 and the APROPOS studies used the American dosing regimen for enoxaparin (30 mg twice daily), and both trials were in patients with total knee replacement. Both trials reported no significant differences for any of the outcomes reported.

Indirect and mixed treatment comparisons

As there are no head-to-head randomised controlled trials comparing apixaban with rivaroxaban, dabigatran or fondaparinux, the manufacturer presented an indirect comparison to determine the relative efficacy and safety of the treatments using enoxaparin as a common comparator. The manufacturer identified 15 randomised controlled trials for inclusion in the indirect comparison. Of these, nine studies compared the treatment of interest with enoxaparin 40 mg once daily. The remaining six studies compared the treatment of interest with enoxaparin 30 mg twice daily. Table 3 shows the 15 studies included in the indirect comparison analyses.

Table 3 Randomised controlled trials of head-to-head comparisons of treatments listed as interventions of interest in the NICE scope

The adjusted indirect comparison analyses					
Total hip replacement			**Total knee replacement**		
Study	**Treatment**	**Comparison**	**Study**	**Treatment**	**Comparison**
ADVANCE-3	Apixaban 2.5 mg, twice daily	Enoxaparin 40 mg once daily	ADVANCE-2	Apixaban 2.5 mg twice daily	Enoxaparin 40 mg once daily
RECORD 1	Rivaroxaban 10 mg twice daily	Enoxaparin 40 mg once daily	RECORD 3	Rivaroxaban 10 mg once daily	Enoxaparin 40 mg once daily
RECORD 2	Rivaroxaban 10 mg once daily	Enoxaparin 40 mg once daily	RE-MODEL	Dabigatran 220 mg once daily	Enoxaparin 40 mg once daily
RE-NOVATE	Dabigatran 220 mg once daily	Enoxaparin 40 mg once daily	APROPOS	Apixaban 2.5 mg twice daily	Enoxaparin 30 mg twice daily
Huo 2010 (RE-NOVATE II)	Dabigatran 220 mg once daily	Enoxaparin 40 mg once daily	ADVANCE 1	Apixaban 2.5 mg twice daily	Enoxaparin 30 mg twice daily
Lassen 2002	Fondaparinux 2.5 mg once daily	Enoxaparin 40 mg once daily	RECORD 4	Rivaroxaban 10 mg once daily	Enoxaparin 30 mg twice daily
Turpie 2002	Fondaparinux 2.5 mg once daily	Enoxaparin 30 mg, twice daily	RE-MOBILIZE	Dabigatran 220 mg once daily	Enoxaparin 30 mg twice daily
			Bauer 2001	Fondaparinux 2.5 mg once daily	Enoxaparin 30 mg, twice daily

The manufacturer reported three different types of adjusted indirect comparisons:

- using only the UK does of enoxaparin
- using only the US doses of enoxaparin
- using the pooled UK and US doses of enoxaparin.

The manufacturer also undertook a mixed treatment comparison that included 43 studies. The manufacturer reported two different types of mixed treatment comparisons:

- using only the UK dose of enoxaparin

- using the pooled UK and US doses for enoxaparin.

The results of the indirect and mixed treatment comparisons relative to apixaban are presented in tables 4 and 5 (taken from pages 29 and 30 of the ERG report.)

Table 4 Results from indirect comparisons and MTC relative to apixaban in total hip replacement (THR)

	VTE Comp OR (95% CI/CrI)	Any DVT OR (95% CI)	Major VTE OR (95% CI)	PE OR (95% CI)	Any bleeding OR (95% CI)	Major bleeding OR (95% CI)
Apixaban vs Enoxaparin						
IC1	[redacted]	0.31 (0.191, 0.504)	[redacted]	[redacted]	[redacted]	[redacted]
IC2	NR	NR	NR	NR	NR	NR
IC3	NR	NR	NR	NR	NR	NR
MTC1	[redacted]	0.317 (0.09883, 0.991)	NR	NR	[redacted]	[redacted]
MTC2	[redacted]	0.315 (0.0898, 1.108)	NR	NR	[redacted]	[redacted]
Rivaroxaban vs Apixaban						
IC1	[redacted]	0.709 (0.304, 1.652)	[redacted]	[redacted]	[redacted]	[redacted]
IC2	NR	NR	NR	NR	NR	NR
IC3	NR	NR	NR	NR	NR	NR
MTC1	[redacted]	0.698 (0.133, 3.698)	NR	NR	[redacted]	[redacted]
MTC2	[redacted]	0.622 (0.131, 2.924)	NR	NR	[redacted]	[redacted]
Dabigatran vs Apixaban						
IC1	[redacted]	2.63 (1.402, 4.931)	[redacted]	[redacted]	[redacted]	[redacted]

IC2	NR	NR	NR	NR	NR	NR
IC3	v	NR	NR	NR	NR	NR
MTC1	[redacted]	2.601 (0.5151, 13.1)	NR	NR	[redacted]	[redacted]
MTC2	[redacted]	2.6 (0.45, 14.65)	NR	NR	[redacted]	[redacted]
Fondaparinux vs Apixaban						
IC1	NR	1.339 (0.713, 2.514)	NR	[redacted]	NR	[redacted]
IC2	NR	NR	NR	NR	NR	NR
IC3	NR	1.643 (0.838, 3.222)	NR	3.524 (0.413, 30.063)	NR	1.295 (0.618-2.716)
MTC1	[redacted]	0.631 (0.043, 7.752)	NR	NR	NR	[redacted]
MTC2	[redacted]	1.668 (0.366, 7.491)	NR	NR	NR	[redacted]

Abbreviations:CI, confidence interval; DVT, deep vein thrombosis; NR, not reported; OR, odds ratio; PE , pulmonary embolism; VTE comp, venous thromboembolic events composite outcome.

