NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

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

> This guidance was developed using the single technology appraisal (STA) process.

1   Guidance

1.1   Apixaban is recommended as an option for the prevention of venous thromboembolism in adults after elective hip or knee replacement surgery.

2   The technology

2.1   Apixaban (Eliquis, Bristol-Myers Squibb and Pfizer) is an anticoagulant that affects the blood coagulation cascade by directly inhibiting activated factor X (factor Xa), so inhibiting thrombin formation and the development of thrombi. Apixaban has a marketing authorisation for the 'prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery'.

2.2   The recommended dosage of apixaban in the summary of product characteristics is 2.5 mg orally twice daily. The initial dose should be taken 12–24 hours after surgery. The duration of treatment depends on the individual risk of the patient for venous

thromboembolism, which is determined by the type of orthopaedic surgery. Recommended treatment durations are 32–38 days for patients having hip replacement surgery and 10–14 days for patients having knee replacement surgery.

2.3 According to the summary of product characteristics, 11% of patients treated with apixaban 2.5 mg twice daily in clinical trials experienced adverse reactions. As with other anticoagulants, bleeding may occur during apixaban therapy in patients with risk factors such as lesions liable to bleed. Common adverse reactions are anaemia, haemorrhage, confusion and nausea. For full details of side effects and contraindications, see the summary of product characteristics.

2.4 Apixaban costs £17.15, £34.30 and £102.90 for packs of 10, 20 and 60 tablets respectively excluding VAT (NHS list price as reported by the manufacturer). The cost of treatment is estimated to be £41.16 (based on 12 days' treatment) for knee replacement surgery and £116.62 for hip replacement surgery (based on 34 days' treatment). Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of apixaban and a review of this submission by the Evidence Review Group (ERG; appendix B).

3.1 The manufacturer's submission compared apixaban with enoxaparin, a low molecular weight heparin (LMWH), using direct evidence from randomised controlled trials, and with dabigatran etexilate, rivaroxaban and fondaparinux, using evidence from randomised controlled trials that had been incorporated into an adjusted indirect comparison and a mixed treatment comparison.

Outcomes analysed included mortality, incidence of venous thromboembolism and adverse reactions to treatment. All of these were specified in the decision problem for this appraisal. The clinical evidence submitted by the manufacturer did not include analysis of outcomes such as joint infection, length of hospital stay, complications after deep vein thrombosis or health-related quality of life because these were not available from the clinical trials of apixaban. However, the manufacturer included complications after deep vein thrombosis and health-related quality of life in its economic submission.

3.2   The manufacturer identified four randomised controlled trials comparing apixaban with enoxaparin for the prevention of venous thromboembolism. ADVANCE 1 ('Apixaban dosed orally versus anticoagulation with enoxaparin'), ADVANCE 2 and APROPOS ('Apixaban prophylaxis in patients undergoing total knee replacement surgery') recruited patients having total knee replacement surgery. ADVANCE 3 recruited patients having total hip replacement surgery.

3.3   ADVANCE 1 (n = 3195) and ADVANCE 2 (n = 3057) were multicentre parallel-group randomised controlled trials. In ADVANCE 1, apixaban was given at a dosage of 2.5 mg twice daily for 12 days and enoxaparin at a dosage of 30 mg twice daily for 12 days. Treatment in both arms was started 12–24 hours after surgery. In ADVANCE 2, apixaban was given at a dosage of 2.5 mg twice daily for 11 days and enoxaparin at a dosage of 40 mg once daily for 11 days. Apixaban was started 12–24 hours after surgery and enoxaparin 9–15 hours before surgery. APROPOS (n = 305) was a dose-finding clinical study in which patients 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. ADVANCE 2 used the UK dosing regimen for enoxaparin (40 mg once daily) whereas ADVANCE 1 and APROPOS used the US dosing regimen (30 mg twice daily). The manufacturer considered ADVANCE 2 to be the most relevant study for the prevention of venous thromboembolism after total knee replacement surgery in the context of UK clinical practice because it was the only study that compared apixaban with the UK licensed dose of enoxaparin.

3.4   ADVANCE 3 (n = 5407) was a multicentre parallel-group randomised controlled trial comparing apixaban with enoxaparin for the prevention of venous thromboembolism after total hip replacement surgery. Apixaban was given at a dosage of 2.5 mg twice daily for 32–38 days and enoxaparin at a dosage of 40 mg once daily for 32–38 days. Apixaban was started 12–24 hours after surgery and enoxaparin 9–15 hours before surgery.

3.5   The primary efficacy end point for ADVANCE 1 and ADVANCE 2 was the composite of all incidences of venous thromboembolism (pulmonary embolism, symptomatic and asymptomatic deep vein thrombosis), and death from any cause during the intended treatment period. The primary safety end point was bleeding and included confirmed major bleeding events, a composite of confirmed major bleeding events and confirmed non-major bleeding events, and all bleeding events. The primary efficacy end point for ADVANCE 3 was the composite of symptomatic or asymptomatic deep vein thrombosis, non-fatal pulmonary embolism, 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 end point for APROPOS was the composite of symptomatic or asymptomatic

deep vein thrombosis, non-fatal pulmonary embolism and death from any cause. The primary safety end point was major bleeding.

