NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism

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

1 Guidance

1.1 Apixaban is recommended, within its marketing authorisation, as an option for treating and for preventing recurrent deep vein thrombosis and pulmonary embolism in adults.

2 The technology

2.1 Apixaban (Eliquis, Bristol-Myers Squibb and Pfizer) is an anticoagulant which directly inhibits factor X (factor Xa), inhibiting thrombin formation and the development of thrombi (blood clots). It is administered orally. To treat deep vein thrombosis (DVT) or pulmonary embolism (PE), 10 mg apixaban should be taken twice a day for the first 7 days, followed by 5 mg twice a day for at least 3 months. For the prevention of recurrent disease, people who have completed 6 months of treatment for DVT or PE should take 2.5 mg twice a day. The summary of product characteristics states that apixaban should be used with caution in people with severe renal impairment.

2.2 The most frequent adverse reactions to apixaban are bleeding, bruising, nausea and anaemia. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The cost of apixaban is £1.10 per tablet for either the 2.5 mg or 5 mg dose (excluding VAT; British national formulary [BNF] accessed January 2015). The daily cost of apixaban is £4.40 for the first 7 days followed by £2.20 thereafter. Costs may vary in different settings because of negotiated procurement discounts.

3 The company's submission

The Appraisal Committee (section 9) considered evidence submitted by Bristol-Myers Squibb and Pfizer, and a review of this submission by the Evidence Review Group (ERG; section 10).

Clinical effectiveness

3.1 The company submission presented clinical effectiveness data from 2 trials: AMPLIFY and AMPLIFY-EXT. AMPLIFY was a randomised, active-controlled, parallel-group, double-blind, triple-dummy study carried out in 28 countries including 14 in Europe (but not the UK). The aim of AMPLIFY was to determine if apixaban was non-inferior to the low molecular weight heparin (LMWH) enoxaparin followed by a vitamin K antagonist (in this case warfarin) for the composite end point of confirmed recurrent symptomatic non-fatal venous thromboembolism (VTE) or VTE-related death over 6 months of therapy. The criteria to demonstrate non-inferiority were an upper boundary of the 95% confidence interval surrounding the relative risk of less than 1.8 and a risk difference of less than 3%. Patients were randomised 1:1 to apixaban (n=2691) or enoxaparin/warfarin (n=2704). Apixaban was dosed at 10 mg twice a day for 7 days followed by 5 mg twice a day for the remainder of the study. Patients in the enoxaparin/warfarin

arm had 1 mg/kg subcutaneous enoxaparin twice a day for at least 5 days and warfarin to achieve an international normalised ratio (INR) of between 2.0 and 3.0: enoxaparin was stopped when the target INR was achieved. The median duration of enoxaparin treatment was 6.5 days (interquartile range 5.0 to 8.0). Patients were treated for 6 months and were followed-up for 30 days after they stopped treatment.

3.2 The mean age of patients in AMPLIFY was 57 years and 58% were men. Most patients in the study (65%) had been randomised following a deep vein thrombosis (DVT), 25% had a pulmonary embolism (PE) and 9% had both a DVT and PE (qualifying diagnosis for entry into the study could not be evaluated in the other patients). Around 90% of patients had a VTE that was considered to be unprovoked. Sixty six (2.5%) patients in the apixaban arm and 77 (2.9%) patients in the enoxaparin/warfarin arm had active cancer.

3.3 In AMPLIFY, the efficacy population was defined as the intention-to-treat population for whom the outcome status at 6 months was documented (this comprised 2609 patients in the apixaban arm and 2635 patients in the enoxaparin/warfarin arm). There were 59 patients (2.3%) in the apixaban arm and 71 patients (2.7%) in the enoxaparin/warfarin arm who had a recurrent VTE or died because of a VTE (relative risk 0.84, 95% confidence interval [CI] 0.60 to 1.18, $p<0.01$ for non-inferiority).

3.4 In AMPLIFY, fewer people had a major bleed in the apixaban arm than in the enoxaparin/warfarin arm (15 [0.6%] compared with 49 [1.8%]; relative risk 0.31, 95% CI 0.17 to 0.55; $p<0.001$). Three patients (0.1%) in the apixaban arm and 6 (0.2%) in the enoxaparin/warfarin arm had an intracranial bleed, and 7 patients (0.3%) in the apixaban arm and 18 (0.7%) in the

enoxaparin/warfarin arm had a major gastrointestinal bleed. One patient in the apixaban arm and 2 in the enoxaparin/warfarin arm died because of their bleed. The company noted that the rates of major bleeds across the prespecified subgroups were consistent with the full population. Fewer people had a clinically relevant non-major bleed with apixaban (103 [3.8%]) than with enoxaparin/warfarin (215 [8.0%] relative risk 0.48, 95% CI 0.38 to 0.60). In terms of events, 67.1% of patients in the apixaban arm and 71.5% in the enoxaparin/warfarin arm had an adverse event, and similar proportions of patients in both arms had a serious adverse event (15.6% and 15.2% respectively).

3.5 AMPLIFY-EXT was a randomised, parallel-group, double-blind, placebo-controlled study carried out in 28 countries including 7 centres in the UK. The aim of the study was to determine if 2.5 mg or 5 mg twice-daily apixaban was superior to placebo for the composite end point of symptomatic recurrent non-fatal VTE or all-cause death in people who had a proximal symptomatic DVT or symptomatic PE, and who had completed 6–12 months of anticoagulant therapy for this index event. The study included patients for whom there was uncertainty about the need for continued anticoagulation treatment (termed 'clinical equipoise'); patients who definitely needed further anticoagulation were excluded from the study. Patients were randomised 1:1:1 to 2.5 mg apixaban twice daily (n=840), 5 mg apixaban twice daily (n=813) or placebo (n=829). Treatment was given for 12 months and patients were followed-up for 30 days after they stopped treatment. The company presented only the results for the 2.5 mg dose of apixaban compared with placebo, because it is the licensed dose if anticoagulation with apixaban is continued beyond 6 months (see section 2.1).

3.6 The mean age of the patients in AMPLIFY-EXT was also 57 years and 57% of the population were male. Qualifying diagnosis for inclusion in the study was DVT in 65% and PE in 35%. In most patients (92%) the VTE was considered to be unprovoked. Fifteen patients (1.8%) in the 2.5 mg twice-daily apixaban arm and 18 patients (2.2%) in the placebo arm had active cancer.

3.7 In AMPLIFY-EXT, all efficacy outcomes were analysed in the intention-to-treat population. Patients lost to follow-up were counted as having had a primary outcome event. There were 13 patients in the 2.5 mg twice-daily apixaban arm (1.5%) and 19 in the placebo arm (2.3%) who were lost to follow-up. The results showed that 32 patients (3.8%) in the 2.5 mg twice-daily apixaban arm and 96 patients (11.6%) in the placebo arm had recurrent VTE or died by 12 months (relative risk 0.33, 95% CI 0.22 to 0.48; the company has stated that the p value is academic in confidence and is not reported here).

