NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Rivaroxaban for the treatment of DVT and prevention of recurrent DVT and PE

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Bayer	Bayer plc welcomes the opportunity to respond to the NICE Appraisal Consultation Document (ACD) for rivaroxaban in the treatment of deep vein thrombosis (DVT), and to provide further evidence. We recognise that the Committee concluded that rivaroxaban was `more effective than enoxaparin followed by a vitamin K antagonist for preventing recurrent venous thromboembolism', and that the ICERs calculated for the appraisal under `reasonable and relevant' assumptions `for 6 and 12 months were within the range that is normally considered a cost-effective use of NHS resources'. We note further that `the Committee heard from the clinical specialists that they were not aware of any clinical reasons why rivaroxaban would be less effective in patients who received 3 months of treatment'. However, we appreciate that further information is required of Bayer. In response to the request for further consideration as to differences in populations within the EINSTEIN-DVT trial according to treatment duration assigned, we provide additional data and new commentary describing differences in the characteristics of patients in each subgroup. This is given in section 2. We believe biological, clinical and statistical plausibility for differential relative effectiveness is absent. The relative efficacy and safety of rivaroxaban is therefore better characterised by the whole trial measures of treatment effect described in the New England Journal of Medicine publication.	Comments noted.

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td>Bayer</td><td>
We answer the request for the data on the cost-effectiveness of rivaroxaban in patients in whom long-term anticoagulation is intended in section 3. The economic model has required some adaptation to produce this analysis, and our methods and assumptions are explained and justified by supporting evidence appropriate for this subgroup. The INR monitoring intensity assumptions in the MS were evidence-based, and we consider it unfair if the judgement of one clinical expert should unreasonably override evidence from guidelines, a published study and the view of another clinical expert advising the ERG.

We conclude that rivaroxaban is cost-effective as a lifelong treatment, a group with a greater prevalence of older patients and male patients than others. Furthermore we conclude that rivaroxaban is cost-effective across the whole indication, based on a weighted averaging across the durations of treatment considered. An overview is provided in Table 1 with further detail in Tables 7 and 8 in section 3.5.2.

Table 1: Overview of ICERs (with probability % of cost-effectiveness at a willingness to pay of £20,000 per QALY)
<table>
<tr><th></th><th>Evidence-based INR monitoring intensity (from MS)</th><th>Reduced INR monitoring intensity (as requested in ACD)</th></tr>
<tr><td>Patients requiring 3 months treatment</td><td>RIV dominant (99%)</td><td>RIV dominant (99%)</td></tr>
<tr><td>Patients requiring 6 months treatment</td><td>RIV dominant (99%)</td><td>£85 (98%)</td></tr>
<tr><td>Patients requiring 12 months treatment</td><td>RIV dominant (99%)</td><td>£6,583 (92%)</td></tr>
<tr><td>Patients requiring lifelong treatment</td><td>£6,037 (85%)</td><td>£15,847 (58%)</td></tr>
<tr><td>Whole indication (weighted average)</td><td>£2,057 -</td><td>£10,269 -</td></tr>
</table>
Finally, we comment on the text of the ACD is also given, where certain issues were noted. We believe rivaroxaban should be recommended by NICE as a safe, effective and highly cost-effective option in the treatment of DVT with built-in simplicity.
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Consultee	Comment	Response
Bayer	**Differences within trial populations by assigned duration** The Appraisal Committee requested in the ACD that Bayer provide the following: `*Comments on the differences between the populations that were assigned treatment durations of 3, 6 and 12 months, and further details of any clinical criteria or algorithm used by the treating physician for assigning patients to the three groups.'* ***Summary of response*** • There were no clinical criteria or algorithms mandated for use in the EINSTEIN-DVT trial. Treatment periods were at trial investigator's discretion, on consideration of individual patient risk-profile and local guidelines. • Resulting populations, described below, were similar in their risk profiles. A greater prevalence of risk factors tended to exist in the longer duration groups. This is consistent with application of UK guidelines. • There was no evidence of differences in the relative efficacy or safety of rivaroxaban between duration groups. The hazard ratio for VTE recurrence in the 3 month group should be considered in light of: the small number of patients in that duration group, the shorter follow-up for that group, the few events occurring in that group (5 vs 3), the [redacted] This is consistent with the view stated in EPAR, and views stated by clinical specialists advising this appraisal. ***[Please see manufacturer's comments on the ACD for additional evidence submitted]***	Comment noted. The Committee considered all the evidence submitted concerning the heterogeneity of the EINSTEIN-DVT trial – including the additional clarification on clinical criteria from the manufacturer. The Committee noted that there were no specific clinical criteria used to allocate people into different intended treatment duration groups, and heard from clinical experts that they were not aware of any clinical reasons why rivaroxaban would be less effective than LMWH and a vitamin K antagonist in the shorter term. The Committee accepted that there is insufficient evidence to demonstrate that rivaroxaban had a substantially different effectiveness across treatment durations, and was not aware of any biological reason to expect a differential effect in the first 3 months. The Committee therefore concluded that evidence of treatment effect should be based on the whole trial population of EINSTEIN-DVT. See 4.7 of the FAD.