3.6 The primary efficacy analysis dataset included all randomised patients who had a bilateral venogram that was evaluable, venous thromboembolism, or who died from any cause. The manufacturer stated that the intention-to-treat analysis assumed that no readable venogram represented no event, which potentially underestimated the number of venous thromboembolic events in the intention-to-treat population. The remaining efficacy and safety analyses were conducted on the intention-to-treat population.

3.7 ADVANCE 2 showed that apixaban was statistically significantly superior to enoxaparin in terms of the primary composite end point of all venous thromboembolism and death from any cause (relative risk [RR] 0.62, 95% confidence interval [CI] 0.51 to 0.74), as well as in terms of major venous thromboembolism (RR 0.5, 95% CI 0.26 to 0.97) and all deep vein thrombosis (RR 0.6, 95% CI 0.5 to 0.72). For major bleeding events and all bleeding events, the relative risks were 0.65 (95% CI 0.28 to 1.49) and 0.83 (95% CI 0.65 to 1.06) respectively. ADVANCE 1 and APROPOS both used the US dosing regimen for enoxaparin and neither reported significant differences for any of the outcomes reported.

3.8 ADVANCE 3 showed that apixaban was statistically significantly superior to enoxaparin in terms of the primary composite end point of all venous thromboembolism and death from any cause (RR 0.36, 95% CI 0.23 to 0.56), as well as in terms of major venous thromboembolism (RR 0.4, 95% CI 0.19 to 0.83) and all deep vein thrombosis (RR academic in confidence). For major bleeding events and all bleeding events the relative risks were 1.22 (95% CI 0.65 to 2.26) and 0.93 (95% CI 0.81 to 1.08) respectively.

3.9   In the absence of direct evidence comparing apixaban with dabigatran etexilate, rivaroxaban and fondaparinux, the manufacturer presented results of an adjusted indirect comparison using enoxaparin as the common comparator. The manufacturer did not include an assessment of apixaban compared with other LMWHs in the indirect comparison. It considered enoxaparin to be the most widely used LMWH in the UK. Moreover, enoxaparin was the comparator used in the apixaban registration trials (ADVANCE 2 and 3). The manufacturer identified 15 randomised controlled trials for inclusion in the indirect comparison. Of these, nine compared the treatment of interest with enoxaparin at the UK dosage of 40 mg once daily. The remaining six studies compared the treatment of interest with enoxaparin 30 mg twice daily.

3.10   The manufacturer reported adjusted indirect comparisons using pooled data from studies using the UK dosage of enoxaparin alone, US dosage of enoxaparin alone and combined UK and US dosages of enoxaparin as the common comparator. Results were expressed as odds ratios for apixaban versus the other treatments of interest. For the outcome of composite venous thromboembolic events, and other end points of any deep vein thrombosis, asymptomatic deep vein thrombosis and major venous thromboembolism, results from the primary efficacy population were reported. For symptomatic deep vein thrombosis, pulmonary embolism, any bleeding, major bleeding, clinically relevant non-major bleeding and minor bleeding, results were reported from the intention-to-treat population.

3.11   The manufacturer stated that it considered the adjusted indirect comparisons of apixaban 2.5 mg twice daily against other anticoagulants of interest using the UK dosage of enoxaparin to be the most relevant to UK clinical practice. The results of such analyses for hip replacement showed that there were no significant

differences for apixaban when compared with rivaroxaban for total venous thromboembolism and death from any cause, any deep vein thrombosis, major venous thromboembolism, pulmonary embolism, any bleeding or major bleeding. These results were the same for total knee replacement, except for the number of pulmonary embolic events, which was statistically significantly reduced with rivaroxaban. When compared with dabigatran etexilate, total venous thromboembolism, death from any cause and any deep vein thrombosis were statistically significantly reduced with apixaban; there were no significant differences for the other main outcomes (major venous thromboembolism, pulmonary embolism, any bleeding and major bleeding). These results were the same for total hip replacement and total knee replacement. When compared with fondaparinux in patients with total hip replacement, apixaban showed no significant differences for any deep vein thrombosis, pulmonary embolism or major bleeding. Other main outcomes (total venous thromboembolism and death from any cause, major venous thromboembolism and any bleeding) were not reported using indirect comparisons. There were no randomised controlled trials comparing fondaparinux with the UK dosage (40 mg daily) of enoxaparin in patients having total knee replacement surgery, therefore an adjusted indirect comparison was not possible. The results of the adjusted indirect comparisons using data with US dosages of enoxaparin and pooled data with UK and US dosages of enoxaparin were considered to be academic in confidence by the manufacturer and therefore cannot be presented.

3.12 The manufacturer also undertook a mixed treatment comparison that included 43 studies. Results were expressed as odds ratios and were for the same outcomes as for the adjusted indirect comparisons. The manufacturer reported mixed treatment comparisons using only the UK dosage of enoxaparin and also

National Institute for Health and Clinical Excellence   Page 7 of 33
Final appraisal determination – Apixaban for the prevention of venous thromboembolism
Issue date: November 2011

using pooled data for UK and US dosages. The results of the mixed treatment comparisons cannot be reported because the manufacturer considers the results to be academic in confidence.