3.8 In AMPLIFY-EXT similar proportions of patients in the 2.5 mg twice-daily apixaban arm (71.0%) and the placebo arm (73.4%) had an adverse event, although a higher proportion of patients in the placebo arm (19.1%) had a serious adverse event than in the 2.5 mg twice-daily apixaban arm (13.3%). DVT was classed as an adverse event. Approximately 3% of patients in both the 2.5 mg twice-daily apixaban and placebo arms had major or clinically relevant non-major bleeding. There was no statistically significant difference between the 2 study arms because the confidence interval around the calculated relative risk crossed 1.

3.9 The company did not identify any head-to-head trials comparing apixaban with rivaroxaban or dabigatran etexilate for the treatment or secondary prevention of VTE. It therefore carried out 2 network meta-analyses. The first (NMA 1) included trials which assessed

anticoagulant therapy for the treatment of an initial VTE event, and the second (NMA 2) included trials which assessed extended anticoagulant therapy in patients who had already had treatment for a VTE event and were having continued anticoagulant treatment for secondary prevention.

3.10 NMA 1 was carried out to estimate the relative treatment effect and safety of apixaban compared with rivaroxaban and dabigatran etexilate for treating an initial VTE event. It included the following trials:

- AMPLIFY: comparing apixaban (10 mg twice daily for 7 days followed by 5 mg twice daily) with LMWH (enoxaparin)/ warfarin. The intention-to-treat dataset was used for efficacy analyses and the on-treatment population was used for safety analyses.
- RE-COVER and RE-COVER II: 2 trials, identical in design, comparing unfractionated heparin (UFH) or LMWH/dabigatran etexilate with UFH or LMWH/warfarin. A modified intention-to-treat dataset was used for efficacy analyses in which patients who did not have any study drug were excluded. The on-treatment population was used for safety analyses.
- EINSTEIN DVT and EINSTEIN PE: 2 trials that differed by the index event of the trial population (DVT or PE). Both trials compared rivaroxaban (15 mg twice daily for 21 days followed by 20 mg once daily) with LMWH/vitamin K antagonist (VKA, either warfarin or acenocoumarol). The company used a pooled data set from these trials. The intention-to-treat dataset was used for efficacy analyses and the on-treatment population was used for safety analyses.

The company noted that most trials in the network used a modified intention-to-treat analysis (patients from that population who had no

outcome data were excluded from the analysis). The company presented results using a fixed-effects model, because there were few studies in the network.

3.11 There were no differences in the number of recurrent VTE or VTE-related deaths with apixaban compared with LMWH/VKA LMWH/dabigatran etexilate or rivaroxaban. There were lower rates of bleeding (the composite outcome of major or clinically relevant non major bleeding, major bleeding assessed separately and clinically relevant non-major bleeding) with apixaban compared with LMWH/VKA, LMWH/dabigatran etexilate and rivaroxaban. In response to clarification, the company re-ran the meta-analysis using different statistical modelling assumptions as requested by the Evidence Review Group (ERG). These results resulted in marginal differences to the company's base-case results. The company carried out 3 further sensitivity analyses in which it used a modified intention-to-treat population, used pooled results from RE-COVER and RE-COVER II (rather than using the results from each trial separately) and excluded the dabigatran etexilate trials from the meta-analysis. These sensitivity analyses also showed only a marginal effect. The company has stated that the exact results of NMA1 are academic in confidence and so are not reported here.

3.12 NMA 2 was carried out to compare apixaban with rivaroxaban or dabigatran etexilate for secondary prevention of VTE. It included the following trials:

- AMPLIFY-EXT: comparing 2.5 mg apixaban twice daily with placebo for 12 months after initial treatment of 6–12 months.
- EINSTEIN- EXT: comparing 20 mg rivaroxaban once daily with placebo over 6–12 months after an initial treatment of 6–12 months.

- RE-SONATE: comparing 150 mg dabigatran etexilate twice daily with placebo over 6 months after an initial treatment of 6–18 months.
- RE-MEDY: comparing 150 mg dabigatran etexilate twice daily with warfarin (INR 2.0–3.0) over 6–36 months following an initial treatment of 3–12 months.
- LAFIT and PREVENT: trials comparing warfarin with placebo over 24 months (LAFIT) or a mean of 2.1 years (PREVENT) after an initial treatment of 3 months. In LAFIT the target INR for people taking warfarin was 2.0 to 3.0; in PREVENT it was 1.5 to 1.9.
- WODIT DVT, WODIT PE: comparing VKA continuation with VKA discontinuation 3–9 months after an initial 3-month treatment.
- WARFASA, ASPIRE: comparing 100 mg aspirin once daily over 2–4 years after an initial treatment of 6 weeks to 18 months.

3.13 The company noted that the network of studies included a mixture of open-label and double-blind studies, as well as differences in the proportions of patients who had an unprovoked VTE rather than a VTE which could be attributed to a specific cause. Other differences between the studies were the proportion of patients with active cancer, treatment duration with anticoagulants before entering the trials and study follow-up. The company also noted that there may have been differences in clinical judgement regarding the need for continuation of anticoagulation across the trials, and the patients in the trials may have had different baseline characteristics. The company tested for heterogeneity of the studies included in the network meta-analysis using the I^2 statistic and found little evidence for heterogeneity. The meta-analysis was done using a random-effects model.

3.14 There were no differences between apixaban, LMWH/dabigatran etexilate, rivaroxaban or LMWH/VKA in the rates of recurrent VTE or VTE-related death because the 95% credible intervals crossed 1. Apixaban was associated with fewer recurrent VTE or VTE-related deaths than aspirin or placebo. Apixaban was associated with statistically significantly fewer major or clinically relevant non-major bleeding events (assessed as a composite outcome) than the comparators. When major bleeding and clinically relevant non-major bleeding were assessed as separate outcomes, patients taking apixaban had statistically significantly fewer bleeds of either severity than those having LMWH/VKA or rivaroxaban, but the rates were not statistically significantly different between apixaban and LMWH/dabigatran etexilate. In response to clarification, the company re-ran the meta-analysis using different statistical modelling assumptions as requested by the ERG. The results of these analyses were broadly consistent with the company's base case but the likelihood of a major bleed was no longer statistically significantly lower with apixaban than with rivaroxaban. The company did 3 further sensitivity analyses: using the intention-to-treat population from the trials, excluding the WODIT DVT/PE trials and excluding the dabigatran etexilate trials. These sensitivity analyses gave similar results to the company's base case, although the sensitivity analysis using the intention-to-treat population resulted in statistically significantly fewer recurrent VTE events or VTE-related deaths with apixaban than LMWH/VKA. The company has stated that the full results of NMA 2 are academic in confidence and so are not reported here.