Consultee	Comment	Response
Bayer	**Cost-effectiveness of lifelong anticoagulation** The Appraisal Committee requested in the ACD that Bayer provide the following: `*Consideration of the cost effectiveness of rivaroxaban compared with low molecular weight heparin (LMWH) and a vitamin K antagonist in patients in whom long-term anticoagulation is intended. Ideally this should be supported by a cost-effectiveness analysis of rivaroxaban as a lifelong treatment after the index event. This analysis should use data from the whole population of the EINSTEIN-DVT trial for estimating clinical effectiveness and should include sensitivity analyses that assume a less intensive INR monitoring program of 6 visits in the first 3 months, followed by 2 or 3 visits every 3 months thereafter in the comparator arm.'* ***Summary of response*** • Various adaptations have been made to the economic model in order to accommodate the request to conduct the evaluation. See below `methods in developing lifelong model'. • The INR monitoring intensity assumptions in the MS were evidence-based, and we consider it unfair if the judgement of one clinical expert should unreasonably override evidence from guidelines, a published study and the view of another clinical expert advising the ERG. • We conclude that rivaroxaban is cost-effective as a lifelong treatment.	Comment noted. The Committee acknowledged the multiple models of provision for INR monitoring across the UK and the uncertainty about the costs. It noted that estimates of INR monitoring costs varied greatly, and some community based monitoring programmes appeared to be much cheaper than the manufacturer's estimate. It noted that the ERG estimate appeared to be in the region of the estimated INR costs used in NICE technology appraisal 249. Comments from consultees also indicated that the manufacturer's estimate of INR monitoring costs was higher than was plausible for UK practice. The Committee therefore concluded that the ERG's alternative assumptions and estimate of £320 for INR monitoring in the first year of treatment to be reasonable and relevant for this appraisal. See section 4.12 of the FAD.