3.13   The manufacturer considered the adjusted indirect comparison using the UK dosage of enoxaparin to be the most appropriate analysis for informing the relative efficacy and safety of apixaban compared with enoxaparin, rivaroxaban, dabigatran etexilate and fondaparinux. This was because results from the mixed treatment comparison were inconsistent with some of the head-to-head data from the randomised controlled trials. The manufacturer noted that the inconsistent results and wider credibility intervals may be a result of the large number of trials contributing to the enoxaparin 40 mg once daily node in the network analysis. These trials tended to be older, with fewer study criteria reported and small sample sizes, and compared enoxaparin 40 mg once daily with treatments other than the comparators in the scope. The manufacturer highlighted inconsistencies between the results of the mixed treatment comparison and the head-to-head trial for the following comparisons: apixaban 2.5 mg twice daily compared with enoxaparin 40 mg once daily, and rivaroxaban 10 mg once daily compared with enoxaparin 40 mg once daily for the primary composite end point (venous thromboembolism plus death from any cause) and on some of the secondary outcomes.

3.14   The ERG considered that the three clinical trials, ADVANCE 1, 2 and 3, 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.

3.15   The manufacturer submitted an economic model assessing the cost effectiveness of apixaban compared with enoxaparin, dabigatran etexilate and rivaroxaban. A two-stage modelling approach was adopted, based on an approach previously used for 'Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults' (NICE technology appraisal guidance 157). A decision tree was used to model treatment in the prophylactic phase (from the time of surgery to 90 days after surgery) and a Markov model was used to model long-term events (90 days after surgery and beyond). The differential effects of treatment are only realised in the prophylactic phase of the model. The Markov model has a cycle length of 1 year and a maximum time horizon of 60 years (base case 35 years).

3.16   In the decision tree model, a hypothetical patient can experience a venous thromboembolic event (total venous thromboembolic events or death from any cause) or no event. When death is not a result of venous thromboembolism, death can result from a major bleed or other cause. Deaths from other causes refer to deaths not related to venous thromboembolism and deaths not related to anticoagulation during the prophylactic phase. A venous thromboembolic event can be a pulmonary embolism, symptomatic or asymptomatic deep vein thrombosis (both either distal or proximal). Pulmonary embolism may or may not result in death. A

cohort of hypothetical patients surviving pulmonary embolism and a cohort with symptomatic deep vein thrombosis receive treatment and progress to the non-fatal bleeding events state of the model. A cohort of hypothetical patients with asymptomatic deep vein thrombosis progress to the non-fatal bleeding events state without treatment. A cohort of hypothetical patients without venous thromboembolic events also progress directly to the non-fatal bleeding state. Probabilities of bleeding are independent of what happened earlier in the model. A cohort of hypothetical 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, hypothetical 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 treatment and 90 days after surgery, hypothetical patients without symptoms can become symptomatic. Asymptomatic deep vein thrombosis that becomes symptomatic after prophylactic treatment is assumed to be of the same type (distal thrombosis remains distal and proximal thrombosis remains proximal).

3.17   At 90 days after surgery a cohort of hypothetical patients leave the decision tree model and enter the long-term Markov model. Hypothetical patients who have not experienced a venous thromboembolic event enter the Markov model in the 'well' state, whereas hypothetical patients who have asymptomatic deep vein thrombosis enter the Markov model in the untreated venous thromboembolic state. Hypothetical patients who have had a pulmonary embolism or a deep vein thrombosis or have made the transition from asymptomatic to symptomatic deep vein thrombosis enter the Markov model in the treated venous thromboembolic state. Hypothetical patients who have had an intracranial

haemorrhage enter in the 'disabled' health state. A cohort of hypothetical patients who died while in the decision tree model enter the Markov model in the 'dead' state. In the long-term Markov model, a cohort of hypothetical patients can remain well, die, have a pulmonary embolism, a deep vein thrombosis, mild-to-moderate post-thrombotic syndrome (divided into year 1 and subsequent years) or a severe post-thrombotic syndrome (divided into year 1 and subsequent years). The same transitions are possible for treated and untreated patients. Once a hypothetical patient has a pulmonary embolism or deep vein thrombosis they make the transition to the treated venous thromboembolic state. There is no differential treatment effect in this long-term phase of the model.

3.18 Key assumptions in the economic evaluation included the assumption that during the prophylactic phase, deaths from pulmonary embolism and other causes occur at 35 days for total hip replacement and 14 days for total knee replacement in each treatment arm. It was assumed that during the phase after prophylaxis, deaths from pulmonary embolism occur at 63 days for total hip replacement and 52 days for total knee replacement. These are the midpoints of the post-prophylactic phase for each indication. It was also assumed that deaths from major bleeds occur at 35 days for total hip replacement and 14 days for total knee replacement, regardless of whether the bleeding rates were based on the duration of prophylaxis or 90 days.

