

Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation

Technology appraisal guidance

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This guidance should be read in conjunction with NG196.

1 Recommendations

- 1.1 Rivaroxaban is recommended as an option for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with non-valvular atrial fibrillation with 1 or more risk factors such as:
- congestive heart failure
 - hypertension
 - age 75 years or older
 - diabetes mellitus
 - prior stroke or transient ischaemic attack.
- 1.2 Decide whether to start treatment with rivaroxaban after an informed discussion with the person about its risks and benefits compared with warfarin, apixaban, dabigatran etexilate and edoxaban. For people taking warfarin, consider the potential risks and benefits of switching to rivaroxaban taking into account their level of international normalised ratio (INR) control.

2 The technology

- 2.1 Rivaroxaban (Xarelto, Bayer HealthCare) is an anticoagulant that directly inhibits activated factor X (factor Xa). Factor Xa is a key component in the formation of blood clots. Rivaroxaban has a UK marketing authorisation for the 'prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with 1 or more risk factors such as: congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, prior stroke or transient ischaemic attack'.
- 2.2 According to the summary of product characteristics, approximately 14% of people treated with rivaroxaban in clinical studies experienced adverse reactions. Bleeding occurred in approximately 3.3% of patients and anaemia in approximately 1% of patients. Other common adverse reactions were nausea and an increase in transaminases. The summary of product characteristics states that the risk of bleeding may be increased in certain patient groups, for example those with uncontrolled severe arterial hypertension and/or those taking other treatments that affect haemostasis. For full details of adverse reactions and contraindications see the summary of product characteristics.
- 2.3 The price of rivaroxaban is £58.80 for a pack of 28×15-mg tablets and £58.80 for a pack of 28×20-mg tablets (MIMS, March 2012). Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee considered evidence submitted by the manufacturer of rivaroxaban and a review of this submission by the Evidence Review Group (ERG).

- 3.1 The main clinical effectiveness evidence came from 1 multicentre, double-blind randomised controlled trial. The ROCKET-AF trial ('Rivaroxaban once daily oral direct factor Xa inhibitor compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation') compared rivaroxaban with dose-adjusted warfarin. The manufacturer also compared rivaroxaban with aspirin and dabigatran etexilate (110 mg or 150 mg twice a day) using a network meta-analysis in people for whom anticoagulation therapy was considered suitable. The ROCKET-AF trial was designed as double-blind, double dummy trial comparing rivaroxaban (20 mg or 15 mg once a day) with warfarin (target INR of 2.0 to 3.0) for the prevention of stroke and thromboembolic events in people with non-valvular atrial fibrillation at risk of future thromboembolic events. People were randomly allocated to 1 of the 2 treatment groups with equal probability (1:1 allocation ratio). The study took place in 45 countries, including the UK, and a total of 14,264 people were enrolled across the 2 treatment arms (rivaroxaban n=7,131, warfarin n=7,133). Treatment continued until approximately 405 adjudicated primary efficacy end point events had occurred in the per-protocol population on treatment. As a result, the time on treatment varied from patient to patient depending on when they enrolled in the trial. The median duration of treatment was 590 days.
- 3.2 The primary efficacy end point in ROCKET-AF was a composite of stroke (ischaemic and haemorrhagic stroke) and non-central nervous system systemic embolism. The primary safety end point was defined as a composite of major bleeding and clinically relevant non-major bleeding. To show non-inferiority in preventing stroke and non-central nervous system embolism, the upper boundary of the confidence interval of the hazard ratio (HR) for rivaroxaban compared with warfarin had to be less than 1.46. Once non-inferiority was demonstrated for the primary outcome, further analyses investigated superiority of rivaroxaban over warfarin.
- 3.3 More than 50% of people in the trial received treatment for at least 18 months.

The median age of study participants was 73 years and 60.3% were men. The majority of the trial population (62.4%) had previously received warfarin therapy and 36.5% had previously received aspirin. Risk of stroke at baseline was classified according to CHADS₂ score, which is used to predict the risk of stroke in people with atrial fibrillation. The trial entry criteria included a history of stroke, transient ischaemic attack or systemic embolism, or a CHADS₂ score of 2 or more. The mean CHADS₂ score was 3.48 for the rivaroxaban group and 3.46 for the warfarin group; 99.98% of the trial population had a baseline CHADS₂ score of 2 or more and 86.95% a baseline CHADS₂ score of 3 or more. Three participants (0.02% of the trial population) had a baseline CHADS₂ score of 1. In the warfarin group the mean time in therapeutic range for the INR range of 2.0 to 3.0 was 55% (58% median). Some variability was observed in time in therapeutic range by region: north America had the highest overall INR control, followed by western Europe, Latin America, Asia Pacific, and eastern Europe.