Consultee	Comment	Response
Bayer	○ Under the evidence-based monitoring intensity of the MS, the ICER for lifelong rivaroxaban vs dual LMWH/VKA was £6,037 per QALY gained, with a 85% probability of cost-effectiveness at a threshold of £20,000 per QALY. ○ Under the reduced intensity assumptions requested in the ACD, the corresponding ICER is £15,847, with a 58% probability of cost-effectiveness. • Furthermore we conclude that rivaroxaban is cost-effective across the whole indication, based on a weighted averaging across the durations of treatment considered ○ Under the evidence-based monitoring intensity of the MS, the weighted average ICER across all patient groups/durations was £2,057. ○ Under the reduced intensity assumptions requested in the ACD, the weighted average ICER across all patient groups/durations was £10,269. • Additionally, there are further factors that it has not been possible to capture in the economic model which suggest that the cost-effectiveness of rivaroxaban above may be underestimated. See section 3.5.1. ***[Please see manufacturer's comments on the ACD for additional evidence submitted]***	The Committee concluded an ICER, based on an ERG exploratory analysis, of £19,400 per QALY gained was a plausible estimate for people who require ongoing anticoagulation. The committee concluded that rivaroxaban was a cost-effective treatment option for people who need anticoagulation treatment for longer than 12 months. See section 4.16 of the FAD.
Bayer	***Bayer's commitment to obtaining additional long-term data*** Bayer agreed with the EMA a Risk Management Plan which includes the conduct of the phase IV non-interventional study, XALIA (Xarelto® for Long-term and Initial Anticoagulation in venous thromboembolism). This study will provide additional evidence as to the long-term effectiveness and safety of rivaroxaban. The main objectives of XALIA are to study recurrence of VTE, incidence of major bleeding and mortality, with additional objectives covering other cardiac and symptomatic thromboemboic events, treatment satisfaction and adherence. Adult patients with a diagnosis of acute DVT and who have an indication for anticoagulation for at least 12 weeks will be eligible for inclusion in the study. It is planned to enrol 4800 patients from Europe into the study. The study ends 12 months after end of enrolment.	Comment noted. The committee's consideration of long term use of rivaroxaban and a reference to the XALIA study is included in section 4.8 of the FAD.

Consultee	Comment	Response
Bayer	***Comments on wording of the ACD*** Paragraph 2.2. It is recognised in the MS and SmPC that although over 16,000 patients have been exposed to rivaroxaban in the course of eight RCTs, experience with rivaroxaban beyond 12 months in this indication is limited. The latter point, but not the former, is reflected in paragraph 2.2 of the ACD. Paragraph 3.1. The final sentence is unclear as to the inclusion criteria of EINSTEIN-Ext. It may instead be said that patients were recruited to this study based on the risk-benefit of further anticoagulation. Paragraph 3.2. It is not true that 53% of patients had necessarily participated in EINSTEIN-DVT; this proportion also includes patients who had participated in EINSTEIN-Ext. Please see response to ERG clarification question D4. Later in this paragraph, it is slightly misleading to say `some people were excluded from the EINSTEIN-DVT and EINSTEIN-Ext trials' – as with other clinical trials, these two trials had inclusion/exclusion criteria. Paragraphs 3.7-3.8. There are several errors in connection with the description of the cancer subgroup and mixed treatment comparison analyses presented by Bayer. • The first sentence should note that the analysis was conducted for the subgroup of patients with cancer. To omit this point suggests that the analysis reflected the full indication, which is quite misleading. This is compounded by an erroneous description later of a secondary analysis. • We presented three analyses not two. There was a primary analysis and two secondary analyses. These were described in the MS and in response to ERG clarification question D13.	Comment noted. This paragraph is an excerpt of the EMA's Summary of Product Characteristics. Comment noted. Section 3.1 of the FAD states that patients were recruited if the risks and benefits of further anticoagulation were finely balanced, that is, there was 'clinical equipoise' for the decision to continue anticoagulation. Comment noted. Comments noted. Section 3.7 of the FAD has been amended to clarify that the analysis relates to patients with cancer. The description of the secondary analyses has also been amended.