Evidence Review Group's comments on the company's clinical-effectiveness evidence

3.15 The ERG noted that the patients in both AMPLIFY and AMPLIFY-EXT were younger than those seen in clinical practice and that

relatively few people were older than 75 years (14.3% in AMPLIFY and 13.3% in AMPLIFY-EXT). The ERG stated that a UK cohort study had found that the mean age of people having an unprovoked PE was 64 years and that 47% were men. The ERG further commented that the proportion of men in the UK cohort study was smaller than the proportion of men in AMPLIFY and AMPLIFY-EXT (58% and 56% respectively).

3.16 The ERG discussed whether the population in AMPLIFY and AMPLIFY-EXT was representative of people who would have apixaban for secondary prevention of VTE. The ERG commented that AMPLIFY-EXT included only patients for whom there was uncertainty about the need for continued anticoagulation treatment (termed 'clinical equipoise'). People who definitely needed extended anticoagulation were not included. The ERG noted that in its submission the company had not discussed the extent to which the results of the AMPLIFY-EXT trial are directly applicable to people who definitely need anticoagulation beyond 6 months. The ERG also noted that there were no clinical data for people who had a provoked index event but were not considered to be at risk of a recurrent event, because these people were not included in the trial.

3.17 The ERG commented that the company had stated that apixaban is not licensed for people with active cancer. It further noted that patients with active cancer for whom treatment with LMWH was planned were excluded from AMPLIFY, and that they were unlikely to meet the clinical equipoise criteria for AMPLIFY–EXT because patients with active cancer are treated with LMWH for extended periods of time.

3.18 The ERG considered that the characteristics of the trials included in NMA 1 were similar enough that combining the results was

appropriate. However, it noted that the trials of rivaroxaban compared with LMWH/VKA included a higher proportion of people with PE (58%) than the other trials in the network of evidence (which ranged from 21.2% to 25.2%).

3.19 The ERG was concerned that there were substantial differences between the time spent on treatment (from 6 months in RE-SONATE to 37.2 months in ASPIRE) and the follow-up periods of trials (from 10 months in LAFIT to 37.2 months in ASPIRE) in NMA 2 (which included trials that had assessed anticoagulants for secondary prevention). The ERG did not consider it appropriate to combine data from these trials and did not agree with the company's assertion that the different treatment periods and follow-up times would not have a substantial effect on the results. The ERG stated that there are likely to be more events in studies with longer treatment periods and follow-up times. It concluded that because of this, the prevention network meta-analysis (NMA 2) was not appropriate and only direct clinical evidence for apixaban from AMPLIFY–EXT could be used to assess the clinical effectiveness of apixaban for secondary prevention of VTE.

3.20 The ERG noted that the company had provided continuity correction factors for outcomes in which there were no events in 1 of the study arms in the trials. This had resulted in high estimates of relative risk for some outcomes, such as the relative risk of major bleeding with apixaban compared with rivaroxaban. However, the ERG was satisfied that the company's analyses provided in response to clarification resulted in less extreme estimates of the underlying treatment effect (that is, they were less likely to over- or underestimate the treatment effect).

Cost effectiveness

3.21 The company developed a new Markov model with a 3-month cycle length and lifelong time horizon (patients were assumed to live to a maximum age of 100 years). Patients entered the model following a PE or a DVT. In the model it was assumed that patients could have a recurrent DVT/PE, have a bleed (an intracranial bleed, a non-intracranial major bleed or a clinically relevant non major bleed), discontinue treatment or die (either because of a recurrent DVT/PE, bleed or other reasons). Patients with an intracranial bleed were assumed to discontinue treatment permanently. The company assumed that approximately half of the patients who survived a non-intracranial major bleed would discontinue treatment permanently. The others would have a 2-week treatment break before resuming treatment (the company has stated that the precise proportion is academic in confidence and is not reported here). Patients who had a clinically relevant non-major bleed were assumed to have a 2-day treatment break then resume treatment. Patients who had a PE could develop chronic thromboembolic pulmonary hypertension (CTEPH), and patients who had a DVT could develop post-thrombotic syndrome (PTS). The company only modelled the cost and effect on quality of life of severe PTS; it stated that mild and moderate PTS had little effect on a patient's utility or resource use.

3.22 In the model it was assumed that all patients treated with LMWH had enoxaparin and all patients treated with a vitamin K antagonist had warfarin. The risks of having a recurrent DVT/PE or bleeding for patients having enoxaparin/warfarin or apixaban in the first 6 months were derived from the absolute risks of these events in AMPLIFY; for those having apixaban or no treatment after this period, risks were derived from AMPLIFY-EXT. The company used

the estimates from the 2 network meta-analyses of the risks of DVT/PE or bleeding relative to apixaban for rivaroxaban, dabigatran etexilate and aspirin, which it then applied in its model. The company noted that the clinical trial evidence showed that the risk of recurrent DVT/PE decreased over time. The company ran the model for 2 treatment durations: 6 months' treatment followed by no treatment for the rest of a patient's life, and lifelong treatment. In the 6-month treatment analysis, the risks of recurrent DVT/PE for patients having no treatment after 6 months were derived from the rates in a prospective cohort of 1626 patients over 10 years. In the lifelong treatment duration analysis, the risks of recurrent VTE for patients having treatment were derived from AMPLIFY-EXT (for 6–18 months after index event) and from the prospective cohort study (for 18 months to 10 years after index event). In the model, the risks of major bleeding were derived from the AMPLIFY trials and the network meta-analyses. In the base case the risks of bleeding were unadjusted for aging. The company said that this was a conservative assumption because bleeding risks were lower for apixaban compared with the other comparators and the risk of bleeding would be expected to increase as the age of the modelled cohort increased. In the base case it was also assumed that 13.46% of major bleeds would be fatal and that of the remaining non-fatal bleeds, 13.97% would be intracranial. These assumptions were based on a published pooled analysis of randomised trials in which patients had anticoagulant treatment for at least 6 months and were assumed to be consistent across different types of anticoagulant. The model assumed a constant risk of CTEPH and PTS over time and that the risk of these complications would be the same irrespective of treatment. Patients who had an intracranial bleed or CTEPH were assumed to have a

higher mortality rate (hazard ratio [HR] 2.6, 95% CI 2.2 to 3.0 for intracranial bleed; HR 1.3, 95% CI 0.98 to 1.73 for CTEPH).

3.23 No quality of life data were collected in the AMPLIFY or AMPLIFY-EXT trials and the company used utility values from published studies identified through a systematic review in its model. The baseline utility for the model population (0.825) was based on a UK population-average score from Kind et al. (1999). Utility decrements associated with PE (0.32) and DVT (0.11) came from a study by Locadia et al. (2004). Patients with an intracranial bleed were assumed to have a utility value of 0.33 while they had acute care (for 91 days), after which their utility was assumed to increase to 0.61 during post-acute care. A major non-intracranial bleed was associated with a utility decrement of 0.30, meaning that a single patient's utility value in this case would be 0.5224. Clinically relevant non-major bleeds were assumed to have a utility decrement of 0.0054. Patients who had CTEPH were assumed to have a utility value of 0.65; patients with PTS were assumed to have a utility decrement of 0.07. Taking enoxaparin/warfarin was associated with a utility decrement of 0.013. Taking apixaban, rivaroxaban, enoxaparin/dabigatran etexilate or aspirin was assumed to have a utility decrement of 0.002.