- 3.4 Three analyses were defined in the manufacturer's submission for the efficacy analysis: the intention-to-treat set (all patients randomised), the safety-on-treatment set (all intention-to-treat patients who had taken at least 1 dose of the study drug and were followed for events) and the per-protocol set (all intention-to-treat patients excluding those who had major pre-defined protocol deviations). The primary non-inferiority analysis of the ROCKET-AF trial was conducted on the per-protocol and the safety-on-treatment population data sets. The superiority analyses were conducted on the safety-on-treatment population data sets. In addition to these analyses, sensitivity analyses were performed to assess non-inferiority and superiority in the intention-to-treat population. The primary safety analysis was conducted on the safety-on-treatment population data.
- 3.5 Pre-planned subgroup analyses were conducted. These were by region, prior use of vitamin K antagonists (such as warfarin), and history of stroke, transient ischaemic attack, and non-central nervous system systemic embolism. Other subgroups included prior chronic aspirin use, sex, age, family origin, renal function, body mass index, weight, CHADS₂ score, congestive heart failure, hypertension, diabetes, type of atrial fibrillation, proton pump inhibitor use at baseline, and prior myocardial infarction. Results were summarised by subgroup based on data from the safety-on-treatment and intention-to-treat populations.
- 3.6 The non-inferiority of rivaroxaban compared with warfarin was demonstrated for

the primary outcome (composite of stroke and non-central nervous system systemic embolism) in both the per-protocol and safety-on-treatment populations. The results for the per-protocol population were HR 0.79 (95% confidence interval [CI] 0.66 to 0.96) and HR 0.79 (95% CI 0.65 to 0.95) for the safety-on treatment population. Superiority of rivaroxaban over warfarin was also demonstrated in the safety-on-treatment population, but was not demonstrated for this outcome in the sensitivity analysis using the intention-to-treat population data set (HR 0.88, 95% CI 0.75 to 1.03).

- 3.7 For the primary safety end point of major or non-major clinically relevant bleeding, the results from the safety-on-treatment population data for ROCKET-AF suggest a comparable safety profile for rivaroxaban and warfarin, with no statistically significant difference between the 2 treatments (HR 1.03, 95% CI 0.96 to 1.11). Bleeding sites for the primary safety end point differed between treatment groups. Rivaroxaban was more often associated with bleeding at sites throughout the gastrointestinal tract (3.15% compared with 2.16%, $p < 0.001$) but intracranial haemorrhage rates were significantly lower with rivaroxaban than with warfarin (0.5% compared with 0.7%, $p = 0.02$). Following a request from the ERG the manufacturer provided subgroup analyses for the safety-on-treatment and intention-to-treat populations in people who had previously used vitamin K antagonists, people who had not previously used vitamin K antagonists, people with a time in therapeutic range below 60%, and those with a time in therapeutic range above 60%. In the safety-on-treatment population, superiority of rivaroxaban compared with warfarin was demonstrated for the primary outcome (composite of stroke and non-central nervous system systemic embolism) in people who had not previously used vitamin K antagonists (HR 0.72, 95% CI 0.53 to 0.97) but not in people who had previously used vitamin K antagonists (HR 0.84, 95% CI 0.66 to 1.08).
- 3.8 The manufacturer undertook a Bayesian network meta-analysis comparison of rivaroxaban with warfarin, aspirin, no treatment and dabigatran etexilate. The clinical evidence for the rivaroxaban with warfarin comparison was taken from the ROCKET-AF trial. Evidence for the other comparators was obtained from studies found by a systematic literature search. The manufacturer identified 18 studies for inclusion in the network meta-analysis:
- 1 comparing rivaroxaban with warfarin

- 7 comparing aspirin with placebo or control
- 8 comparing warfarin with aspirin
- 1 comparing a vitamin K antagonist with clopidogrel plus aspirin
- 1 comparing dabigatran etexilate with warfarin (the RE-LY study).

The manufacturer reported network meta-analysis results for the outcomes using the ROCKET-AF safety-on-treatment population data set. At the request of the ERG, the manufacturer also provided the results for the outcomes using the ROCKET-AF intention-to-treat population dataset. The efficacy estimates from this network meta-analysis using the ROCKET-AF safety-on-treatment population data set were used in the manufacturer's cost-effectiveness analyses.

3.9 The ERG undertook an exploratory network meta-analysis comparing rivaroxaban with dabigatran etexilate, aspirin, placebo, and adjusted standard dose warfarin. It included data from 8 of the 18 studies from the manufacturer's network meta-analysis:

- 1 comparing dabigatran etexilate with warfarin
- 1 comparing rivaroxaban with warfarin
- 3 comparing aspirin with warfarin
- 3 comparing warfarin with placebo.

The ERG judged that including only these 8 trials would reduce the amount of heterogeneity in the network. Only dosing strategies that the ERG considered to be comparable were included (that is, rivaroxaban 20 mg per day, dabigatran etexilate 150 mg twice a day, aspirin 300 mg per day, and adjusted dose warfarin aiming at a target INR range between 2 and 3). Dabigatran etexilate at a dose of 110 mg twice daily was not included in the analysis because the economic model could not accommodate a dosing regimen in which the dose is reduced from 150 mg twice daily to 110 mg twice daily when the patient reaches the age of 80 years. A fixed-effect model was used because of the high degree of homogeneity between the

included trials. The efficacy estimates from this network meta-analysis were used in the ERG's cost-effectiveness analyses.

3.10 The manufacturer developed a Markov model that compares rivaroxaban (20 mg once a day) with warfarin (adjusted dose warfarin at 4.5 mg once a day, target INR 2.5, range 2.0 to 3.0), aspirin (150 mg once a day), dabigatran etexilate (110 mg to 150 mg twice a day) and no treatment. The population in the model is the same as the ROCKET-AF safety-on-treatment population. The model has a lifetime time horizon and a UK NHS perspective.