3.19 The manufacturer modelled the efficacy (total venous thromboembolic events and all deaths) and safety (total bleeds) of the treatments in line with the corresponding end points in the two clinical trials of apixaban (ADVANCE 2 and 3) and in the indirect comparison of apixaban with rivaroxaban and with dabigatran etexilate. The manufacturer stated that because data were not

available for an indirect comparison of apixaban with fondaparinux in patients having total knee replacement surgery, apixaban could not be compared with fondaparinux in the economic model. The manufacturer also stated that relative risks were used in the economic model rather than odds ratios because they can be directly applied to an absolute probability of an event to generate the absolute event rate for the comparator treatment. The manufacturer's original economic model did not distinguish between types of bleed and types of venous thromboembolism for each comparator individually, but assumed that they were all the same. Since this assumption may favour apixaban, the ERG asked the manufacturer to provide an adjusted model that allowed the differences in type of bleed and type of venous thromboembolism. This adapted model was provided by the manufacturer.

3.20   The probabilities of other clinical events in the decision tree element of the model were assumed to be treatment independent and assumed not to differ between apixaban, enoxaparin, rivaroxaban and dabigatran etexilate. Where possible, the probabilities for the post-event treatment-independent probabilities were obtained from a synthesis of all the trials on rivaroxaban and dabigatran etexilate. The manufacturer undertook a literature review to identify parameter estimates of long-term recurrent venous thromboembolism and post-thrombotic syndrome.

3.21   The manufacturer presented drug acquisition costs for a course of treatment depending on the treatment durations assumed for each treatment. The treatment durations applied were: for apixaban, total knee replacement 12 days and total hip replacement 34 days (mean duration in ADVANCE 2 and 3 trials) ; for enoxaparin, total knee replacement 12 days and total hip replacement 34 days (mean duration in ADVANCE 2 and 3 trials) ;for rivaroxaban total

knee replacement 12 days and total hip replacement 33 days (mean duration in RECORD 1 and 3 trials) ; for dabigatran etexilate ,and total knee replacement 8 days and total hip replacement 32 days (median duration in RE-MODEL and RE-NOVATE) . The costs per course of treatment for total knee replacement were £48.48, £52.97, £33.60 and £41.16 for enoxaparin, rivaroxaban, dabigatran etexilate and apixaban respectively. For total hip replacement the costs per course of treatment were £137.36, £145.68, £134.40 and £116.62 for enoxaparin, rivaroxaban dabigatran etexilate and apixaban respectively.

3.22   The manufacturer presented base-case analyses for people having total hip replacement surgery and for those having total knee replacement surgery. In the base-case analyses a comparison was made between enoxaparin, apixaban, dabigatran etexilate and rivaroxaban. For both total hip replacement surgery and total knee replacement surgery, apixaban, dabigatran etexilate and rivaroxaban were less expensive than enoxaparin. The quality-adjusted life year (QALY) differences between the treatments were small. For people having total hip replacement surgery, total QALYs ranged from 9.520 for enoxaparin to 9.536 for rivaroxaban. For patients having total knee replacement surgery, total QALYs ranged from 9.023 for enoxaparin to 9.090 for rivaroxaban.

3.23   For patients having total hip replacement, apixaban, rivaroxaban and dabigatran etexilate all dominated enoxaparin, that is they were less expensive and provided more benefit than enoxaparin. Apixaban was the least expensive technology. Both apixaban and rivaroxaban were more effective and less costly, and thus dominant, compared with dabigatran etexilate and enoxaparin. Rivaroxaban generated more QALYs compared with apixaban. The incremental cost-effectiveness ratio (ICER) of rivaroxaban was

£21,661 per QALY gained compared with apixaban. For people having total knee replacement surgery, apixaban was less expensive than dabigatran etexilate and enoxaparin, but more expensive than rivaroxaban. Apixaban was also more clinically effective than dabigatran etexilate and enoxaparin. Both apixaban and rivaroxaban dominated dabigatran etexilate and enoxaparin in the analyses for total knee replacement.

3.24 The manufacturer conducted deterministic one-way sensitivity analysis. For patients having total hip replacement, apixaban remained dominant compared with enoxaparin and dabigatran etexilate for all changes in the sensitivity analysis. Rivaroxaban was cost effective compared with apixaban, except when the time horizon was 10 years or less, when the age at surgery was 80 years, or when a smaller relative difference in the risk of the primary end point (total venous thromboembolic events and death from any cause) was assumed. For patients having total knee replacement, apixaban remained dominant compared with enoxaparin and dabigatran etexilate for all changes in the deterministic sensitivity analysis, whereas rivaroxaban dominated apixaban for all changes.

3.25 The manufacturer also presented probabilistic sensitivity analysis, which showed that in total hip replacement apixaban had a 53% probability of being the most cost-effective drug at a maximum acceptable ICER of £20,000 per QALY gained and rivaroxaban had a probability of 47%. At a maximum acceptable ICER of £30,000 per QALY gained these probabilities were 47% and 53% respectively. For total knee replacement, at a maximum acceptable ICER of £20,000 per QALY gained, apixaban had an 11% probability of being the most cost-effective drug. For rivaroxaban this probability was 89%. At a maximum acceptable ICER of

£30,000 per QALY gained, these probabilities were 10% and 90% respectively.