Analyses:

IC1:Indirect comparison using Enoxaparin 40 mg once daily

IC2: Indirect comparison using Enoxaparin 30 mg twice daily

IC3: Indirect comparison using Enoxaparin 40 mg once daily and 30 mg twice daily

MTC1: mixed treatment comparison using Enoxaparin 40 mg once daily

MTC2: mixed treatment comparison using Enoxaparin 40 mg once daily and 30 mg twice daily

OR < 1: favours first treatment over second.

Notes: RECORD-2 excluded because Enoxaparin 40mg once daily arm had short duration (see p.70, MS)**;** BISTRO-2 excluded, 220 mg once

daily is standard UK dose for Dabigatran (see p.70, MS); ODIXa excluded, treatment duration only 5-9 days for both arms (see p.79, MS); For apixaban, one dose was used: 2.5mg twice daily . For enoxaparin, the European dose (40 mg once daily) and the US dose (30 mg twice daily) were used. For the other comparators the following doses were used: rivaroxaban 10mg once daily, fondaparinux 2.5mg once daily, and dabigatran 220mg once daily; For all the results the UK indication doses were considered and any doses for specific populations have not been included; For the outcome "Any bleed", MTC base model has included 'Enoxaparin 40 mg (UK indication)+Ext > 1 week' (instead of only UK indication); For outcomes 'VTE composite, 'Any DVT' and 'Major VTE' results from primary efficacy population were reported. Whereas, for outcomes 'PE', 'Any Bleeding' and 'Major Bleeding' results from intention-to-treat population were reported.

Table 5 Results from indirect comparisons and MTC relative to apixaban in total knee replacement (TKR)

	VTE comp OR (95% CI/CrI)	Any DVT OR (95% CI)	Major VTE OR (95% CI)	PE OR (95% CI)	Any bleeding OR (95% CI)	Major bleeding OR (95% CI)
Apixaban vs Enoxaparin						
IC1	[redacted]	0.531 (0.423 to 0.668)	[redacted]	[redacted]	[redacted]	[redacted]
IC2	0.894 (0.571 to 1.401)	0.902 (0.678 to 1.201)	0.93 (0.28 to 3.086)	1.043 (0.108 to 10.071)	0.77 (0.58 to 1.02)	0.5 (0.24 to 1.03)
IC3	0.71 (0.437 to 1.154)	0.686 (0.435 to 1.08)	0.735 (0.313 to 1.726)	1.885 (0.393 to 9.044)	0.79 (0.65 to 0.96)	0.55 (0.32 to 0.96)
MTC1	[redacted]	0.872 (0.4 to 1.865)	NR	NR	[redacted]	[redacted]
MTC2	[redacted]	0.681 (0.267 to 1.697)	NR	NR	[redacted]	[redacted]
Rivaroxaban vs Apixaban						
IC1	[redacted]	0.895 (0.621 to 1.294)	[redacted]	[redacted]	[redacted]	[redacted]
IC2	0.742 (0.426 to 1.29)	0.759 (0.487 to 1.185)	0.625 (0.156 to 2.496)	0.591 (0.047 to 7.402)	1.468 (1.013 to 2.126)	4.96 (1.26 to 19.518)
IC3	0.768 (0.417 to 1.412)	0.82 (0.46 to 1.47)	0.652 (0.24 to 1.767)	0.238 (0.03 to 1.861)	1.38 (1.05 to 1.814)	3.055 (1.169 to 7.981)
MTC1	[redacted]	0.857 (0.319 to 2.773)	NR	NR	[redacted]	[redacted]
MTC2	[redacted]	0.832 (0.205 to 3.609)	NR	NR	[redacted]	[redacted]
Dabigatran vs Apixaban						
IC1	[redacted]	1.772	[redacted]	[redacted]	[redacted]	[redacted]

		(1.258 to 2.498)				
IC2	1.489 (0.892 to 2.485)	1.458 (0.997 to 2.131)	1.646 (0.416 to 6.515)	1.171 (0.09 to 15.167)	1.117 (0.616 to 2.024)	0.84 (0.237 to 2.975)
IC3	1.577 (0.874 to 2.847)	1.618 (0.923 to 2.836)	1.456 (0.47 to 4.508)	0.552 (0.08 to 3.785)	1.177 (0.863 to 1.607)	1.291 (0.426 to 3.91)
MTC1	[redacted]	1.83 (0.513 to 9.639)	NR	NR	[redacted]	[redacted]
MTC2	[redacted]	1.406 (0.24 to 8.438)	NR	NR	[redacted]	[redacted]
Fondaparinux vs Apixaban						
IC1	NR	NR	NR	NR	NR	NR
IC2	NR	0.42 (0.26 to 0.68)	NR	0.24 (0.01 to 5.34)	NR	22.3 (2.52 to 197.47)
IC3	NR	0.55 (0.31 to 1.00)	NR	0.13 (0.01 to 1.85)	NR	20.27 (2.42 to 169.57)
MTC1	[redacted]	0.44 (0.11 to 1.798)	NR	NR	[redacted]	[redacted]
MTC2	[redacted]	0.561 (0.085 to 3.442)	NR	NR	[redacted]	[redacted]

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; NR, not reported; OR, odds ratio; PE, pulmonary embolism; VTE comp, venous thromboembolic events composite outcome.

Analyses:

IC1:Indirect comparison using Enoxaparin 40 mg once daily

IC2: Indirect comparison using Enoxaparin 30 mg twice daily

IC3: Indirect comparison using Enoxaparin 40 mg once daily and 30 mg twice daily

MTC1: mixed treatment comparison using Enoxaparin 40 mg once daily

MTC2: mixed treatment comparison using Enoxaparin 40 mg once daily and 30 mg twice daily

OR < 1: favours first treatment over second.