3.11 The model included the following health states:

- anticoagulant initiation
- stable atrial fibrillation (on or off therapy)
- minor stroke (on or off therapy)
- major stroke (on or off therapy)
- post minor stroke (on therapy)
- post major stroke (on therapy)
- minor bleed (on or off therapy)
- major bleed (on or off therapy)
- intracranial bleed (on or off therapy)
- post intracranial bleed (on or off therapy)
- systemic embolism (on or off therapy)
- myocardial infarction (on or off therapy)
- post myocardial infarction (on or off therapy)
- death.

The ROCKET-AF trial results for the safety-on-treatment population were used to inform the efficacy estimates for rivaroxaban compared with

warfarin, rivaroxaban compared with warfarin in people whose atrial fibrillation is poorly controlled on warfarin, and the vitamin K antagonist-naïve model populations. The characteristics of the population for the analyses of rivaroxaban compared with aspirin, dabigatran etexilate and no treatment were based on the patient characteristics of a UK GP practice-based survey (Gallagher et al. 2008). Efficacy estimates for rivaroxaban compared with dabigatran etexilate and aspirin were obtained from the manufacturer's network meta-analysis.

- 3.12 The manufacturer classified all model events as either transient or permanent depending on associated long-term costs and consequences:
- Systemic embolism, minor extracranial bleeds and major extracranial bleeds were assumed to have no lasting clinical or economic consequences and as such were considered transient events in the model.
 - Minor stroke, major stroke, intracranial bleeding and myocardial infarction were considered by the manufacturer to be permanent events, in the sense that they have lasting clinical and economic consequences. Consequently, the manufacturer developed post-event health states to account for the different risks, costs and utilities associated with surviving a permanent event.
- 3.13 The manufacturer highlighted that increasing age was an important risk factor for ischaemic stroke and systemic embolism, and adjusted the baseline risk of these events to account for patients aging as they move through the model. Risks were calculated using the Framingham risk equations. In the model, a weighted average relative risk (weighted by the proportion of patients in each risk group at initiation) is calculated for each age group and applied to the baseline risk as patients enter that age group. The risks of extracranial bleeding, intracranial bleeding and myocardial infarction were assumed to be independent of time and, therefore, were not adjusted for.
- 3.14 The baseline risk of each event was adjusted according to the treatment regimen the patient was receiving. Patients may stop their primary therapy and switch to a pre-specified secondary therapy at any time, although the risk adjustment applied for the remainder of that cycle is that of the primary therapy. The probabilities of treatment discontinuation for warfarin and rivaroxaban were

based on data from the ROCKET-AF trial. The manufacturer assumed that treatment-discontinuation rates for aspirin, dabigatran etexilate and placebo were equivalent to that for rivaroxaban, given the similarity of administration between these interventions.

- 3.15 The health-state utility values and treatment-related utility values in atrial fibrillation were obtained from published sources identified by a systematic literature search. The ROCKET-AF trial did not include a generic measure of health-related quality of life (such as the EQ-5D) that could be used to estimate utilities in the model. The estimates of resources and costs were obtained from NHS reference costs for 2009 to 2010 and systematic literature searching. The manufacturer's model categorised monitoring costs into the following distinct phases: initiation, maintenance, and re-initiation. The manufacturer's model calculated the quarterly cost of initiation, maintenance and re-initiation by taking a weighted average of each cost; the costs of the individual phases were weighted by the proportion of people treated in primary and secondary care, as indicated by the manufacturer's survey. The resulting annual cost estimates for warfarin monitoring were £663 (£448 in primary care and £215 in secondary care) for the first year and £525 (£359 in primary care and £166 in secondary care) for subsequent years.
- 3.16 The manufacturer's base-case analysis of rivaroxaban compared with warfarin used only statistically significant data from the ROCKET-AF safety-on-treatment population. The analysis produced an incremental cost of £740 and a QALY gain of 0.039 resulting in an incremental cost-effectiveness ratio (ICER) of £18,883 per quality-adjusted life year (QALY) gained. The manufacturer also presented the results of 4 subgroup analyses:
- For rivaroxaban compared with warfarin in people whose INR is poorly controlled on warfarin, rivaroxaban dominated (was more effective and cost less) warfarin.
 - For rivaroxaban compared with warfarin in people who had not previously received warfarin, the ICER was £15,494 per QALY gained.
 - For rivaroxaban compared with aspirin, the ICER was £2,083 per QALY gained.
 - For rivaroxaban compared with dabigatran etexilate, rivaroxaban dominated

dabigatran etexilate.

The manufacturer carried out univariate sensitivity analysis on the base case, scenario analyses and subgroup analyses. The main drivers of the model results were consistent across analyses, with the cost of warfarin monitoring in primary care having a major impact on all ROCKET-AF-based analyses. The probabilistic sensitivity analyses indicated that, using the base case, rivaroxaban had a 75% probability of being cost effective at a maximum acceptable ICER of £20,000 per QALY gained and an 88% probability at £30,000 per QALY gained. The manufacturer's scenario analysis of rivaroxaban compared with warfarin used all point estimates from the ROCKET-AF safety-on-treatment population regardless of their statistical significance (that is, both statistically significant and non-statistically significant point estimates were used). The resulting ICER was £8,732 per QALY gained.