3.24 The company used the NHS list prices for apixaban, rivaroxaban, dabigatran etexilate and enoxaparin. It modelled the cost of enoxaparin and noted that the recommended dose for enoxaparin in the UK is 1.5 mg/kg, but the dose of enoxaparin in AMPLIFY was 1.0 mg/kg. The company used the cost of the lower UK dose in its model, but the efficacy estimates were based on the higher dose. For patients having enoxaparin it was assumed that 92% would self-inject following a 1-time training cost of £17. It was assumed

that for the other 8% of patients, enoxaparin would be administered by a nurse at a cost of £8.78.

3.25 For patients having warfarin it was assumed that 6 monitoring visits would be needed in the first 3 months followed by 3 visits every 3 months thereafter. It was assumed that 66.45% of INR monitoring visits would be carried out in primary care and 33.55% would be in secondary care. It was further assumed that half the first INR monitoring visits conducted in primary care would be delivered by a GP with the remainder delivered by a nurse. The resulting annual cost of monitoring was £319.19 in the first year of the model and £252.52 in subsequent years.

3.26 It was assumed in the model that 69% of patients who had a DVT and 17% of patients who had a PE would be treated as outpatients. Longer-term monitoring and post-acute care was assumed to be done in primary care, whereas treating bleeds and CTEPH was assumed to be carried out in secondary care.

3.27 The company presented deterministic pairwise and fully incremental results for 2 treatment durations: treatment over 6 months and lifelong treatment. If taken for 6 months the incremental cost effectiveness ratio (ICER) for apixaban compared with enoxaparin/warfarin was £2406 per quality adjusted life year (QALY) gained. Apixaban dominated (that is, was less costly and more effective than) rivaroxaban and enoxaparin/dabigatran etexilate. If taken lifelong, the ICER for apixaban compared with enoxaparin/warfarin was £16,676 per QALY gained. Rivaroxaban was dominated by enoxaparin/warfarin and enoxaparin/dabigatran etexilate was extendedly dominated by enoxaparin/warfarin and apixaban (a treatment is ‘extendedly dominated’ when its ICER is higher than that of the next, more effective, option – in this case

apixaban – when compared with a common baseline). The company did not present probabilistic ICERs.

3.28 The company carried out 1-way sensitivity analyses and scenario analyses. For 6 months' treatment, sensitivity analyses showed that the ICER for apixaban compared with enoxaparin/warfarin ranged from £1628 to £5330 per QALY gained. The highest of these was a result of decreasing the baseline utility value to 0.385. For lifelong treatment, the ICER for apixaban compared with enoxaparin/warfarin ranged from £2157 to £41,394 per QALY gained. Three sensitivity analyses resulted in an ICER above £30,000 per QALY gained; these were reducing the relative risk of major bleeding for enoxaparin/warfarin to be approximately the same as that for apixaban, setting the risk of bleeding to 0 for all treatments and reducing the baseline utility to 0.385. The company also tested the effect of over 30 scenarios. For 6 months' treatment, apixaban dominated rivaroxaban and enoxaparin/dabigatran etexilate in all scenarios. The ICER for apixaban compared with enoxaparin/warfarin was under £5000 per QALY gained in all scenarios. The scenarios that had the greatest effect on the ICER were assuming fewer warfarin monitoring costs and excluding the costs of enoxaparin. For lifelong treatment, assuming fewer warfarin monitoring visits (4 visits on initiation, 1 visit subsequent) increased the ICER for apixaban compared with enoxaparin/warfarin from £16,676 per QALY gained in the base case to £21,301 per QALY gained. The only other scenarios that increased the ICER for apixaban compared with enoxaparin/warfarin to over £20,000 per QALY gained were: assuming that the utility decrements for all treatments were the same as that assumed for warfarin (that is a utility decrement of −0.0013, which resulted in an ICER of £25,999 per QALY gained), and assuming an alternative distribution of fatal major bleeds and

non-fatal intracranial bleeds for patients who had a major bleed (which resulted in an ICER of £24,038 per QALY gained).

Evidence Review Group's critique of the company's cost-effectiveness model

3.29 The ERG noted that the model used age-specific mortality rates for all-cause death but did not adjust the model parameters (such as the risk of VTE event or bleeding) by age or sex. The ERG further commented that the age-specific mortality rates did not take into account that the ratio of men to women in the model cohort would be expected to change over time, because women tend to live longer than men. The ERG stated that the company's approach may have overestimated the mortality rates of the modelled cohort by up to 4% per year. The ERG further considered that the company's assumption surrounding baseline utility was flawed because the model did not account for the mean utility value of the modelled cohort decreasing as the age of the cohort increased over time.

3.30 The ERG commented that for lifelong treatment, the efficacy estimates of apixaban over the first 6 months were based on AMPLIFY; after this, data from AMPLIFY-EXT were used. The ERG noted that the characteristics of the populations included in these 2 trials differed, and only a third of patients from AMPLIFY had then taken part in AMPLIFY-EXT. The ERG noted that AMPLIFY-EXT excluded patients who had a recurrent VTE event during earlier treatment of their index VTE event, and so at 6 months the characteristics of the modelled cohort effectively changes. The ERG suggested that 2 distinct decision models should have been developed, each based exclusively on a single trial: short-term use of apixaban compared with comparators using AMPLIFY data and

long-term use of apixaban compared with no-treatment using AMPLIFY-EXT data.

3.31 The ERG commented that in the model, the cost of anti-thromboembolic therapies for each 3-month cycle was based on the average number of patients alive and on treatment over the course of the cycle. The ERG considered that this may underestimate the true costs, because oral medications prescribed at the start of a 3-month treatment cycle could not be returned if they were not used.

3.32 The ERG commented that the cost of enoxaparin treatment in the model was based on a daily dose of 1.5 mg/kg, assuming a mean body weight of 84.6 kg (based on the mean weight of patients in AMPLIFY). However, the ERG considered this to be considerably higher than the mean adult weight of 77.4 kg reported in the Health Survey for England 2012.

3.33 The ERG commented on the company's approach to discounting. It noted that the company had assumed a 3.5% discount rate, which is consistent with the NICE reference case. However, the ERG noted that the company applied discounting at a different rate for every 3-month model cycle based on the time elapsed rather than using a more conventional approach of applying the discount every 4 cycles (that is, yearly) after the first year.