3.26 The ERG considered the modelling approach to be reasonable because it had followed previous economic models, including a previous submission to NICE for NICE technology appraisal guidance 157. The ERG considered that the health states modelled were appropriate. The ERG also considered it appropriate for enoxaparin to be restricted to 40 mg once daily, which is the dosage licensed in Europe. The ERG considered it reasonable that the manufacturer had 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 and that there are no bleeding events in the long-term Markov model.

3.27 The ERG noted that all parameter uncertainty was not reflected in the probabilistic sensitivity analyses. The ERG therefore commented that the probabilistic sensitivity analyses probably underestimate the total uncertainty.

3.28 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from www.nice.org.uk/guidance/TAXXX

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of apixaban for the prevention of venous thromboembolism after elective total hip or knee replacement surgery in adults having considered evidence on the nature of the condition and the value placed on the benefits of apixaban by people with the condition, those who represent them,

and clinical specialists. It also took into account the effective use of NHS resources.

4.2   The Committee discussed the decision problem and agreed that this appraisal would focus on choice among drugs for preventing venous thromboembolism. The Committee discussed 'Venous thromboembolism: reducing the risk' (NICE clinical guideline 92). It noted the recommendation that in addition to mechanical prophylaxis, people having elective hip replacement or elective knee replacement should be offered LMWH, dabigatran etexilate, rivaroxaban or fondaparinux. It also noted the written comments received from one of the clinical specialists that the newer oral anticoagulant agents for the prevention of venous thromboembolism are not used by all surgical units because some surgeons are concerned that they may increase the incidence of bleeding at the operation site, increasing the risk of infection, delayed wound healing and delayed mobilisation. The Committee was aware of these concerns, but concluded that any recommendations made would be limited to situations in which drugs for the prevention of venous thromboembolism were already recommended in 'Venous thromboembolism: reducing the risk' (NICE clinical guideline 92).

4.3   The Committee discussed the benefits of oral treatments compared with subcutaneous injection, in particular the greater acceptability and ease of management of oral administration. The Committee noted the written evidence from one of the clinical specialists and the patient expert that for treatments given by subcutaneous injection, people would have to be taught to self-inject before discharge from hospital or a district nurse would have to continue the treatment after discharge. The Committee heard from patient experts and the clinical specialist present at the Committee meeting

that people prefer oral dosing to subcutaneous injection and therefore adherence to treatment after discharge might improve, although this remained uncertain. The Committee noted the twice-daily regimen for apixaban compared with the once-daily regimens for rivaroxaban and dabigatran etexilate. The Committee heard from the patient experts that if people received enough information about the effectiveness of apixaban and the importance of preventing venous thromboembolism they would be likely to adhere to apixaban treatment even though they needed to take it twice a day.

4.4   The Committee discussed the clinical effectiveness of apixaban compared with LMWH, rivaroxaban, dabigatran etexilate and fondaparinux in people having elective hip or knee surgery. It noted the direct evidence from randomised controlled trials of apixaban and enoxaparin, and the indirect and mixed treatment comparison of apixaban versus rivaroxaban, dabigatran etexilate and fondaparinux. It also noted that the direct evidence was limited to a comparison of apixaban and enoxaparin and that the manufacturer assumed that all LMWHs were equivalent in terms of their clinical effectiveness. The Committee heard that enoxaparin is the most widely used LMWH in the UK, and agreed that the comparison using enoxaparin as the only LMWH was appropriate. It discussed the applicability of the clinical trials to UK clinical practice, understanding that there is variation in strategies for preventing venous thromboembolism. The Committee agreed that data from the ADVANCE 2 and ADVANCE 3 randomised controlled trials, in which the patients in the control arm received 40 mg enoxaparin once daily, were applicable to UK clinical practice. It agreed that the ADVANCE 1 and APROPOS trials, which used an alternative dosing regimen of 30 mg enoxaparin twice daily, did not use the UK

licensed dosage, and that they were less relevant to the evaluation of clinical effectiveness of apixaban than ADVANCE 2 and 3.

4.5   The Committee discussed the outcome data from these trials. It noted the written concerns of one of the clinical specialists about the use of surrogate markers as valid predictors of clinically relevant outcomes. The clinical specialist highlighted that there were limited data available to show a relationship between one of the major components of the composite primary outcome of the studies (asymptomatic deep vein thrombosis) and clinically relevant venous thromboembolic events, and that the data that were available did not suggest that asymptomatic deep vein thrombosis was a good predictor of clinical thromboembolic events after joint-replacement surgery. The clinical specialist present at the meeting stated that in his opinion there was sufficient evidence to suggest an association between asymptomatic deep vein thrombosis and acute pulmonary embolism. The Committee acknowledged the difference of opinion expressed by clinician specialists about asymptomatic deep vein thrombosis but agreed that asymptomatic deep vein thrombosis was widely used as an outcome measure in research studies, and was relevant for consideration.