- 3.17 In the ERG's view, a Markov model was an appropriate choice for modelling the chronic condition of atrial fibrillation. The ERG noted that the manufacturer chose a cycle length of 3 months and that only 1 event per 3-month cycle was possible because of the nature of the model. The manufacturer acknowledged that, in reality, people may experience more than 1 event in 3 months, but clinical opinion was that the probability of this would be low. The ERG agreed that assuming 1 event per model cycle was necessary and reasonable. However, the ERG noted that the manufacturer's model also suspends the risk of further events in the subsequent model cycle. The ERG considered that this additional suspension of risk was likely to bias the analysis against the more effective treatment because the overall event rate would be lower, and the potential to demonstrate clinical and economic benefits would also be lower.
- 3.18 The ERG identified the following limitations to the model's structural assumptions and parameter sources:
- not separating out the number of hospital visits needed by people who were within and outside recommended INR control
 - not adjusting risk of bleeding by age; not adjusting utility by age
 - the source of myocardial infarction risk for people treated with aspirin

- out of date source of post-myocardial infarction mortality risk
- double counting of re-initiation costs of warfarin monitoring
- suspending the risk of further events for the subsequent model cycle after an event
- excluding transient ischaemic attack as a potential event.

3.19 The ERG presented an exploratory analysis in which, if possible, adjustments were made to account for the limitations identified (see section 3.18). The analysis for rivaroxaban compared with warfarin produced an incremental cost of £1,134 and a QALY gain of 0.034, resulting in an ICER of £33,758 per QALY gained. Similarly, for warfarin-naïve people, after incorporating the ERG's model adjustments, the ICER for rivaroxaban compared with warfarin increased from £15,494 to £29,894 per QALY gained. However, rivaroxaban remained dominant in people whose INR was poorly controlled on warfarin after the ERG's model adjustments were incorporated. The structure of the manufacturer's model meant it wasn't possible to remove risk suspension or add transient ischaemic attack as a potential event. Consequently, the ERG was unable to fully quantify the impact of these limitations on the ICERs. However, the ERG considered that suspending risk and excluding transient ischaemic attack as an event would favour rivaroxaban (that is, the removal of these limitations would decrease the ICER for rivaroxaban compared with warfarin), because warfarin is generally less effective than rivaroxaban (based on the safety-on-treatment population of ROCKET-AF).

3.20 In the ERG's view, the manufacturer's base-case model is driven by the cost of anticoagulation monitoring rather than the differential effectiveness of rivaroxaban and warfarin. The ROCKET-AF trial showed that, for most outcomes, there was no statistically significant difference between rivaroxaban and warfarin. The ERG highlighted that when the cost of anticoagulation monitoring was separated out by INR range the ICER substantially increased from £18,883 per QALY gained to £27,281 per QALY gained. In addition, the ERG's scenario analysis using the alternative anticoagulation monitoring costs of £242 per person (discussed by the Committee in the ongoing appraisal of dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation) increased the ICER to £62,568 per QALY gained.

3.21 The ERG was concerned that the trials included in the network meta-analysis presented by the manufacturer to compare rivaroxaban with aspirin and dabigatran etexilate were heterogeneous. The high levels of heterogeneity were not shown when the ERG conducted its own network meta-analysis restricting the network to the comparators specified in the final scope. When the ERG applied the treatment effects estimated by its network meta-analysis to the manufacturer's model, and a full incremental analysis of rivaroxaban, dabigatran etexilate, warfarin and aspirin was conducted, an ICER of £34,680 per QALY gained was obtained for dabigatran etexilate compared with rivaroxaban, whereas rivaroxaban had dominated dabigatran etexilate in the manufacturer's analysis. The ERG applied further adjustments to account for the following limitations:

- the absence of a post-systemic embolism health state
- not adjusting bleeding risk by age
- not adjusting utility by age
- out of date source of post-myocardial infarction mortality risk
- assuming equivalent discontinuation rates.

This reduced the ICER to £12,701 per QALY gained for dabigatran etexilate compared with rivaroxaban. Exploratory analysis assuming an equivalent ability of rivaroxaban and dabigatran etexilate to prevent myocardial infarction further decreased the ICER to £3,578 per QALY gained for dabigatran etexilate compared with rivaroxaban.

3.22 The ERG noted the presence of potential biases in the model, with limitations of risk suspension and the absence of transient ischaemic attack and dyspepsia as adverse reactions. Removing risk suspension is likely to favour dabigatran etexilate whereas including transient ischaemic attack and dyspepsia is likely to reduce the ICER for rivaroxaban compared with dabigatran etexilate. Furthermore, the ERG noted that there is a large amount of uncertainty in the model and that the model is highly sensitive to even small changes to the discontinuation rates. Therefore, the ERG concluded that the results of the probabilistic sensitivity analysis should be taken into account when considering its alternative ICER for dabigatran etexilate compared with rivaroxaban. The

probabilistic sensitivity analysis indicated that dabigatran etexilate was dominant in 45% of the 1,000 runs and dominated in 35% of runs.

Manufacturer's additional analyses

3.23 The manufacturer provided additional analyses in response to the Appraisal Committee's request for further clarification on the cost effectiveness of rivaroxaban presented in the appraisal consultation document. The manufacturer provided a revised cost-effectiveness analysis incorporating the following amendments requested by the Appraisal Committee:

- data from the General Practice Research Database to provide event rates according to baseline level of stroke risk and the distribution of patients with different CHADS₂ scores from the study of Gallagher et al. (2008)
- all the efficacy point estimates from the safety-on-treatment population of the ROCKET-AF trial
- revised event rate in the warfarin arm to reflect the time in therapeutic range achieved in trial centres in western Europe (60.62%)
- fixed annual warfarin INR monitoring cost of £242 per person in the sensitivity analysis only.