Consultee	Comment	Response
Bayer	• The following sentence is incorrect: `Following a request from the ERG, the manufacturer also presented an additional analysis for the subgroup of patients with active cancer'. The mixed treatment comparison was included in the original MS and related to the cancer subgroup. The original MS also included a cost-minimisation analysis for the cancer subgroup. The ERG requested in their clarification questions an `indicative cost-effectiveness analysis' for the cancer subgroup based on the results of the mixed treatment comparison, and Bayer provided this. • The results quoted as being Bayer's mixed treatment comparison results are not Bayer's primary analysis, but instead appear to be one of the two secondary analyses. • Paragraph 3.11. NHS Reference Costs for 2009-10 were used, as noted in the MS. Paragraph 3.12. Utility values were all sourced from literature. It may be important to recognise that the Kind study measured health preference via EQ-5D, which is NICE's preferred instrument. Utility estimates were additionally made for patients experiencing CTEPH using a disease-specific utility index (reference 120 of MS). It may also be important to recognise that treatment satisfaction has been reported from EINSTEIN-DVT as being significantly higher with rivaroxaban than dual LMWH/VKA (reference 18 of MS). Paragraph 3.20. It should be made clear that this paragraph relates to an analysis specific to the subgroup of patients with cancer.	Comment noted. Section 3.11 of the FAD has been amended. Comment noted.

Consultee	Comment	Response
Bayer	Paragraph 3.21. The ACD mixes two distinct issues on which the ERG have provided advice. The concerns about validity described in sentence one appear to refer to the use of composite endpoints in assessing relative clinical effectiveness, not cost-effectiveness. Differential impacts of constituent outcomes of a composite endpoint on cost and quality of life are not particularly relevant in considering relative clinical effectiveness, but the aggregation of constituent health states into a composite health state in an economic model, would not be advisable. DVT and PE are manifestations of the same underlying condition and so rivaroxaban is expected to affect incidence/recurrence of each similarly, which explains why a composite endpoint in the trial was appropriate and is valid. The economic model Bayer presented in its MS distinguishes clearly between DVT and PE states, treating each outcome distinctly, an appropriate and valid approach. Paragraph 3.23. The first sentence recognises only two of the three principle differences between the basis for the MS economic model outcomes and those given later in the paragraph. The ERG's analyses took into account duration-specific effectiveness data and corrected errors the ERG perceived to exist. A crucial additional difference is that the ERG have chosen to present mean probabilistic outcomes rather than deterministic outcomes. Paragraph 3.24. The manufacturer's analysis should be referred to as our `illustrative analysis', as we and the ERG were well-aware of its limitations and had only provided such illustrative results at the explicit request of the ERG. It may be helpful to use the terminology `mixed treatment comparison' here rather than `network meta-analysis' for consistency with the rest of the ACD (eg paras 3.7-8) so as to avoid confusion that there exists an additional analysis.	Comment noted. Section 3.22 of the FAD now refers to the cancer subgroup. Comment noted. Reference to composite endpoints has been removed. Comment noted. Section 3.21 of the FAD contains revised outcomes from an analysis that used the whole trial population effectiveness data, corrected certain errors in the model and took into account a less intensive INR monitoring strategy comprising 6 INR monitoring visits in the first 3 months and 3 visits every 3 months thereafter. Comment noted. Section 3.16 of the FAD refers to the exploratory nature of the analysis.

Consultee	Comment	Response
Bayer	Paragraph 4.14. It is clear from the ERG report (Table 36 in section 5.2.1.8 for example) that further analyses in relation to frequency of INR monitoring adopted an assumption that there were 3 visits every 3 months after the first 3 months. This paragraph refers to an evaluation of `2 or 3' visits, as if there was some doubt as to the model assumption, yet the model assumption is clearly stated. We note that this has been reflected in the manufacturer comments requested in paragraph 1.2. Related NICE guidance. We suggest two additions to this list: • Published. Atrial fibrillation – dabigatran etexilate. NICE technology appraisal guidance 249. • Under development. Atrial fibrillation (stroke prevention) – rivaroxaban. NICE technology appraisal. ID420.	Comment noted. Section 4.12 of the FAD has been revised based on the ERG analysis outlined in section 3.21. Comment noted.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
NHS North of Tyne	We endorse the opinions of CSAS.	Comment noted.
Vascular Society	Endorse ACD recommendation not to recommend rivaroxaban for DVT and prevention and recurrence of DVT and PE.	Comment noted.