4.6   The Committee discussed the results of the ADVANCE trials and concluded that apixaban was significantly more effective than enoxaparin in preventing venous thromboembolism. The Committee considered adverse events such as bleeding, noting that the bleeding rates were lower for apixaban than for enoxaparin, although the difference was not statistically significant. It concluded that apixaban could, using the evidence available, be considered more clinically effective than enoxaparin in preventing venous thromboembolic events, but was broadly comparable to enoxaparin in terms of short-term adverse effects.

National Institute for Health and Clinical Excellence   Page 18 of 33
Final appraisal determination – Apixaban for the prevention of venous thromboembolism
Issue date: November 2011

4.7   The Committee considered the evidence on the clinical effectiveness of apixaban compared with rivaroxaban, dabigatran etexilate and fondaparinux through the indirect and mixed treatment comparisons. The Committee noted the ERG's critique of the indirect and mixed treatment comparisons and the manufacturer's response to the clarification requested by the ERG. It also noted that the manufacturer had undertaken three indirect and two mixed treatment comparison analyses which took account of the differences in UK and USA dosages of enoxaparin. The Committee agreed with the manufacturer and the ERG that the indirect and mixed treatment comparisons using the UK dosage of enoxaparin were most relevant to UK clinical practice and therefore it was reasonable to consider the results of these comparisons. The Committee was aware of the uncertainty associated with the results from the indirect comparison and the mixed treatment comparison as demonstrated by the wide confidence intervals (surrounding the point estimates from the indirect comparison analysis) and the credibility intervals (surrounding the point estimates from the mixed treatment comparison). The Committee was also aware of the inconsistency of some results between the indirect comparison and the mixed treatment comparison and between the indirect comparison and the direct randomised controlled trials, and the manufacturer's explanation for these inconsistencies. The Committee agreed that based on the evidence presented it was not possible to estimate the relative effectiveness of apixaban compared with rivaroxaban, dabigatran etexilate or fondaparinux.

4.8   The Committee then considered the factors that clinicians take into account when prescribing anticoagulant therapy for people having total hip and knee replacement surgery. The Committee discussed the concerns raised by orthopaedic surgeons about the effect of anticoagulants on local bleeding, infection and wound healing. The

Committee noted the written statement from one clinical specialist that bleeding caused by anticoagulation is clinically important because it can contribute to deep surgical site infection. The Committee also noted from the written statement that some orthopaedic surgeons believed that new oral antithrombotic agents such as rivaroxaban and dabigatran etexilate may be associated with more treatment-related bleeds than enoxaparin and result in worse patient outcomes. The Committee heard from the clinical specialist present at the meeting that there was a 'trade-off' to be made between the benefits of reduced thrombotic events and increased risk of bleeding.

4.9   The Committee discussed the risk of bleeding into the joint and the association between the time between surgery and anticoagulant therapy taking effect, that is, the greater the time between surgery and anticoagulant therapy taking effect the lower the risk of bleeding. The Committee was aware of the different starting times in the summaries of product characteristics for each of the anticoagulants and noted that apixaban had the longest time window for administration following surgery (12–24 hours after surgery, compared with rivaroxaban 6–10 hours after surgery, dabigatran etexilate 1–4 hours after surgery and enoxaparin 6–12 hours after surgery). The Committee had not seen any evidence assessing the association between the different drug regimens and the risk of bleeding. The Committee agreed that the longer time window for administration of apixaban could allow clinicians to assess a patient's bleeding risk before starting thromboprophylaxis after total hip or knee replacement surgery

4.10   The Committee then discussed the choice of anticoagulants for people with renal disease. The Committee heard from the clinical specialist that in patients with severe renal disease all

anticoagulant therapy carries additional risks and oral agents would be unsuitable. The Committee noted that for mild-to-moderate renal disease, the summary of product characteristics for apixaban did not specify a dose adjustment whereas the summary of product characteristics for dabigatran etexilate did. The Committee agreed that although there was insufficient evidence to determine the relative clinical effectiveness of the oral anticoagulants, apixaban and rivaroxaban shared a potential benefit for clinical practice in that there is no need to modify the dose in people with mild to moderate kidney function impairment.

4.11 The Committee discussed the evidence submitted by the manufacturer on the cost effectiveness of apixaban for the prevention of venous thromboembolism in people having hip or knee replacement, the ERG's critique of the manufacturer's submission, and the manufacturer's response to the clarification requested by the ERG. The Committee noted the two-phase structure of the economic model and accepted that the modelling approach used by the manufacturer was appropriate for modelling the prevention of venous thromboembolism.

4.12 The Committee discussed the base-case analysis in the manufacturer's submission. It noted that the manufacturer had not included fondaparinux in the economic evaluation because there was insufficient clinical evidence available for the indirect comparison of apixaban and fondaparinux in patients having total knee replacement surgery. It also noted that the manufacturer had highlighted that fondaparinux was used in less than 1% of people in current UK clinical practice. The Committee noted that in the base-case analysis apixaban dominated enoxaparin and dabigatran etexilate in both total hip and knee replacement, that is, apixaban was associated with larger QALY gains and lower costs. It further

noted that for total knee replacement the ICER for rivaroxaban compared with apixaban was £21,700 per QALY gained, but for total hip replacement rivaroxaban dominated apixaban. The Committee then considered the plausibility of the ICERs, in particular in relation to the strength of the evidence for clinical effectiveness. The Committee recognised that there were uncertainties associated with the ICERs for rivaroxaban and dabigatran etexilate because the clinical data for these drugs included in the model were originally derived from the indirect comparison, unlike the ICER for enoxaparin which was derived from direct head-to-head trials. The Committee therefore agreed that the cost-effectiveness results for apixaban compared with enoxaparin were the most robust.