The manufacturer considered the adjusted indirect comparison to be the most appropriate analysis for informing the relative efficacy and safety of apixaban compared with enoxaparin, rivaroxaban, dabigatran and fondaparinux. This was because the mixed treatment comparison results were inconsistent with some of the head-to-head randomised controlled trial data. The manufacturer highlighted inconsistencies in the following comparisons between the results of the mixed treatment comparison and the head-to- head trial: apixaban 2.5 mg twice daily compared with enoxaparin 40 mg once daily; and rivaroxaban 10 mg once daily compared with enoxaparin 40mg once daily on the primary composite end point (VTE plus all-cause death) and on some of the secondary outcomes.

Furthermore, the manufacturer stated that it considered the adjusted indirect comparison analyses of apixaban 2.5 mg twice daily with another anticoagulant of interest, with enoxaparin 40 mg once daily as the common comparator, to be the most relevant of all the adjusted indirect comparison analyses (that is 'IC 1' results in tables 4 and 5 of this document). A summary of the results of this adjusted indirect comparison is provided below:

- When compared with rivaroxaban, apixaban showed no significant differences for [redacted] any DVT, [redacted] [redacted].
- When compared with dabigatran, apixaban was significantly superior [redacted] [redacted] any DVT; [redacted] [redacted] . These results were the same for total hip replacement and total knee replacement.
- When compared with fondaparinux in total hip replacement, apixaban showed no significant differences for any DVT , [redacted]. Other main outcomes (total VTE and all-cause mortality, major VTE and any bleeding) were not reported using indirect comparisons. For total knee replacement, an indirect comparison with enoxaparin 40 mg once daily was not possible.

2.2 Evidence Review Group comments

The ERG reviewed the literature search strategy and concluded that it was effective in identifying relevant literature to the decision problem and showed use of relevant search techniques for systematic reviews.

The ERG stated that the search methods were clearly presented and reported. The manufacturer searched the necessary databases. The manufacturer's submission provided sufficient detail for the ERG to appraise the searches. Additional searches of conference abstracts were undertaken for the clinical-effectiveness and cost-effectiveness sections. The ERG noted that several of the errors identified were not major, because of the comprehensiveness of the rest of the strategies.

The ERG considered the three 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. It stated that processes and validation of study screening and data extraction appeared to be appropriate.

The ERG agreed with the chosen doses for each treatment included in the adjusted indirect and mixed treatment comparisons. The ERG commented that the statistical methods were explicitly described for the meta-analyses and indirect comparisons, and all relevant analyses were performed. In addition, the ERG commented that the manufacturer's conclusion that the mixed treatment comparison was less reliable than the adjusted indirect comparison seemed reasonable.

The ERG highlighted that an abstract for RE-NOVATE-II (dabigatran 200 mg compared with enoxaparin 40 mg) was used in the adjusted indirect comparison for total hip replacement surgery. The ERG noted that the full paper for this study was published after the completion of the manufacturer's submission. Five outcomes were reported in the full paper, which were not reported in the abstract: any DVT, symptomatic DVT, any bleeding, clinically relevant non major (CRNM) bleeding and minor bleeding. All other outcomes

were the same in the full paper. The ERG added the results reported in the full paper for RE-NOVATE II to those from RE-NOVATE alone. The ERG stated that adding the results produced very small changes and slightly smaller confidence intervals and that these changes were unlikely to cause significant changes to the analyses in the manufacturer's submission.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

A two stage modelling approach was adopted. A decision tree was used to model treatment in the acute phase (surgery to 90 days after surgery) and a Markov model was used to model the long-term events (90 days after surgery and beyond). The differential effects of treatment were only realised in the acute phase of the model. For the model schema, please see appendix B.

In the decision tree model, a patient can experience no event or an event (total VTE or all-cause death). In case of an event that is not a VTE, the patient dies from a major bleed or other cause. Other cause deaths refer to non-VTE and non-treatment-related deaths occurring during the prophylactic phase. A VTE event can be a PE, symptomatic DVT or asymptomatic DVT (both either distal or proximal). Patients with a PE can die or survive. Patients surviving PEs and all patients with asymptomatic receive treatment and progress to the non-fatal bleeding events state of the model. Patients with symptomatic DVT progress to the non-fatal bleeding events state without treatment. Patients without events directly progress to this state. Probabilities of bleeding are independent of what happened earlier in the model. Patients experiencing an intracranial haemorrhage proceed immediately to the disabled health state and remain there for the duration of the model or until they die. Alternatively patients can experience no bleeding, minor bleeding, a non-major clinically relevant bleed or a major bleed (other than an intracranial haemorrhage).

In the period between the end of prophylaxis and 90 days after surgery, asymptomatic patients can become symptomatic. Asymptomatic DVTs that

convert to symptomatic DVT during the post-prophylaxis period are assumed to be of the same type. At 90 days after surgery patients leave the decision tree model and enter the long-term Markov model. Patients that have not experienced a VTE event enter the Markov model in the well state, whereas patients that are asymptomatic enter the Markov model in the untreated VTE state. Patients that have had a PE or a DVT or have transitioned from asymptomatic to symptomatic (had a DVT) enter the Markov in the treated VTE state. Patients that have had an intracranial haemorrhage enter in the disabled state. Patients that died in the decision tree enter the Markov in the dead state. In the long-term Markov model, patients can remain well, die, have a PE, have a DVT, have mild to moderate post-thrombotic syndrome (segregated into year 1 and subsequent years) or a severe post-thrombotic syndrome (segregated into year 1 and subsequent years). The same transitions are possible for treated and untreated patients. Once a patient has a PE or DVT they transition to the treated VTE state. There is no differential treatment effect in this long-term phase of the model.

The following assumptions are made in the model:

- During the prophylactic phase, other and PE deaths are assumed to occur at 35 days for total hip replacement and 14 days for total knee replacement in each treatment arm.
- During the post-prophylactic phase PE deaths are assumed to occur at 63 days for total hip replacement and 52 days for total knee replacement, which are midpoints of the post-prophylactic phase for each indication.
- Major bleed deaths are assumed to occur at 35 days for total hip replacement and 14 days for total knee replacement, regardless of whether the bleed rates are based on the prophylactic duration or 90 days.