3.34 The ERG noted that the model structure (in which patients who have a non-fatal VTE without a permanent adverse event return to the index DVT or PE health state after 3 months) led to an implicit assumption that the risk of a second or third recurrent VTE was the same as that of a first recurrent VTE. The ERG stated that there was no evidence to support this assumption and that a published study had suggested that the risk of a second recurrent VTE

relative to a first recurrence of VTE was about 2-fold (relative risk 2.1, p=0.02). The ERG stated that as a consequence the long-term estimates of future VTE events (including deaths) were likely to be underestimated, meaning that the costs and disutility value of events would also be underestimated.

3.35 The ERG stated that there were differences in the proportion of patients who at 90 days had discontinued treatment in the model compared with the AMPLIFY trial results. The ERG further commented that it was unable to validate other model parameters against the trial data to determine whether a similar error had been made across the whole range of time-to-event model variables, because the Kaplan–Meier data it requested during the clarification process had not been provided.

3.36 The ERG carried out a number of exploratory analyses including the following:

- Age and sex modelling: to assess the effect over time of the changing age and sex distribution of the modelled cohort on survival.
- Treatment costs: the treatment costs were calculated using the full number of patients who began treatment at the start of each 3-month cycle.
- Age-stratified utility values: incorporating the baseline utility values by 10-year age band (under 25, 25–34 up to 65–74, and 75+) from the Measurement and Valuation of Health survey.
- Applying the discount yearly rather than applying the discount per cycle as had been done by the company in its base case.
- Body weight: assuming a mean adult body weight of 77.4 kg when calculating amount of LMWH administered to achieve a 1.5 mg/kg dose.

- Rebase prevention model (lifelong duration): to address its concerns that the modelled assumption in the first 6 months of lifelong treatment (based on the AMPLIFY population) did not reflect the experience of those patients on whom lifelong treatment estimates were based (the population from AMPLIFY-EXT), the ERG excluded the first 2 cycles from the model to determine lifelong treatment results. The ERG noted that this would reflect the third of patients who had 6 months' treatment in the AMPLIFY trial before joining AMPLIFY-EXT.
- Hazard ratios requested by ERG: using the results from NMA 2 which incorporated the changes to the meta-analysis modelling as requested by the ERG during clarification (these included using an alternative vague prior for the trial effect and treating the trial effect as random rather than fixed).
- Poisson hazard ratios: using Poisson distributions in the model for NMA 2, with and without Bayesian assumptions. The ERG carried out these analyses because the trials in NMA 2 have different follow-up lengths. Using a Poisson assumption in the model relates the incidence of events to the length of time that patients are exposed to the risk of event, and so it limits the potential bias of different follow-up times in the meta-analysis.

3.37 Overall, the exploratory analyses had a small effect on the company's base-case ICERs in the 6-month treatment analyses. The ICER for apixaban compared with enoxaparin/warfarin remained under £3000 per QALY gained and apixaban dominated rivaroxaban and enoxaparin/dabigatran etexilate in all analyses. In the lifelong treatment analyses, most of the ERG's exploratory analyses had only a small effect on the company's base-case ICERs. Only using data from the network meta-analyses that incorporated Poisson assumptions increased the ICER for

apixaban compared with enoxaparin/warfarin to over £20,000 per QALY gained.

3.38 The ERG carried out a further scenario analysis in which it assumed that the efficacy and bleeding risks of apixaban, rivaroxaban and dabigatran etexilate were the same over the secondary prevention period. In this scenario, the ERG also applied its preferred assumptions on age/sex modelling and utility values, treatment costs, discounting method and body weight (see section 3.36). In this scenario the ICER for apixaban compared with rivaroxaban increased from £809 per QALY gained to £21,798 per QALY gained. The ICER for apixaban compared with enoxaparin/dabigatran etexilate increased from £5058 to £9139 per QALY gained.

3.39 Full details of all the evidence are in the committee papers.

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of apixaban, having considered evidence on the nature of venous thromboembolism and the value placed on the benefits of apixaban by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.1 The Committee discussed the options for treating and preventing deep vein thrombosis (DVT) and pulmonary embolism (PE). It was aware that the NICE guideline on venous thromboembolic diseases and the role of thrombophilia testing recommends that DVT and PE are treated with immediate parenteral anticoagulation, most commonly with low molecular weight heparin (LMWH) delivered by subcutaneous injection together with an oral vitamin K antagonist

such as warfarin. Both treatments are continued for at least 5 days or until the person's international normalised ratio (INR) has been within the therapeutic range for at least 24 hours, at which point the LMWH is stopped. The Committee was further aware that following publication of NICE technology appraisal guidance on rivaroxaban for the treatment of deep vein thrombosis and pulmonary embolism, rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism and dabigatran etexilate for the treatment of secondary prevention of deep vein thrombosis and/or pulmonary embolism that rivaroxaban and dabigatran etexilate are also recommended as options for treating and preventing recurrent venous thromboembolism (VTE). The Committee heard from clinical and patient experts that there are regional differences in the uptake of newer oral anticoagulants to treat VTE. The experts explained that this variation is in part because of local protocols and also related to whether treatments can be prescribed in primary or secondary care. The patient experts emphasised that differences in access to newer anticoagulants is of great concern to patients.

4.2 The Committee considered how long patients would remain on anticoagulants. It noted that the NICE clinical guideline on venous thromboembolic diseases recommends that the risks and benefits of continuing anticoagulation following a DVT or PE should be assessed at 3 months. The Committee heard from the clinical experts that treatment for provoked VTE usually lasted for 3 months and treatment for an unprovoked VTE was often longer, and could be lifelong. It heard that although the risk-benefit assessment was increasingly being done at 3 months as recommended, it was also common for people to have a risk-benefit assessment only after completing a 6-month course of treatment following an unprovoked VTE. The clinical experts

explained that the risk-benefit assessment considered the relative risks of a further VTE and the person's risk of having a bleed. They stated that there is no validated standardised algorithm for determining the risks and benefits of continued anticoagulation following VTE, but factors that are considered include type of initial event, time since initial event, experience on anticoagulant, a person's age (because risk of VTE and risk of bleeding increase with age) and frailty. The Committee concluded that there is variation in the length of treatment with anticoagulants, and the decision to continue was dependent on an assessment and discussion of the risks and benefits for the individual.