Nominating organisation	Comment	Response
Royal College of Pathologists/British Society for Haematology	We presume the ERG's opinion that around 20% of people with deep vein thrombosis (DVT) would have long-term anticoagulation treatment because recurrence of venous thromboembolism indicated ongoing risk refers to people with a first episode of DVT, and the best treatment for people with a proven second or subsequent DVT is long-term anticoagulation. Other factors that indicate long-term risk include the discovery of certain thrombophilia markers or the decision that the initial DVT was unprovoked (idiopathic) can be considered as 'ongoing risk'.	Comment noted. The Committee heard from the manufacturer that the non-interventional XALIA study will estimate the long-term recurrence of venous thromboembolism, among other endpoints, and provide further evidence on the proportion of people with deep vein thrombosis who will require ongoing anticoagulation.
	We recognise that the composite endpoint is valid in terms of efficacy, as an effective treatment reduces the incidence of both PE and recurrent DVT to the same degree so there is no 'differential' impact in terms of efficacy. However, it is agreed that DVT and PE entail 'differential impacts on mortality, costs and quality of life'.	Comment noted.
	We understand that opinions from religious authorities to improve access to heparin products derived for porcine on the basis of medical need has occurred on several occasions; therefore contradicts the statement made in 3.22 of the ACD.	Comment noted. The Committee accepts that religious authorities can provide opinions on the use of porcine-based heparin products on the basis of medical care.
	The possible finding of why rivaroxaban would be less effective in patients who received 3 months treatment seems implausible and likely to be a statistical artefact given the small number of events and difficulty to diagnose 'recurrent' DVT in the initial three month period because the initial thrombosis will still be present and the inflammatory reaction (including pain) to it often increases after diagnosis: this may have been misclassified as recurrence in these events. Further, not only are there no intelligible clinical reasons for this possible finding, the reverse is the case: it is well recognised that failure to achieve therapeutic INR, as well as bleeding complications, are both more likely to occur during the first 2-3 months of Warfarin therapy.	Comment noted. See above response to Bayer's ACD comments.

Nominating organisation	Comment	Response
Royal College of Pathologists/British Society for Haematology	An important clinical benefit of rivaroxaban that contributes to patient safety is that it does not have the range of potentially hazardous interactions with entire classes of commonly co-prescribed medications (i.e. antibiotics, amiodarone, etc...) that often interferes with warfarin therapy.	Comment noted. The Committee heard from clinical experts that warfarin is associated with a large number of drug interactions that could pose a risk to patient care. The Committee recognises the benefits of rivaroxaban, in that it appears to have fewer drug-interactions and does not require INR monitoring. The Committee also acknowledged the benefit arising from its oral formulation and the potential to reduce the need for support services. See 4.3 of the FAD for further details.

Comments received from commentators

Commentator	Comment	Response
CSAS	We are in agreement with the recommendation not to recommend rivaroxaban on the basis of the evidence considered. We have concerns about the generalisability of the research and the clinical criteria used to assign treatments were unclear; the manufacturer of rivaroxaban included high INR monitoring costs in the model; the precise cost-effectiveness of rivaroxaban is currently unclear; and the manufacturer did not model long-term treatment with anti-coagulations or treatment of recurrent VTE with rivaroxaban. However, CSAS recognises that rivaroxaban has the potential to improve some patient's access to treatment.	Comment noted. Following consultation, the manufacturer provided further information on the cost-effectiveness of rivaroxaban for people who require ongoing anticoagulation and provided responses to the Committee's request for further information regarding the patient population in the EINSTEIN-DVT trial. The Committee considered the manufacturer's estimate of INR monitoring to be too high, but found the ERG's estimate, which assumed less INR monitoring, to be more plausible. The Committee therefore concluded that the ERG's alternative assumptions and estimate of £320 for INR monitoring in the first year of treatment to be reasonable and relevant for this appraisal After considering the overall evidence, the Committee concluded that rivaroxaban is a cost-effective treatment option of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism following a diagnosis of acute deep vein thrombosis in adults. See sections 4.8, 4.13-4.16 of the FAD.