Clinical evidence

The manufacturer modelled the efficacy and safety of the treatments in line with the corresponding end points in the ADVANCE 2 and 3, RECORD, RE-MODEL and RENOVATE trials:

- Total VTEs and all deaths (all adjusted VTE and all-cause death and adjudicated, symptomatic or asymptomatic DVT, non-fatal PE and death from any cause).
- Total bleeds (bleeding at the surgical site, non-surgical bleeding events, clinically relevant non-major bleeding and minor bleeding).

The manufacturer stated that relative risks are used in the economic model rather than odds ratios as they can be directly applied to an absolute probability of an event to generate the absolute event rate for the comparator treatment. Tables 6 and 7 show the relative risks of composite VTE and bleed rates used in the economic model.

The manufacturer's original economic model did not distinguish between types of bleed and types of VTE for each comparator individually, but assumed they were all the same. Since this assumption may favour apixaban, the ERG requested the manufacturer to provide an adjusted model that allowed for differences in type of bleed and type of VTE. This adapted model was provided by the manufacturer.

Table 6 Composite VTE and bleed rates obtained from the indirect comparison using enoxaparin 40 mg once daily (Table 5.3 ERG report page 42)

	THR: all VTE and all cause death (95% CI)	TKR: all VTE and all cause death (95% CI)	THR: any bleeding (95% CI)	TKR: any bleeding (95% CI)
	Primary efficacy population analysis		**Intention to treat analysis**	
Baseline risk (enoxaparin 40mg once daily)	4.58%	26.29%	9.39%	8.75%
Apixaban RR	0.359 (0.232 to 0.555)	0.618 (0.514 to 0.743)	0.93 (0.81 to 1.08)	0.83 (0.64 to 1.06)
Rivaroxaban RR	0.3 (0.18 to 0.51)	0.507 (0.395 to 0.651)	1.02 (0.81 to 1.29)	1.02 (0.72 to 1.44)
Dabigatran RR	0.887 (0.696 to 1.131)	0.965 (0.822 to 1.133)	1.07 (0.86 to 1.34)	0.96 (0.76 to 1.22)

Abbreviations: CI, confidence interval; THR, total hip replacement, TKR, total knee replacement, RR, relative risk; VTE, venous thromboembolism.

A mixed treatment comparison was also undertaken of relevant trial data. The results were assessed in a scenario analysis.

Table 7 Composite VTE and bleed rates obtained from the mixed treatment comparison group using enoxaparin 40 mg once daily (table 5.4, ERG report, page 43)

	THR: all VTE and all cause death	TKR: all VTE and all cause death	THR: any bleeding	TKR: any bleeding
	Primary efficacy population analysis		Intention to treat analysis	
Baseline risk	5.4%	19.4%	9.4%	7.0%
Apixaban	0.357	0.895	0.927	0.809
Enoxaparin 30 mg twice daily	0.925	1.000	0.825	1.000
Enoxaparin 40 mg	0.638	1.410	0.821	1.037
Rivaroxaban	0.302	0.731	1.009	1.094
Dabigatran	0.893	1.354	1.074	1.003
Fondaparinux	0.306	0.582		0.888
Abbreviations: THR, total hip replacement; TKR,total knee replacement ; VTE, venous thromboembolism.				

Utility values

The manufacturer undertook a systematic literature review to identify utility inputs for use in the model. Each year 0.00029 was subtracted from a patient's health state utility value before the QALYs for that year were calculated. This age decrement was based on the EQ-5D US tariff. The utility values and decrements used in the model by health state are shown in table 8.

Table 8 Utility input (table 69 and 71–74, manufacturer's submission)

State	Utility value or decrement	Confidence interval or standard error	Reference	Duration		Reference
				THR	**TKR**	
General male population	0.78	0.018543	Kind	N/A	N/A	
General female population	0.78	0.015504	Kind	N/A	N/A	
Death	0	N/A	Assumption			
Hospitalisation period				**Days**	**Days**	
PE	−0.08	0.004082[a]	Ingelgard	5.63	7.49	Assumption
Symptomatic distal DVT	−0.08			0.949	1.73	
Symptomatic proximal DVT	−0.08			0.949	1.73	
Asymptomatic DVT	0.0	N/A		N/A	N/A	
Intracranial haemorrhage	−0.49	0.03[a]	Boehringer	90	90	
Major bleed – other	−0.03	0.001531[a]	Robinson	5.63	7.49	
NMCR bleed	0	-	Assumption	0.949	1.73	
Minor bleed	0	-		0.949	1.73	
Post-discharge period				**Days**	**Days**	
PE	0	-		30	30	Assumption
Symptomatic distal DVT	−0.08	0.004082[a]	Ingelgard	30	30	
Symptomatic proximal DVT	–0.08			30	30	
ICH disabled	−0.49	0.03[a]	Boehringer	90	90	
Long-term Markov phase				**Months**	**Months**	
Aging (annual impact)	−0.00029	−0.000015[a]	Sullivan	12	12	Sullivan
Treated VTE	−0.01	0.000510[a]	Gage	1	1	Assumption

State	Utility value or decrement	Confidence interval or standard error	Reference	Duration		Reference
				THR	TKR	
ICH disabled state	−0.49	−0.025000[a]	Boehringer	12	12	NCC for Acute Care
PE	−0.08	−0.004082[a]	Ingelgard	1	1	
DVT	−0.08	−0.004082[a]		1	1	
Mild/moderate PTS (year 1)	−0.02	−0.001020[a]	Lenert	12	12	Lenert
Mild/moderate PTS (year 2+)	−0.02	−0.001020[a]		12	12	
Severe PTS (year 1)	−0.07	0.003571[a]		12	12	
Severe PTS (year 2+)	−0.07	0.003571[a]		12	12	

[a] 95% confidence interval assumed to be ±10%.