4.3 The Committee heard from the patient experts about the experience of taking the currently available treatments for VTE. They noted that treatment with warfarin requires attendance at clinics for monitoring and dose adjustments which can affect a person's lifestyle. Some people self-monitor their INR, but only a few would make the dose adjustments needed without contact with a health professional. The clinical experts stated that apixaban, rivaroxaban and dabigatran etexilate have the advantage of not requiring monitoring or individual dose adjustments. They also stated that these anticoagulants have a shorter half-life than warfarin, meaning that the effect of the drug wears off in a short time. This can be an advantage if the person has a bleed, but may be a disadvantage if the person misses a dose because the anticoagulant effect will wear off more quickly. The patient experts stated that even though there are fewer opportunities to check that people are taking these anticoagulants appropriately compared with warfarin, having a VTE has a major emotional and psychological effect on people so they are very likely to take their medication to avoid a recurrent event. The Committee noted that apixaban and dabigatran etexilate are taken twice a day and

rivaroxaban is taken once a day after an initial 3-week period. The clinical experts stated that taking a drug once a day may be considered more convenient by some patients, but a twice-daily drug has the advantage that if a dose is missed patients have inadequate anticoagulation for a shorter time before they take their next tablet. The Committee noted that apixaban is the only anticoagulant for which the licensed dose is lower for secondary prevention than for initial treatment of VTE. The clinical experts stated that patients and doctors may welcome the option of an anticoagulant which can be used at a lower dose for secondary prevention when considering the risk and benefits of continued treatment, and this may result in a higher chance that a person would take apixaban long term. The Committee heard that studies were currently underway to assess whether lower long-term dosage may also be appropriate for other anticoagulants. The patient experts stated that it is essential patients have the opportunity to discuss the anticoagulation options available to them and be involved in the decision about which anticoagulant is best suited for them. The Committee concluded that there are advantages and disadvantages associated with all anticoagulants used to treat VTE and patients should have the opportunity for an informed discussion to decide the best treatment option for them.

Clinical effectiveness

4.4 The Committee discussed the company's decision problem. It noted that the company had not compared apixaban with fondaparinux because fondaparinux is rarely used in UK clinical practice. The Committee considered this appropriate. The Committee noted that the company had included dabigatran etexilate as an additional comparator to those listed in the final scope issued by NICE. It was aware that NICE technology

appraisal guidance for dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism has only recently been published and so clinical experience with dabigatran etexilate may be limited. The Committee agreed that warfarin was the most established treatment for DVT and PE and that clinical experience with rivaroxaban is increasing. It concluded that the company's decision problem was appropriate for its decision making.

4.5 The Committee considered the evidence presented by the company on the clinical effectiveness of apixaban. It noted that the main source of evidence was from 2 trials: AMPLIFY and AMPLIFY-EXT. It noted that the average age of people in both trials was lower than the average age of people being treated for VTE in clinical practice in England. It was aware that both the risk of bleeding and VTE increases with age and a younger trial population would be expected to have a lower risk of these events. However, it accepted that the average age of the population in the AMPLIFY and AMPLIFY-EXT trials was similar to that in other trials of anticoagulants for the treatment and secondary prevention of VTE. The Committee also noted that AMPLIFY included people in whom a minimum of 6 months treatment with an anticoagulant was considered appropriate and that people who were likely to need only 3 months of anticoagulation, such as those with a provoked VTE without risk factors for a further VTE, were excluded from the study. The Committee further noted that AMPLIFY-EXT included only people who were considered to be at clinical equipoise (there was uncertainty about the balance of risks and benefits of continued anticoagulation). It understood that because AMPLIFY-EXT was a placebo-controlled trial, people who were in definite need of continued anticoagulation were not included in the trial. It further understood that people who had a recurrent VTE while

having 6–12 months of anticoagulation for their initial VTE were also excluded from AMPLIFY-EXT. The Committee accepted that there were limited data for people who needed less than 6 months' treatment and for people still at high risk of recurrent VTE after 6 months of treatment. The Committee concluded that despite these limitations, the AMPLIFY trials had informed the marketing authorisation for apixaban, and as such were appropriate to make a recommendation for the whole population covered by the marketing authorisation.

4.6 The Committee discussed whether apixaban could be considered clinically effective with an acceptable safety profile for treating and preventing recurrent VTE. It noted that in AMPLIFY apixaban had been demonstrated to be similarly effective to enoxaparin/warfarin, and that although bleeding is a risk with all anticoagulants the risk of bleeding was lower with apixaban than with enoxaparin/warfarin. The Committee noted that the marketing authorisation for apixaban states that a lower dose of 2.5 mg rather than 5 mg twice daily should be used for secondary prevention beyond 6 months following an initial VTE. The Committee noted that in the AMPLIFY-EXT trial, both doses of apixaban had similar efficacy in reducing the rate of recurrent VTE compared with placebo, but the 2.5 mg twice-daily dose had a lower rate of bleeds than the 5 mg twice-daily dose. No statistically significant difference in the incidence of bleeds was seen between the 2.5 mg twice-daily apixaban dose and placebo. The Committee concluded that apixaban had been demonstrated to be effective in treating VTE and was associated with fewer bleeds than warfarin. It also concluded that over the long term the lower dose was as effective as the higher dose in preventing VTE, with a lower risk of bleeding.

4.7 The Committee discussed the network meta-analyses which were done in the absence of head-to-head trials to evaluate the relative effectiveness of apixaban compared with rivaroxaban and dabigatran etexilate for treating and preventing VTE. The Committee noted that the ERG considered the combination of data from the trials in the 6-month treatment meta-analysis (NMA 1) to be appropriate because the trials had similar characteristics, but that the trials included in the secondary prevention meta-analysis (NMA 2) were too different for appropriate combination of the results since the time spent on treatment and follow-up periods were different. The Committee noted that the results of both meta-analyses suggested that apixaban, rivaroxaban and dabigatran etexilate were similarly effective in terms of reducing recurrent VTE and that apixaban had lower rates of bleeding. The Committee commented that indirect comparisons of any outcome will be subject to more uncertainty than from a direct comparison and the uncertainty will be greater for outcomes which have a low incidence (that is, are uncommon) such as bleeding or VTE. The Committee agreed with the ERG that the estimates from the secondary prevention treatment meta-analysis were subject to additional uncertainty, because the trials included in the network had very different follow-up periods (and the longer people remain in a trial the more likely a bleed or VTE would be observed). The Committee noted that the ERG's alternative modelling assumptions, which attempted to account for the potential bias from different trial lengths, resulted in point estimates in which the relative risks of major bleeding were more similar between the apixaban, rivaroxaban and dabigatran etexilate than in the company's analysis, and had wider credible intervals which crossed 1. The Committee concluded that the meta-analysis results should be interpreted with some caution in light of these uncertainties. It

agreed that no evidence had been shown of a difference in the effectiveness of apixaban, rivaroxaban and dabigatran etexilate. The Committee concluded that although it was reasonable to conclude that there was a difference in bleeding between apixaban and warfarin as had been demonstrated in AMPLIFY, the estimates from the network meta-analyses were not sufficiently robust to differentiate between apixaban, rivaroxaban and dabigatran etexilate in terms of bleeding.

4.8 The Committee considered the effectiveness and safety of apixaban in people with active cancer. It was aware that in clinical practice in England, people with cancer who have a VTE have at least 6 months' treatment with LMWH. It was aware that AMPLIFY and AMPLIFY-EXT included very few people who had active cancer and that there were no head-to-head data available comparing apixaban with LMWH for treating VTE in people who have cancer. The Committee concluded that there were insufficient data to assess the effectiveness and safety of apixaban in people with active cancer who had DVT or PE, and that it was not possible to make a specific recommendation for this group of people.