3.24 In addition to the amendments requested by the Appraisal Committee, the manufacturer also amended the model to include the following:

- Revised annual warfarin INR monitoring cost of £580. The manufacturer used the same unit costs as the original model; however, the number of visits needed for the re-initiation was reduced from 7 to 5 per 3-month cycle. The costs associated with warfarin monitoring in primary care in the updated model were £175.50 for initiation of warfarin (calculated as a weighted average of patients who had, and had not received previous warfarin), £135 for maintenance on warfarin and £135 for re-initiation of warfarin.
- Case fatality rates of 90 days instead of the 30-day rates in the original model.

- Updated 'real world' discontinuation rates. For warfarin these came from the General Practice Research Database. For rivaroxaban they were calculated by applying relative risks from the General Practice Research Database to discontinuation rates from the ROCKET-AF trial.
- Treatment-related disutility applied to warfarin of 0.05. This was obtained from a study evaluating how patients with atrial fibrillation (attending GP- and hospital-led clinics) value different health outcomes. The disutility figures for warfarin were weighted by the UK distribution of primary and secondary care anticoagulation management.
- Updated results for rivaroxaban compared with aspirin based on an additional indirect comparison. This comparison used only trials comparing rivaroxaban with warfarin and warfarin with aspirin, to reduce the network heterogeneity.

3.25 The manufacturer presented the following cost-effectiveness results when all the amendments in sections 3.23 and 3.24 were applied, with an annual warfarin INR monitoring cost of £580 (that is, excluding the Appraisal Committee's request to incorporate a fixed annual warfarin INR monitoring cost of £242 per person):

- for rivaroxaban versus warfarin in the licensed population (the population with 1 or more risk factors for stroke), an incremental cost of £705, an incremental QALY of 0.2459 resulting in an ICER of £2,869 per QALY gained
- for rivaroxaban versus warfarin in the population whose INR is poorly controlled on warfarin, rivaroxaban dominated warfarin
- for rivaroxaban versus warfarin in the population for whom warfarin is considered unsuitable, the ICER was £9,170 per QALY gained.

3.26 The manufacturer presented the following cost-effectiveness results when all the amendments detailed in sections 3.23 and 3.24 were applied, with an annual warfarin INR monitoring cost of £242 per person (that is, including all of the Appraisal Committee's requests):

- for rivaroxaban versus warfarin in the licensed population (the population with 1 or more risk factors for stroke), an incremental cost of £2,220, a QALY gain of 0.2459 resulting in an ICER of £9,031 per QALY gained

- for rivaroxaban versus warfarin in the population whose INR is poorly controlled on warfarin, the ICER was £4,350 per QALY gained.

- 3.27 The ERG provided a critique and exploratory analysis of the manufacturer's additional analyses. The ERG agreed that the manufacturer had adequately provided a model cohort representative of people with atrial fibrillation in the UK, and that the analysis was based on all efficacy point estimates from the ROCKET-AF trial. The ERG also agreed that it was reasonable to use a discontinuation rate of 5 and a 90-day case fatality rate in the model. However, the ERG noted that the Committee's request to evaluate the effect of low time in therapeutic range was addressed as an amendment to the base case rather than the subgroup analysis requested. The ERG noted that varying the risk of stroke and systemic embolism according to level of INR control resulted in an increase in the ICER of £3,742 per QALY gained.
- 3.28 In the ERG's view, the manufacturer's inclusion of a disutility for warfarin in the model was not appropriate. The ERG noted that the manufacturer had not provided any justification for the assumption that no disutility is associated with rivaroxaban, aspirin or dabigatran etexilate. The ERG pointed out that there is evidence of disutility associated with other oral anticoagulants such as dabigatran etexilate and therefore it is unreasonable to assume there is no disutility associated with rivaroxaban. The ERG found that removing the disutility for warfarin has a substantial impact on the ICER, increasing it from £2,869 to £10,764 per QALY gained.
- 3.29 The ERG re-ran the manufacturer's updated cost-effectiveness analysis. The ERG noted that in both the original and updated models the manufacturer had categorised systemic embolism as a temporary event. The ERG judged that in order to adequately approximate a post-systemic embolism health state (which would account for the increased risk of stroke following a systemic embolism) it was appropriate to amend the model so that after a systemic embolism patients move into the post-minor stroke health state. The ERG also noted that the manufacturer's updated model continues to use the out-of-date source of post-myocardial infarction mortality risk. The ERG judged that it was more appropriate to use an updated mortality risk post myocardial infarction that took account of current use of statins. The ERG's analysis included a fixed annual warfarin INR monitoring cost of £242 per person as requested by the Appraisal Committee

(see section 3.23) but did not include any disutility associated with warfarin or any other treatment (see section 3.24). The ERG's revised analysis for rivaroxaban compared with warfarin produced an incremental cost of £1,815, an incremental QALY of 0.061 and an ICER of £29,537 per QALY gained.

- 3.30 See the [manufacturer's submission](#) and the [ERG report](#) for full details of all the evidence.