Abbreviations: DVT, deep vein thrombosis; ICH, intracranial haemorrhage ; NMCR, non major clinically relevant bleed; PE, pulmonary embolism; PTS, post thrombotic syndrome ; THR, Total hip replacement ; TKR, Total knee replacement ; VTE, venous thromboembolism.

Post-event treatment probabilities

The remaining clinical probabilities in the decision tree element of the model were assumed to be treatment independent and assumed to not differ between apixaban, enoxaparin, dabigatran and rivaroxaban. The manufacturer stated that this approach was taken because the trials for apixaban, rivaroxaban and dabigatran were only powered to detect differences in the composite primary efficacy and safety end points. If possible the probabilities for the post event treatment independent probabilities were obtained from a synthesis of all trials on new oral anticoagulants (all new oral anticoagulant trials; RECORD RE-MODEL and RE-NOVATE). To synthesise the data, the sum of events was taken across the trials and event types thus providing a total count for each event type. For further details of the probabilities used in the economic model, see table 5.5, page 44 of the ERG report.

Long-term recurrent risks of VTE and post-thrombotic syndrome

The manufacturer undertook a literature review to identify parameter estimates for the long-term risk of recurrent VTE and/or the development of post-thrombotic syndrome in patients who had a total knee replacement or total hip replacement and who suffered a VTE event. For further details of the rates used in the economic model, see tables 5.6–5.8, pages 45 and 46 of the ERG report.

Costs

Drug acquisition costs for a course of treatment depend on the treatment durations assumed for each treatment. The treatment durations applied were apixaban: total knee replacement 12 days, total hip replacement 34 days (mean duration in ADVANCE 2 and 3 trials); enoxaparin/LMWH total knee replacement 12 days, total hip replacement 34 days (mean duration in ADVANCE 2 and 3 trials); rivaroxaban total knee replacement 12 days, total hip replacement 33 days (mean duration in RECORD 1 and 3 trials); and dabigatran total knee replacement 8 days, total hip replacement 32 days (median duration in RE-MODEL and RE-NOVATE).

Only the costs that differ by intervention were considered. Details of the drug costs of apixaban and its comparators are included in table 9.

Table 9 Drug costs (Table 77, page 166 of manufacturer's submission)

Drug	Dose	Per pack		Per day		Days of treatment		Costs per course	
		Pack	Pills	Pills	Cost	TKR	THR	TKR	THR
Enoxaparin	40mg[a]	£40.36[b]	10	1	£4.04	12	34	£48.48	£137.36
						ADVANCE			
Rivaroxaban	10mg [a]	£441.45[b]	100	1	£4.41	12	33	£52.97	£145.68
						RECORD			
Dabigatran[c]	220mg[a]	£126.00[b]	60	2	£4.20	8	32	£33.60	£134.40
						RE-MODEL			
Apixaban	2.5mg[c]	£102.90[e]	60	2	£3.43	12	34	£41.16	£116.62
						ADVANCE			

[a] Once a day.
[b] Price from (MIMS 2010)
[c] Twice a day
[d] Price from Pfizer/Bristol-Myers Squibb
Abbreviations: THR, total hip replacement; TKR, total knee replacement

The manufacturer highlighted that during the course of this appraisal, it is anticipated that dabigatran will be licensed for use in patients with atrial fibrillation and that the daily cost of dabigatran will fall. The manufacturer therefore undertook a sensitivity analysis in which the acquisition cost of dabigatran was reduced by 50% to assess the impact of such a change on the cost effectiveness of apixaban. For details of the health state and adverse event costs see pages 167–168 of the manufacturer's submission.

Results

In the base-case analyses a comparison was made between enoxaparin, apixaban, dabigatran and rivaroxaban. For both total hip replacement surgery and total knee replacement surgery apixaban, dabigatran and rivaroxaban were less expensive than enoxaparin. In general, QALY differences were very small between the comparators.

Total hip replacement

In the deterministic base-case analysis, apixaban, rivaroxaban and dabigatran all dominated enoxaparin. Apixaban was the least expensive technology, whereas rivaroxaban was the most clinically effective comparator. Both apixaban and rivaroxaban were more effective and less costly, and thus dominant, compared with dabigatran and enoxaparin. Rivaroxaban was £29.47 more expensive, and yielded 0.001 more QALYs than apixaban, resulting in an ICER of £21,661 per QALY gained.

Total knee replacement

Apixaban was less expensive than dabigatran and enoxaparin, but more expensive than rivaroxaban. Apixaban was also more clinically effective than dabigatran and enoxaparin, but less effective than rivaroxaban. Both apixaban and rivaroxaban dominated dabigatran and enoxaparin in the total knee replacement analyses. Rivaroxaban dominated apixaban. The base-case results are summarised in tables 10 and 11.

Table 10 Base-case results in total hip replacement (taken from table 5.15, ERG report page 54)

Technologies	Total costs (£)	Total QALYs	Comparison with conventional treatment (enoxaparin)			Full incremental analysis			
			Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Comparator	Incremental costs (£)	Incremental QALYs	ICER (£/ QALY)
Apixaban	196.81	9.535	−238.98	0.015	Dominant				
Rivaroxaban	226.28	9.536	−209.51	0.016	Dominant	Apixaban	29.47	0.001	21,661
Dabigatran	263.89	9.523	−171.90	0.003	Dominant	Rivaroxaban	37.61	−0.013	Dominated
Enoxaparin	435.79	9.520				Rivaroxaban	209.51	−0.016	Dominated
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.									

Table 11 Base-case results in total knee replacement (taken from table 5.16, ERG report page 54)

Technologies	Total costs (£)	Total QALYs	Comparison with conventional treatment (enoxaparin)			Full incremental analysis			
			Incremental costs (£)	Incremental QALYs	ICER (£/ QALY)	Comparator	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Rivaroxaban	332.66	9.090	−301.51	0.068	Dominant				
Apixaban	360.54	9.075	−273.63	0.052	Dominant	Rivaroxaban	27.88	−0.015	Dominated
Dabigatran	514.80	9.028	−119.36	0.005	Dominant	Rivaroxaban	182.15	−0.063	Dominated
Enoxaparin	634.17	9.023				Rivaroxaban	301.51	−0.068	Dominated
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.									