4.13   The Committee concluded that apixaban was more clinically effective and cheaper than enoxaparin. It also concluded that there was insufficient clinical evidence to determine whether or not apixaban was more or less clinically effective than rivaroxaban and dabigatran etexilate and therefore the ICERs presented for these anticoagulants had to be interpreted with caution. However, the Committee did accept that any differences between the agents were likely to be small, and apixaban might provide some clinical advantages compared with the other agents. The Committee therefore concluded that apixaban should be recommended as an option for preventing venous thromboembolism in adults after elective total hip and total knee replacement surgery.

4.14   The Committee considered whether its recommendation was associated with any issues related to equality legislation and the requirement for fairness. The Committee noted that no issues had been highlighted during the scoping exercise or during the course of the appraisal. The Committee was aware that consultees and

commentators had raised the issue of providing non-injectable medication for people with needle phobia but concluded that the recommendations do not affect access to the technology for any specific groups.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title: 'Apixaban for the prevention of venous thromboembolism after total hip or knee replacement in adults'	Section
Key conclusion		
Apixaban is recommended as an option for the prevention of venous thromboembolism in adults after elective hip or knee replacement surgery.		1.1
The Committee concluded that apixaban was more clinically effective and cheaper than enoxaparin. It also concluded that there was insufficient clinical evidence to determine whether or not apixaban was more or less clinically effective than rivaroxaban and dabigatran etexilate and therefore the ICERs presented for these anticoagulants had to be interpreted with caution.		4.13
Current practice		
Clinical need of patients, including the availability of alternative treatments	The Committee noted the recommendation in the NICE clinical guideline 'Venous thromboembolism' (NICE clinical guideline 92) that people having elective hip replacement or elective knee replacement should be offered LMWH, dabigatran etexilate, rivaroxaban or fondaparinux.	4.2
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	Apixaban appeared to provide a potential benefit for clinical practice. The dose does not need to be adjusted for people with compromised renal function.	4.10
What is the position of the treatment in the pathway of care for the condition?	Apixaban has a marketing authorisation for the 'prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery'.	2.1

Adverse effects	Common adverse events include anaemia, haemorrhage, confusion and nausea. See the summary of product characteristics for full details.	2.3
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	Four good quality randomised controlled trials were identified comparing apixaban with enoxaparin. Fifteen randomised controlled trials were identified for inclusion in the indirect comparison of apixaban with dabigatran etexilate, rivaroxaban and fondaparinux. The manufacturer included 43 studies for the mixed treatment comparison.	3.2 3.9 3.12
Relevance to general clinical practice in the NHS	Of the fifteen studies identified for inclusion in the indirect comparison, nine compared the treatment of interest with enoxaparin at the UK dosage of 40 mg once daily. The Committee agreed that the ADVANCE 2 and ADVANCE 3 randomised controlled trials, in which patients in the control arm received enoxaparin 40 mg once daily, were applicable to UK clinical practice.	3.9 4.4
Uncertainties generated by the evidence	The manufacturer highlighted inconsistencies among the results of the mixed treatment comparisons and the head-to-head trials. The Committee was aware of the inconsistency of some results between the indirect comparison and the mixed treatment comparison and between the indirect comparison and the head-to-head trials, and the manufacturer's explanation for these inconsistencies.	3.13 4.7
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	No subgroups were identified.	
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee agreed that based on the evidence presented it was not possible to determine an estimate of relative effectiveness of apixaban compared with rivaroxaban, dabigatran etexilate or fondaparinux.	4.7

Evidence for cost effectiveness		
Availability and nature of evidence	The manufacturer submitted an economic model assessing the cost effectiveness of apixaban compared with enoxaparin, dabigatran etexilate and rivaroxaban. The manufacturer adopted a two-stage modelling approach. A decision tree to model treatment in the prophylactic phase (from the time of surgery to 90 days after surgery) and a Markov model to model the long-term events (90 days after surgery).	3.15
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee recognised uncertainties associated with ICERs for rivaroxaban and dabigatran etexilate because the clinical data were derived from indirect comparison analysis, unlike the ICER for enoxaparin, which was derived from direct head-to-head trials.	4.12
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The QALY differences between the treatments were small. For people having total hip replacement surgery, total QALYs ranged from 9.520 for enoxaparin to 9.536 for rivaroxaban. For patients having total knee replacement surgery, total QALYs ranged from 9.023 for enoxaparin to 9.090 for rivaroxaban.	3.22
Are there specific groups of people for whom the technology is particularly cost effective?	No subgroups were identified.	
What are the key drivers of cost effectiveness?	Rivaroxaban was cost effective compared with apixaban, except when the time horizon was 10 years or less, when the age at surgery was 80 years or when a smaller relative difference in the risk of the primary end point (total venous thromboembolism and death from any cause) was assumed.	3.24