4 Consideration of the evidence

- 4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of rivaroxaban, having considered evidence on the nature of stroke and systemic embolism and the value placed on the benefits of rivaroxaban by people with atrial fibrillation, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.
- 4.2 The Committee was aware that the main concerns for people with atrial fibrillation were fear of having a stroke and anxiety about the difficulty of keeping the INR within the therapeutic range. The Committee heard from the clinical specialists, patient experts and from comments received during consultation that the current standard treatment for preventing stroke and systemic embolism in people with atrial fibrillation is warfarin, and that because aspirin is less effective it is used only in people for whom warfarin is unsuitable. The Committee also heard that warfarin, although an effective treatment, it is associated with a number of problems. The Committee was aware from the patient expert and from comments received during consultation that taking warfarin adversely affects quality of life. This is because people taking warfarin often worry about their level of INR control and they might find regular GP and hospital visits disruptive and inconvenient. The Committee heard from the clinical specialists that a substantial proportion of people taking warfarin have poorly controlled INR and are often not within the target therapeutic range at any 1 time. In particular, older people with atrial fibrillation are more likely to have poorly controlled INR because of comorbidities. The clinical specialists also explained that the need for regular monitoring and dose adjustments, occasionally involving complicated regimens such as different doses on alternate days, can cause difficulties with adherence to treatment. The Committee recognised the potential benefits of alternatives such as rivaroxaban for people with atrial fibrillation, including the positive effect on quality of life of removing the restrictions and difficulties associated with taking warfarin.
- 4.3 The Committee considered the clinical-effectiveness data from the ROCKET-AF trial comparing rivaroxaban with warfarin. It noted that this study was the basis of the clinical-effectiveness evidence in the manufacturer's submission. The Committee noted that the efficacy analysis in the manufacturer's submission had

been undertaken on 3 different populations in the ROCKET-AF trial, the intention-to-treat set (all randomised patients), the safety-on-treatment set (all intention-to-treat patients who had taken at least 1 dose of study drug and were followed for events) and the per-protocol set (all intention-to-treat patients excluding those who have major pre-defined protocol deviations). The Committee noted that the manufacturer had presented data from the safety-on-treatment population for its primary analyses. The Committee heard from the clinical specialists that using a trial intention-to-treat population was considered to be the gold standard for estimating clinical effectiveness in a superiority trial, but the primary objective of ROCKET-AF was to establish non-inferiority of rivaroxaban compared with warfarin so the primary analysis was different. The Committee noted the comments received during consultation that suggested that it would be more appropriate to consider the intention-to-treat population rather than the safety-on-treatment population. The Committee reconsidered which of the 2 study populations was the most appropriate. The Committee noted that the intention-to-treat population included people who had either had no treatment or switched treatment during the trial, and agreed that the estimates derived from the safety-on-treatment population of the ROCKET-AF trial provided an adequate basis for evaluating clinical effectiveness.

- 4.4 The Committee noted that a key uncertainty highlighted by the ERG was the generalisability of the results of ROCKET-AF to people diagnosed with atrial fibrillation in the NHS. The Committee noted that the mean time in therapeutic range for the INR range of 2.0 to 3.0 for warfarin was 55% for the safety-on-treatment population in the ROCKET-AF trial. The clinical specialists confirmed this could be considered to be around the lower end of the level of control that would be expected in UK clinical practice, but there is considerable variation between different centres and also between different settings, depending on the patient group. The Committee noted that the ROCKET-AF trial had been undertaken in a number of countries, which did not all achieve similar levels of time in therapeutic range. The majority (66.5%) of the participants were recruited from centres in eastern Europe, Latin America and Asia, and in these centres the proportion of time in therapeutic range was lower than in the centres in North America and western Europe. The Committee was concerned that the effectiveness of warfarin could be underestimated if the proportion of time in therapeutic range was low, and that the UK context might be better reflected by results from centres where the time in therapeutic range in the warfarin arm more

closely matched the usual levels in the UK. The Committee concluded that the trial results were broadly applicable to a UK setting, but for those already taking warfarin the current level of INR control should be taken into account in any decision to switch to rivaroxaban.

- 4.5 The Committee also noted that patients in the ROCKET-AF trial had a mean CHADS₂ score of 3.47, and that an inclusion criterion of the trial was a baseline CHADS₂ score of 2 or more. The scope specified that the appraisal population would be people with a medium to high risk of stroke. The clinical specialists confirmed that people with a CHADS₂ score of 3 or more would be at high risk of stroke and that this population was typical of people seen in secondary care. However, this did not necessarily represent people with atrial fibrillation treated in primary care, who tended to have a lower risk of stroke. The Committee heard that people with atrial fibrillation treated with warfarin in primary care often have a CHADS₂ score of less than 2 and that it is estimated that between 20 and 75% of people with atrial fibrillation and a CHADS₂ score of less than 2 are prescribed warfarin in the UK. Only 0.02% of the trial population had a CHADS₂ score less than 2. The clinical specialists agreed that it was likely that although people with a CHADS₂ score of 2 or more would benefit similarly to those in the ROCKET-AF trial, this cannot be assumed for people with a CHADS₂ score of less than 2. The Committee noted the comments received during consultation that suggested that consultees and commentators had differing opinions on the generalisability of the results of ROCKET-AF to UK clinical practice. The Committee was made aware by the manufacturer that a systematic review of the literature had suggested that there does not appear to be an interaction between treatment effect and baseline CHADS₂ risk. The Committee heard from the manufacturer that rivaroxaban would be indicated for atrial fibrillation in people with 1 or more risk factors for stroke, which equates to a CHADS₂ score of 1 or more. The Committee noted that the European Medicines Agency had stated in the 'European public assessment report' for rivaroxaban that efficacy results were essentially consistent in important subgroups, such as different CHADS₂ scores (CHADS₂ scores 2 to 6). The Committee accepted that, given the broad spectrum of risk covered by the licensed indication for rivaroxaban, there was no plausible reason to expect that the results of ROCKET-AF would not translate to people with a lower CHADS₂ score. However, the Committee was mindful of the very small number of patients recruited to the ROCKET-AF trial with a baseline CHADS₂ score of less than 2, but concluded that the results of the ROCKET-AF trial were generalisable to UK

clinical practice.