The manufacturer undertook a number of one-way sensitivity analyses. The parameters tested in the one-way sensitivity analyses are presented in table 80 in the manufacturer's submission (pages 169–173). In addition, scenario analyses were undertaken in which the sources of clinical-effectiveness data were changed, that is, data from the indirect comparison using 30 mg enoxaparin, the mixed treatment comparison analysis excluding 30 mg enoxaparin, and the mixed treatment comparison analysis including 30 mg enoxaparin.

For total hip replacement surgery, apixaban remained dominant compared with enoxaparin and dabigatran for all changes in the one-way sensitivity analyses and the scenario analyses. The results of the one-way sensitivity and scenario analyses that change the conclusions of the deterministic analysis for apixaban compared with rivaroxaban are shown in the table below.

Table 13 Results of one-way sensitivity and scenario analysis in total hip replacement that change the conclusions of the deterministic analysis (taken from table 5.19, ERG report page 58)

	Apixaban vs. rivaroxaban		
Results	**Incremental costs**	**Incremental QALYs**	**ICER**
Base case	**-£29.47**	**−0.0014**	**£21,661**
Time horizon 1 year	−£31.98	−0.0001	£269,744
Time horizon 5 years	−£30.33	−0.0005	£63,311
Time horizon 10 years	−£29.93	−0.0008	£35,527
Age at surgery 80 years	−£30.27	−0.0007	£41,990
Comparator worse composite 'Total VTE and all-cause death' + 10%	−£31.83	−0.0007	£47,603
Comparator worse composite 'Total VTE and all-cause death':upper 95% CI	−£45.97	0.0035	Apixaban dominant
Comparator worse 'bleeding events': upper 95% CI	−£44.56	−0.0014	£32,775
Abbreviations: CI, confidence interval; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year; VTE, venous thromboembolism.			

For total knee surgery, apixaban remained dominant compared with enoxaparin and dabigatran for all changes in the one-way sensitivity analyses.

Similarly, rivaroxaban dominated apixaban for all changes. The scenario analyses did not show any changes in the base-case results. Apixaban dominated enoxaparin and dabigatran, and was dominated by rivaroxaban, for all scenario analyses.

In the original model only two treatments could be compared at once. This means that a probabilistic sensitivity analysis for all four comparators was not possible. The ERG requested a full incremental analysis in the clarification letter, which was then provided. The adapted probabilistic sensitivity analysis showed that in total hip replacement, apixaban had a 53% probability of being the most cost-effective drug at a threshold of £20,000 per QALY gained. Rivaroxaban had a probability of 47%. At a threshold of £30,000 these probabilities were 47% and 53%, respectively. For total knee replacement, at a threshold of £20,000, apixaban had an 11% probability of being the most cost-effective drug. For rivaroxaban this probability was 89%. At a threshold of £30,000, these probabilities were 10% and 90%, respectively.

3.2 Evidence Review Group comments

The ERG considered the modelling approach to be reasonable as it had followed the lead from previous economic models including a previous submission to NICE for the appraisal of dabigatran (NICE technology appraisal guidance 157). The ERG considered the health states modelled were appropriate for the required analysis. In addition, the ERG considered it appropriate for enoxaparin to be restricted to 40 mg once daily, which is the licensed dose in Europe. The ERG considered it reasonable that the manufacturer used enoxaparin to represent LMWHs. The ERG noted that the model does not allow movement from mild to moderate post-thrombotic syndrome to severe post-thrombotic syndrome, does not have bleeding events in the long-term Markov model, and does not account for heparin-induced thrombocytopenia. Although the ERG considered this a limitation, it was not expected to strongly affect the cost-effectiveness results. Incorporation of heparin-induced thrombocytopenia would be a disadvantage only to enoxaparin, as the other comparators do not cause it.

The ERG noted that the standard errors for the utilities and the utility decrements were all set to 10%. The ERG considered that it would have been more appropriate to use estimates based on empirical evidence. In the response on the request for clarification, the manufacturer reported standard errors from the literature, if available.

The ERG noted that for some of the utility inputs (post-thrombotic syndrome, impact of age, intracranial haemorrhage, symptomatic DVT) the method used to derive utilities was not mentioned. The ERG requested and received this additional information in the clarification phase. Based on the information provided by the manufacturer, it was clear to the ERG that a variety of instruments (standard gamble, time trade off, several tariffs of EQ-5D), perspectives (patients/general public), and populations (UK/Sweden/US/ various countries) were used to derive utility input. Therefore, the ERG considered the utility values and decrements to be prone to some bias. In addition, the duration for which utility decrements were applied was predominantly based on assumptions, and not further justified. However, the ERG stated that it is likely that the best available sources of information were used.

The ERG highlighted that the costs were different to the costs used in 'Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults' (NICE technology appraisal guidance 170) and 'Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults' (NICE technology appraisal guidance 157). The ERG commented that this was possibly a result of the difference in the cost calculations, and differences in assumptions. However the ERG noted that it was unlikely that the differences in cost inputs between the appraisals would have an impact on the conclusions. In general, the ERG agreed with the approach to estimating costs of the interventions, health states and events.

The ERG stated that it was unclear why all parameter uncertainty was not reflected in the probabilistic sensitivity analyses. The manufacturer's

submission states that the probabilistic sensitivity analyses included parameters that are not in the one-way sensitivity analyses. However, the ERG noted that treatment duration is included in both. The ERG commented that the fact that not all uncertainty was included in the probabilistic sensitivity analyses probably underestimates the total uncertainty.