Cost effectiveness

4.9 The Committee discussed the company's economic model, noting that it had presented base-case results for 2 treatment durations: 6-month treatment and lifelong treatment. The Committee noted the ERG's concerns that when the company modelled lifelong treatment, it had assumed that the risks of bleeding and recurrent VTE would be the same as in AMPLIFY for the first 6 months and the same as AMPLIFY-EXT for the following 12 months, even though the trial populations differed. The Committee agreed that because AMPLIFY-EXT excluded people who had a recurrent VTE during treatment for their initial VTE and people who had a higher

risk of VTE, the populations upon which the risk estimates were based were different. The Committee heard from the ERG that 2 distinct models should have been developed, 1 for short-term use of apixaban and another for long-term use. It also noted its earlier concerns (see section 4.5) about the generalisability of the population in AMPLIFY-EXT to clinical practice in England. The Committee heard from the clinical experts that people do not typically switch anticoagulants once they have started treatment, and during a risk-benefit assessment for continued anticoagulation the decision is whether to continue treatment rather than whether to switch anticoagulants. It therefore considered that modelling treatment in secondary prevention separately would not be appropriate. The Committee concluded that the company's model structure and approach to modelling lifelong treatment was appropriate, but it was aware of the limitations in the data used to inform the model from the network meta-analyses.

4.10 The Committee discussed the assumptions used in the company's model and whether they were similar to assumptions used in previous appraisals of oral anticoagulants. It noted that some assumptions in the company's model, such as those surrounding INR monitoring costs, were similar to those it had accepted as reasonable in its appraisals of rivaroxaban and dabigatran etexilate. The Committee further noted that although the utility value decrements assumed for taking warfarin and for clinically relevant non-major bleeds presented by the company were not the same as in all of the previous appraisals of the anticoagulants that it had seen, they were within the range presented in previous appraisals. The Committee also heard from the ERG that the choice of utility decrement used in the company's base case did not have a large effect on the incremental cost-effectiveness ratio (ICER). The Committee concluded that agreed values have not

been established for INR monitoring costs and utility decrements associated with anticoagulation, and the assumptions used in the company's model were within the range of those used in previous appraisals of apixaban, rivaroxaban and dabigatran etexilate.

4.11 The Committee discussed the company's base-case analyses. It noted that for 6 months' treatment the ICER for apixaban compared with enoxaparin/warfarin was £2400 per quality adjusted life year (QALY) gained, and that apixaban dominated (that is, was more effective and less costly than) rivaroxaban and dabigatran etexilate. For lifelong treatment, the ICER for apixaban compared with enoxaparin/warfarin was £16,700 per QALY gained and rivaroxaban was dominated by enoxaparin/warfarin, and extendedly dominated by enoxaparin/warfarin and apixaban (a treatment is 'extendedly dominated' when its ICER is higher than that of the next, more effective, option when compared with a common baseline). The sensitivity analyses done by the company and the ERG showed that changing the estimate for the relative risk of bleeding derived from the network meta-analyses had the greatest effect on the ICER; the more similar the bleeding risk between treatments, the higher the ICER became. The Committee was aware that although a difference had been demonstrated in the rate of bleeds between apixaban and warfarin, it was unclear what the relative risk of bleeding with apixaban would be compared with the other newer oral anticoagulants. The Committee noted that in most of the company and ERG sensitivity analyses, the ICER was less than £20,000 per QALY gained for either treatment duration. The Committee concluded that apixaban could be considered a clinically and cost effective use of NHS resources and could be recommended as an option for the treatment and secondary prevention of DVT and PE.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title:	Section
Key conclusion		
Apixaban is recommended, within its marketing authorisation, as an option for treating and preventing deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults. The Committee noted that in most of the company and ERG sensitivity analyses, the ICER was less than £20,000 per QALY gained and apixaban could be considered a clinically and cost effective use of NHS resources and could be recommended as an option for the treatment and secondary prevention of DVT and PE.		1.1, 4.11

Current practice		
Clinical need of patients, including the availability of alternative treatments	Currently available treatments for treating and preventing DVT and PE include vitamin K antagonists such as warfarin, low molecular weight heparin, rivaroxaban and dabigatran etexilate. These treatment options differ with regards to whether monitoring of anticoagulation or initial treatment with low molecular weight heparin is needed, number of doses taken per day and dose reductions over time. The Committee concluded that there are advantages and disadvantages associated with all anticoagulants used to treat VTE and patients should have the opportunity for an informed discussion to decide the best treatment option for them. The patient experts emphasised that differences in access to newer oral anticoagulants is of great concern to patients.	4.1, 4.3

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?	The Committee noted that apixaban is the only novel oral anticoagulant for which the licensed dose is lower for secondary prevention than for initial treatment of VTE. The clinical experts stated that patients and doctors may welcome the option of an anticoagulant which can be used at a lower dose for secondary prevention when considering the risk and benefits of continued treatment, and which may result in a higher chance that a person would take apixaban long term. Apixaban has been demonstrated to be effective in treating VTE and was associated with fewer bleeds than warfarin.	4.2, 4.6
What is the position of the treatment in the pathway of care for the condition?	Apixaban is taken at the same position in the treatment pathway as warfarin, rivaroxaban, and dabigatran etexilate	4.1
Adverse reactions	Apixaban was associated with fewer bleeds than warfarin. The estimates from the network meta-analyses were not sufficiently robust to differentiate between apixaban, rivaroxaban and dabigatran etexilate in terms of bleeding.	4.6, 4.7

Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee noted that the main source of evidence was from 2 trials: AMPLIFY and AMPLIFY-EXT. There were limited data for people who needed less than 6 months' treatment and for people still at high risk of recurrent VTE after 6 months of treatment. The Committee concluded that despite these limitations, the AMPLIFY trials were the pivotal trials which informed the marketing authorisation for apixaban, and as such were appropriate to make a recommendation for the whole population covered by the marketing authorisation.	4.5
Relevance to general clinical practice in the NHS	The average age of people in both trials (of apixaban) was lower than the average age of people being treated for VTE in clinical practice in England. However, it accepted that the average age of the population in the trials was similar to that in other trials of anticoagulants for the treatment and secondary prevention of VTE.	4.5

Uncertainties generated by the evidence	There were no head-to-head trials to evaluate the relative effectiveness of apixaban compared with rivaroxaban and dabigatran etexilate for treating and preventing VTE. The company performed 2 meta-analyses to indirectly compare apixaban with warfarin, rivaroxaban and dabigatran etexilate for treating VTE and for the secondary prevention of recurrent VTE. The Committee commented that indirect comparisons of any outcome will be subject to more uncertainty than from a direct comparison and the uncertainty will be greater for outcomes which are less common such as bleeding or VTE. The Committee agreed that the estimates from the secondary prevention treatment meta-analysis were subject to additional uncertainty, because the trials included in the network had very different follow-up periods (and the longer people remain in a trial the more likely a bleed or VTE would be observed). The Committee concluded that the meta-analysis results should be interpreted with some caution in light of these uncertainties.	4.7
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	There were insufficient data to assess the effectiveness and safety of apixaban in people with active cancer who had DVT or PE, and that it was not possible to make a specific recommendation for this group of people.	4.8