- 4.6 The Committee discussed the safety data from the ROCKET-AF trial. It noted that analysis of the primary safety end point of all major and non-major clinically significant bleeding events showed no significant differences between rivaroxaban and warfarin. There was a significant reduction in the rate of fatal bleeds and intracranial haemorrhage with rivaroxaban compared with warfarin, but a higher rate of gastrointestinal bleeds. The Committee heard from the patient experts that intracranial bleeds were considered to be a more serious complication than gastrointestinal bleeds in clinical practice, because they were more difficult to treat and often result in permanent disability. The Committee noted that the possible uncertainty in these results related to the relatively low proportion of time in therapeutic range of 55% in the warfarin arm of the trial, but concluded that the primary safety end point showed no statistically significant difference between rivaroxaban and warfarin.
- 4.7 The Committee then discussed the indirect clinical-effectiveness evidence for rivaroxaban compared with dabigatran etexilate and aspirin. The Committee noted that the population in the study comparing dabigatran etexilate with warfarin (RE-LY) had a lower risk of stroke (mean CHADS₂ score 2.1) than the population in the ROCKET-AF trial (mean CHADS₂ score of 3.47). The Committee noted that the manufacturer's interpretation of its network meta-analysis was that there was no significant difference between rivaroxaban and dabigatran etexilate for any outcome. The Committee noted the ERG's concerns about the validity of the manufacturer's network meta-analysis because of the clinical heterogeneity of the included trials, and the different levels of time in therapeutic range in the warfarin arms of the rivaroxaban and dabigatran etexilate trials. The Committee also noted that both the manufacturer's and ERG's network meta-analyses contained wide confidence intervals, and therefore the resulting efficacy point estimates were subject to considerable uncertainty. The Committee noted the comments received during consultation suggesting that the Committee should reconsider the value of the network meta-analysis. The Committee also noted the additional indirect comparison submitted by the manufacturer during consultation comparing rivaroxaban with aspirin. The Committee reconsidered the data from the manufacturer's and ERG's network meta-analyses and considered the manufacturer's additional indirect comparison comparing rivaroxaban with aspirin. The Committee concluded that it would not

consider further the clinical effectiveness of rivaroxaban compared with aspirin or dabigatran etexilate.

- 4.8 The Committee considered the manufacturer's updated base-case analysis for rivaroxaban compared with warfarin for the licensed population. The Committee noted the ERG's comments on the manufacturer's updated cost-effectiveness analyses and the ERG's revised base-case analysis. The Committee noted that the manufacturer presented an ICER of £2,870 per QALY gained (see [section 3.25](#)) and the ERG presented an ICER of £29,500 per QALY gained (see [section 3.29](#)). The Committee was made aware by both the manufacturer and the ERG that the difference in the ICERs resulted from 2 main factors. One was the manufacturer's inclusion in its updated analysis of a disutility value associated with warfarin treatment. The second was the different costs included by the manufacturer and ERG for warfarin monitoring (£580 and £242 respectively).
- 4.9 The Committee discussed the disutility values used in the manufacturer's updated economic analyses. It noted that the manufacturer had used a small study of 57 patients to justify including a disutility associated with warfarin. The Committee acknowledged that comments received during consultation implied that warfarin was associated with disadvantages. However, the Committee was mindful that the manufacturer had assumed that there was no disutility associated with rivaroxaban and had not provided any rationale for its exclusion. The Committee noted the comments from the ERG and consultees and commentators suggesting that there could be some disutility associated with newer anticoagulation therapy, including concerns about non-reversibility in the case of bleeding. However, the Committee noted that no specific evidence relating to disutility associated with anticoagulation therapy other than warfarin had been submitted by any consultees and commentators or by the ERG. The Committee therefore agreed that although it was appropriate to consider that there might be a disutility associated with warfarin treatment, it was not appropriate to assume that there was no disutility associated with rivaroxaban and other anticoagulant treatments. The Committee concluded that the disutility value used in the economic model for warfarin may have resulted in a bias in the manufacturer's economic analysis in favour of rivaroxaban.
- 4.10 The Committee discussed the costs associated with warfarin INR monitoring. The Committee noted that the manufacturer's model assumed an average annual

anticoagulant monitoring cost of £580 per person in the year that treatment is first initiated and £535 once the person is stabilised on warfarin. The clinical specialists agreed that the annual cost of anticoagulant monitoring for each person treated with warfarin was likely to be lower than the manufacturer's estimate in clinical practice, but a precise estimate could not be given because costs varied considerably between people (for example, they are higher in those with poor INR control) and between centres. The Committee was aware of the uncertainty, but in the interests of consistency had requested that the manufacturer use £242 in its economic model, in line with what it had accepted for the ongoing appraisal of dabigatran etexilate for the same indication. However, the Committee noted the comments received during consultation, which suggested that significant numbers of people have difficulties managing their INR control and could therefore visit a clinic for monitoring up to once a week, making 30 visits a year not implausible. The Committee also noted the manufacturer's comments highlighting its concerns about the plausibility of a cost of £242 per person. The Committee therefore agreed that £242 per person was likely to be a conservative estimate of annual anticoagulant monitoring for warfarin if fixed costs were fully included, and that there was uncertainty about the cost of warfarin INR monitoring in clinical practice.