Additional work undertaken by the ERG

The ERG analysed cost effectiveness, including evidence from the recently published RE-NOVATE-II study on the relative risk of bleeding for dabigatran. A comparison was made between all comparators, including the total costs of fondaparinux. The updated relative risk resulted in total costs of dabigatran of £266.12, which was £2.23 higher than in the previous analysis. The update did not affect the number of QALYs gained by dabigatran, and did not impact on any of the ICERs presented. For further details of the additional work undertaken by the ERG, see pages 66-68 of the ERG report.

4 Equalities issues

No equality and diversity issues relating to population groups protected by equality legislation were highlighted when the scope for this appraisal was developed or in any of the submissions

5 Authors

Alfred Sackeyfio (Technical Lead) and Nicolay Hay (Technical Adviser) with input from the Lead Team (William Turner, David Thomson and Stephen Sharp).

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

A The Evidence Review Group report for this appraisal was prepared by Kleijnen Systematic Reviews Limited in collaboration with Erasmus University Rotterdam and Maastricht University:

- Reimsma R, Joore M, Grutters J et al. Apixaban for the prevention of venous thromboembolism in people undergoing elective knee and hip replacement surgery: a single technology appraisal (October 2011)

B Submissions or statement were received from the following organisations:

I Manufacturer/sponsor:

- Bristol-Myers Squibb and Pfizer

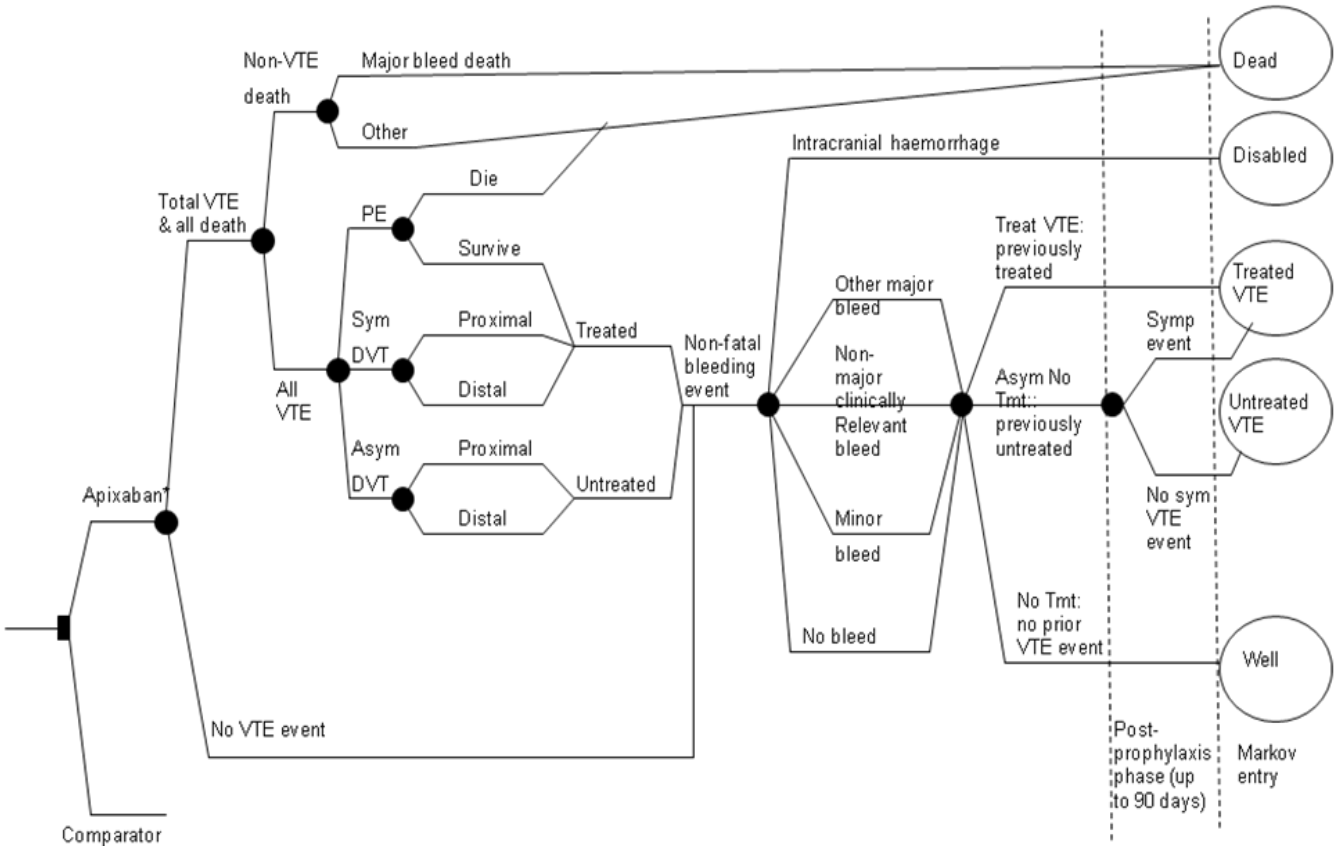
II Professional/specialist, patient/carer and other groups:

- Anticoagulation Europe
- Lifeblood: The Thrombosis Charity
- NHS Warwickshire
- Royal College of Anaesthetists