Most likely cost-effectiveness estimate (given as an ICER)	In base-case analyses apixaban dominated enoxaparin. The Committee agreed that because the ICER for enoxaparin was derived from data from direct head-to-head trials, the cost-effectiveness results for apixaban compared with enoxaparin were the most robust.	4.12
Additional factors taken into account		
Patient access schemes (PPRS)	The manufacturer did not submit a patient access scheme.	
End-of-life considerations	The supplementary advice was not relevant to this appraisal.	
Equalities considerations and social value judgements	No equalities issues were raised in this appraisal.	

5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.

5.2 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website (www.nice.org.uk/guidance/TAXXX). [NICE to amend list as needed at time of publication]

National Institute for Health and Clinical Excellence   Page 26 of 33
Final appraisal determination – Apixaban for the prevention of venous thromboembolism
Issue date: November 2011

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Recommendations for further research

6.1 More trials of apixaban compared with other LMWHs in total hip and knee replacement would decrease the uncertainty of the clinical and cost effectiveness of these treatments. Trials directly comparing apixaban with rivaroxaban, dabigatran etexilate and fondaparinux would strengthen the evidence base for these comparisons.

7 Related NICE guidance

Published

- Venous thromboembolism: reducing the risk. NICE clinical guideline 92 (2010). Available from www.nice.org.uk/guidance/CG92
- Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults. NICE technology appraisal guidance 157 (2008). Available from www.nice.org.uk/guidance/TA157
- Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement surgery in adults. NICE technology appraisal guidance 170 (2009). Available from www.nice.org.uk/guidance/TA170

8 Review of guidance

8.1 The guidance on this technology will be considered for review in January 2015. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

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

A   Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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

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

Dr Jane Adam (Chair)

Department of Diagnostic Radiology, St George's Hospital, London

Professor A E Ades

Professor of Public Health Science, Department of Community Based Medicine, University of Bristol

Dr Jeremy Braybrooke

Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust

Dr Fiona Duncan

Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool

Mr Christopher Earl

Surgical Care Practitioner, Renal Transplant Unit, Manchester Royal Infirmary

Dr Sharon Saint Lamont

Head of Quality and Innovation, North East Strategic Health Authority

Dr Ian Lewin

Consultant Endocrinologist, North Devon District Hospital

Dr Anne McCune

Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust

Dr David Newsham

Lecturer (Orthoptics), University of Liverpool

Ms Pamela Rees

Lay member

Dr Ann Richardson

Lay member

Dr Paul Robinson

Medical Director, Merck Sharp & Dohme

Mr Stephen Sharp

Senior Statistician, MRC Epidemiology Unit, Cambridge

Dr Eldon Spackman

Research Fellow, Centre for Health Economics, University of York

Mr Mike Spencer

Assistant Director Patient Experience, Cardiff and Vale University Health Board

Mr David Thomson

Lay member

Mr William Turner

Consultant Urologist, Addenbrooke's Hospital, Cambridge

Dr John Watkins

Clinical Senior Lecturer/Consultant in Public Health Medicine, Cardiff University and National Public Health Service Wales

Dr Anthony S Wierzbicki

Consultant in Metabolic Medicine/Chemical Pathology, Guy's and St Thomas' Hospitals NHS Trust, London

B   NICE project team

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

Alfred Sackeyfio
Technical Lead

Nicola Hay
Technical Adviser

Bijal Joshi
Project Manager

Appendix B: Sources of evidence considered by the Committee

A   The Evidence Review Group (ERG) report for this appraisal was prepared by Kleijnen Systematic Reviews:

- Riemsma R, Joore M, Grutters J et al. Apixaban for the prevention of venous thromboembolism in people undergoing elective knee and hip replacement surgery, September 2011.

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

I   Manufacturer/sponsor

- Bristol-Myers Squibb and Pfizer (apixaban)

II   Professional/specialist and patient/carer groups:

- Anticoagulation Europe
- British Society for Haematology
- Lifeblood: The Thrombosis Charity
- Royal College of Anaesthetists
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- United Kingdom Clinical Pharmacy Association
- Professor Roger M Atkins (British Orthopaedic Association)

III   Other consultees:

- Department of Health
- Welsh Assembly Government

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

- Bayer Healthcare
- Boehringer Ingelheim
- British National Formulary
- Commissioning Support Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Kleijnen Systematic Reviews
- Leo Laboratories
- National Institute for Health Research Health Technology Assessment Programme
- NHS Quality Improvement Scotland
- Sanofi-aventis

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

- Dr Raza Alikhan, Consultant Haematologist, nominated by the Royal College of Pathologists – clinical specialist
- Annya Stephens-Boal, nominated by Lifeblood: The Thrombosis Charity – patient expert
- Diane Eaton, nominated by Anticoagulation Europe – patient expert

D   Representatives from the following manufacturer/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Bristol-Myers Squibb
- Pfizer