- 4.11 The Committee considered what the most plausible ICER would be for rivaroxaban compared with warfarin. It noted the ICERs of £2,870 per QALY gained presented by the manufacturer (which included disutility associated with warfarin, and warfarin monitoring costs of £580) and £29,500 per QALY gained (which excluded disutility associated with warfarin, and used warfarin monitoring costs of £242) presented by the ERG. The Committee agreed that because there could be some degree of utility decrement associated with treatment, and the estimate of annual anticoagulation monitoring costs of £242 was likely to be conservative, the ICER for rivaroxaban compared with warfarin would be no more than £29,500 per QALY gained and would lie somewhere between £2,870 and £29,500 per QALY gained. The Committee therefore concluded that the most plausible ICER for the whole population eligible for rivaroxaban was within the range that could be considered a cost-effective use of NHS resources.
- 4.12 The Committee considered whether there were any equality considerations affecting population groups protected by equality legislation and concluded that there were no equality issues relating to this appraisal that needed addressing in

the guidance.

5 Implementation

- 5.1 Section 7 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 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.
- 5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has non-valvular atrial fibrillation and the healthcare professional responsible for their care thinks that rivaroxaban is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Appraisal Committee members, 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.

DrJaneAdam(Chair)

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

ProfessorAEAdes

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

DrJeremyBraybrooke

Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust

DrFionaDuncan

Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital

MrsEleanorGrey

Lay member

Professor Jonathan Grigg

Professor of Paediatric Respiratory and Environmental Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University, London

Dr Peter Heywood

Consultant Neurologist, Frenchay Hospital. Bristol

Dr Sharon Saint-Lamont

Head of Quality and Innovation, North East Strategic Health Authority

Dr Ian Lewin

Consultant Endocrinologist, North Devon District Hospital

Dr Louise Longworth

Reader in Health Economics, HERG, Brunel University, Uxbridge

Dr Anne McCune

Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust

Professor John McMurray

Professor of Medical Cardiology, University of Glasgow

Dr Alec Miners

Lecturer in Health Economics, London School of Hygiene and Tropical Medicine

Ms Pamela Rees

Lay member

Dr Ann Richardson

Lay member

Dr Paul Robinson

Medical Director, Merck Sharp & Dohme

Ms Ellen Rule

Programme Director, NHS Bristol

Mr Stephen Sharp

Senior Statistician, MRC Epidemiology Unit

DrPeterSims

General Practitioner, Devon

MrCliffSnelling

Lay member

MrMikeSpencer

Assistant Director Patient Experience, Cardiff and Vale University Health Board

MrsAmeliaStecher

Associate Director of Individual Funding Requests and Clinical Effectiveness, NHS Kent and Medway

MrDavidThomson

Lay member

DrJohnWatkins

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

DrAnthonySWierzbicki

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

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.

HelenTucker

Technical Lead

NicolaHay

Technical Adviser

BijalJoshi

Project Manager

7 Sources of evidence considered by the Committee

The Evidence Review Group (ERG) report for this appraisal was prepared by BMJ Technology Assessment Group (BMJ-TAG):

- Edwards SJ, Hamilton V, Nherera L et al. Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation: a single technology appraisal. BMJ-TAG, London (October 2011)

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). Manufacturers or sponsors were also invited to make written submissions. Professional or specialist, patient or carer groups, and other consultees, had the opportunity to give their expert views.

Manufacturers or sponsors, professional or specialist, patient or carer groups, and other consultees, also have the opportunity to appeal against the final appraisal determination.

Manufacturers or sponsors:

- Bayer HealthCare

Professional or specialist, and patient or carer groups:

- Anticoagulation Europe (ACE)
- Arrhythmia Alliance (AFA Affiliated)
- Atrial Fibrillation Association (AFA)
- British Association of Stroke Physicians
- British Cardiovascular Society
- British Heart Foundation
- British Society for Haematology
- Heart Rhythm UK

- Primary Care Cardiovascular Society
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians

Other consultees:

- Department of Health
- NHS Berkshire East
- Welsh Government

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

- BMJ Technology Assessment Group (BMJ-TAG)
- Boehringer Ingelheim
- Bristol Myers–Squibb
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Health Care Improvement Scotland
- Medicines and Healthcare products Regulatory Agency
- National Institute for Health Research Health Technology Assessment Programme

The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer or sponsor consultees and commentators. They gave their expert personal view on rivaroxaban by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Rhona Maclean, Consultant Haematologist, nominated by Royal College of Pathologists – clinical specialist

- Ms Fiona Sayers, Head of Nursing, Cardiology and Acute Service, nominated by Royal College of Nursing – clinical specialist
- Professor John Potter, Professor of Ageing Stroke Medicine, nominated by Bayer HealthCare – clinical specialist
- Ms Diane Eaton, nominated by Anticoagulation Europe – patient expert
- Ms Joanne Jerrome, nominated by Atrial fibrillation Association – patient expert

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

- Bayer HealthCare

Update information

July 2021: Section 1.2 was updated to include the other anticoagulants approved by NICE.

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