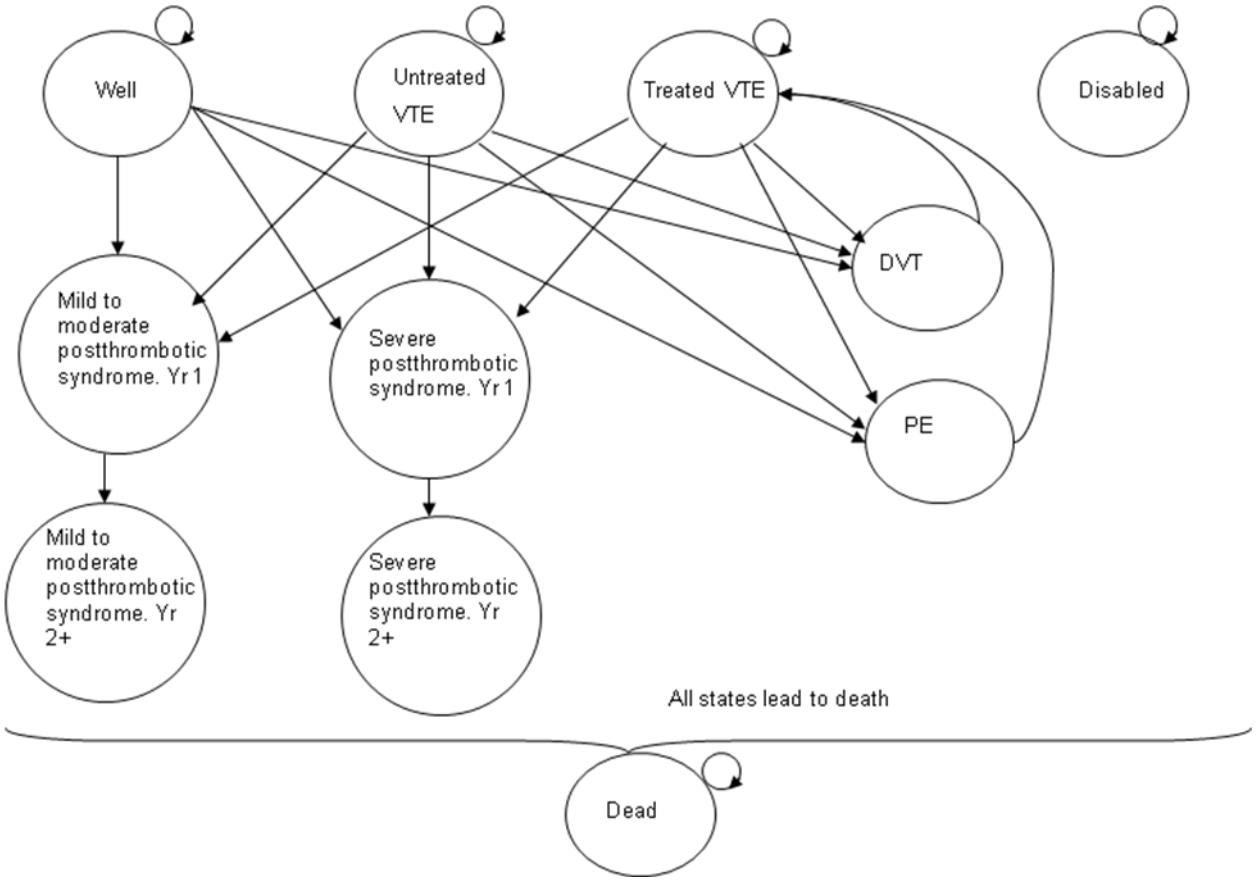
Appendix B

Model structures from manufacturer's submission

Prophylaxis and post-prophylaxis phases – VTE and bleeding events



Long-term Markov model



Appendix C

Recommendations from related NICE guidance

Dabigatran etexilate for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery. NICE technology appraisal guidance 157 (September 2008)

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.

Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults. NICE technology appraisal guidance 170 (April 2009)

Rivaroxaban, within its marketing authorisation, is recommended as an option for the prevention of venous thromboembolism in adults having elective total hip replacement surgery or elective total knee replacement surgery.

Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital. NICE clinical guideline 92 (January 2010)

Elective hip replacement

Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients undergoing elective hip replacement surgery.

- Start mechanical VTE prophylaxis at admission. Choose any one of the following, based on individual patient factors:
  - anti-embolism stockings (thigh or knee length), used with caution
  - foot impulse devices
  - intermittent pneumatic compression devices (thigh or knee length).

  Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Provided there are no contraindications, start pharmacological VTE prophylaxis after surgery. Choose any one of:
  - dabigatran etexilate, starting 1-4 hours after surgery[1]
  - fondaparinux sodium, starting 6 hours after surgical closure provided haemostasis has been established
  - LMWH, starting 6–12 hours after surgery
  - rivaroxaban, starting 6-10 hours after surgery[2]
  - UFH (for patients with renal failure), starting 6–12 hours after surgery.

  Continue pharmacological VTE prophylaxis for 28–35 days, according to the summary of product characteristics for the individual agent being used.

Elective knee replacement

Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients undergoing elective knee replacement surgery.

- Start mechanical VTE prophylaxis at admission. Choose any one of the following, based on individual patient factors:
  - anti-embolism stockings (thigh or knee length), used with caution
  - foot impulse devices
  - intermittent pneumatic compression devices (thigh or knee length).

  Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Provided there are no contraindications, start pharmacological VTE prophylaxis after surgery. Choose any one of:
  - dabigatran etexilate, starting 1-4 hours after surgery[3]

[1] In line with 'Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults' (NICE technology appraisal guidance 157), dabigatran etexilate, within its marketing authorisation, is recommended as an option for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery.

[2] In line with 'Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults' (NICE technology appraisal guidance 170), rivaroxaban, within its marketing authorisation, is recommended as an option for the prevention of venous thromboembolism in adults having elective total hip replacement.

[3] In line with 'Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults' (NICE technology appraisal guidance 157), dabigatran etexilate, within its marketing authorisation, is recommended as an option for the primary

- fondaparinux sodium, starting 6 hours after surgical closure provided haemostasis has been established
- LMWH, starting 6–12 hours after surgery
- rivaroxaban, starting 6-10 hours after surgery[4]
- UFH (for patients with renal failure), starting 6–12 hours after surgery.

Continue pharmacological VTE prophylaxis for 10–14 days, according to the summary of product characteristics for the individual agent being used.

prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery.

[4] In line with 'Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults' (NICE technology appraisal guidance 170), rivaroxaban, within its marketing authorisation, is recommended as an option for the prevention of venous thromboembolism in adults having elective total hip replacement.