Estimate of the size of the clinical effectiveness including strength of supporting evidence	Apixaban has been demonstrated to be effective in treating VTE and was associated with fewer bleeds than warfarin. There was no evidence of a difference in the effectiveness of apixaban, rivaroxaban and dabigatran etexilate. The estimates from the network meta-analyses were not sufficiently robust to differentiate between apixaban, rivaroxaban and dabigatran etexilate in terms of bleeding.	4.6, 4.7
Evidence for cost effectiveness		
Availability and nature of evidence	The company had presented base-case results for 2 treatment durations: 6-month treatment and lifelong treatment. The Committee concluded that the company's model structure and approach to modelling lifelong treatment was appropriate, but it was aware of the limitations in the data used to inform the model from the network meta-analyses.	4.7, 4.9
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee concluded that agreed values have not been established for INR monitoring costs and utility decrements associated with anticoagulation, and the assumptions used in the company's model were within the range of those used in previous appraisals of apixaban, rivaroxaban and dabigatran etexilate.	4.10

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?	Although the utility value decrements assumed for taking warfarin and for clinically relevant non-major bleeds presented by the company were not the same as in all of the previous appraisals of the novel oral anticoagulants that it had seen, they were within the range presented in previous appraisals.	4.10
Are there specific groups of people for whom the technology is particularly cost effective?	Not applicable.	

What are the key drivers of cost effectiveness?	The sensitivity analyses done by the company and the ERG showed that changing the estimate for the relative risk of bleeding derived from the network meta-analyses had the greatest effect on the ICER; the more similar the bleeding risk between treatments, the higher the ICER became. The Committee was aware that although a difference had been demonstrated in the rate of bleeds between apixaban and warfarin, it was unclear what the relative risk of bleeding with apixaban would be compared with the other novel oral anticoagulants.	4.11
Most likely cost-effectiveness estimate (given as an ICER)	The Committee noted that in most of the company and ERG sensitivity analyses, the ICER was less than £20,000 per QALY gained for either treatment duration (6 months or lifelong).	4.11
Additional factors taken into account		
Patient access schemes (PPRS)	None.	
End-of-life considerations	Not applicable.	
Equalities considerations and social value judgements	No equalities issues were raised in this appraisal.	

5 Implementation

5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has deep vein thrombosis or pulmonary embolism and the doctor responsible for their care thinks that apixaban is the right treatment, it should be available for use, in line with NICE's recommendations.

5.3 NICE has developed tools [link to www.nice.org.uk/guidance/TAXXX] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- 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 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the NICE website.

Published

- Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital. NICE clinical guideline 92 (2010)
- Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism. NICE technology appraisal 327 (2014)
- Rivaroxaban for the treating pulmonary embolism and preventing recurrent venous thromboembolism. NICE technology appraisal guidance 287 (2013)
- Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism. NICE technology appraisal guidance 261 (2012)

Under development

- Deep vein thrombosis, pulmonary embolism (treatment, secondary prevention) edoxaban tosylate. NICE technology appraisal guidance, publication expected October 2015.

7 Review of guidance

7.1 The guidance on this technology is considered for review 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Jane Adam
Chair, Appraisal Committee
February 2015

8 Appraisal Committee members, guideline representatives and NICE project team

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 4 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)
Consultant Radiologist, Department of Diagnostic Radiology, St George's Hospital, London

Professor Iain Squire (Vice-Chair)
Consultant Physician, University Hospitals of Leicester

Dr Graham Ash

Consultant in General Adult Psychiatry, Lancashire Care NHS Foundation Trust

Dr Jeremy Braybrooke

Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust

Dr Gerardine Bryant

General Practitioner, Swadlincote, Derbyshire

Professor Aileen Clarke

Professor of Public Health & Health Services Research, University of Warwick

Dr Andrew England

Senior Lecturer, Directorate of Radiography, University of Salford

Dr Ian Lewin

Honorary Consultant Physician and Endocrinologist, North Devon District Hospital

Ms Pamela Rees

Lay member

Dr Paul Robinson

Medical Director, Merck Sharp & Dohme

Ms Ellen Rule

Director of Transformation and Service Redesign, Gloucestershire Clinical Commissioning Group

Dr Brian Shine

Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford

Dr Peter Sims

General Practitioner, Devon

Dr Eldon Spackman

Research Fellow, Centre for Health Economics, University of York

Mr David Thomson

Lay member

Dr John Watkins

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

Professor Olivia Wu

Professor of Health Technology Assessment, University of Glasgow

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Mary Hughes

Technical Lead

Sally Doss

Technical Adviser

Bijal Joshi

Project Manager

9 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Liverpool Reviews and Implementation Group:

- Greenhalgh J, Bagust A, Beale S, et al., Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism: A Single Technology Appraisal, December 2014

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, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to make written submissions. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company:

- Bristol-Myers Squibb and Pfizer (apixaban)

II. Professional/expert and patient/carer groups:

- Anticoagulation Europe
- British Society for Haematology
- British Thoracic Society
- Clinical Leaders of Thrombosis
- Lifeblood: The Thrombosis Charity
- Royal College of Pathologists
- Royal College of Physicians
- United Kingdom Clinical Pharmacy Association

III. Other consultees:

- Department of Health
- NHS England
- Welsh Government

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

- Bayer (rivaroxaban)
- Department of Health and Social Services and Public Safety, Northern Ireland
- Healthcare Improvement Scotland
- National Institute for Health Research Technology Assessment Programme
- Sanofi (enoxaparin)
- LEO Pharma (tinzaparin)
- Liverpool Reviews & Implementation Group, University of Liverpool
- Pfizer (dalteparin)

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on apixaban by attending the initial Committee discussion and providing a written statement to the Committee. They are invited to comment on the ACD.

- Dr Tim Nokes, Consultant Haematologist, nominated by organisation representing Bristol-Myers Squibb and Pfizer – clinical expert
- Dr Will Lester, Consultant Haematologist, nominated by organisation representing Royal College of Pathologists and British Society of Haematology – clinical expert
- Professor Beverley Hunt, Medical Director of Lifeblood: The Thrombosis Charity, nominated by organisation representing Lifeblood: The Thrombosis Charity – patient expert
- Mrs Diane Eaton, Project Development Manager of Anticoagulation Europe, nominated by organisation representing Anticoagulation Europe – patient expert

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

- Bristol-Myers Squibb and Pfizer (apixaban)