Commentator	Comment	Response
LEO Pharma	We are in agreement with the preliminary recommendation not to recommend rivaroxaban for the treatment of DVT and prevention and recurrent DVT and PE. LEO Pharma believes further clarity is required with regard to patients with renal impairment and has concerns with interpretation of 'clinical equipoise' in the EINSTEIN-Ext trial and the criteria used to assess clinical benefit. LEO Pharma also seeks clarity on the Committee's reference to unfractionated heparin as a comparator to rivaroxaban. LEO Pharma acknowledges that heparin products produced from porcine intestinal mucosa would normally be unsuitable for use in practising Muslim and Jewish patients, whose religious beliefs preclude them from using products derived from pigs. However, tinzaparin sodium was approved in 2002 by the Saudi Health Authority issuing a Fatwa (that is, an official ruling) allowing its use in those patients requiring it for medical reasons.	Comments noted. The Committee was aware of the contraindications relating to renal impairment as described in the Summary of Product Characteristics. The guidance relates to the use of rivaroxaban within its licensed indications. Furthermore, the Committee did not consider the EINSTEIN-Ext trial to reflect the clinical population in whom long-term anticoagulation is intended and considered the EINSTEIN-DVT trial more relevant. The Committee heard from the clinical specialists that unfractionated heparin is used infrequently, mainly in people with renal failure, in whom rivaroxaban would not be used. It was therefore satisfied that the comparators presented in the EINSTEIN-DVT trial represented routine and best practice in the NHS. The Committee accepts that religious authorities can provide opinions on the use of porcine-based heparin products on the basis of medical care.

Commentator	Comment	Response
Royal College of Nursing	The fact that the new anticoagulant does not require monitoring is raised as a benefit; however this could be misrepresented because all medication requires patient consultation. There is concern about the twice daily initial dose and the switch to once a day dose. There has to be very clear pathway on how this is introduced. Patient education is vital with particular reference to the NICE Medicine Adherence guideline (CG76); otherwise there is a potential risk of increase in the incidence of pulmonary embolism. We have concerns for increased risk of bleeding and the estimates of the current cost of anticoagulation monitoring. Given the lack of evidence on the use of this drug for longer than twelve months, does this mean that patients need to be switched to warfarin after twelve months? The new oral anticoagulation appears to be less effective compared to LMWH in patients with cancer so there consideration for exclusion criteria maybe warranted.	Comment noted. The committee acknowledged that experience with rivaroxaban in this indication for more than 12 months is limited. However, the Committee concluded that it may not be realistic to assume that people stop treatment once the pre-specified treatment period has ended and some people with ongoing risk factors for recurrence would need ongoing treatment, possibly for many years or lifelong, based on a risk-benefit assessment.. The Committee acknowledged the lack of direct clinical evidence demonstrating that rivaroxaban is superior to LMWH in patients with cancer, and was unable to specifically recommend the use of rivaroxaban in this group of patients.

Commentator	Comment	Response
Anticoagulation Europe (ACE)	We recognise that rivaroxaban offers an alternative treatment option for eligible patients presenting with a pulmonary embolism (PE) and/or a deep vein thrombosis (DVT). Studies show that it is non - inferior to LMWH and the Committee has concluded that it is more effective than enoxaparin and VKA in preventing VT recurrences. From the patient's perspective, as an oral therapy, it is easier to administer than LMWH subcutaneous injections which are painful and cause bruising. We believe the single drug approach will negate the need for patients to be weaned from LMWH onto dose adjusted warfarin which requires monitoring by frequent blood tests wither in primary or secondary care settings. As warfarin is affected by diet and interacts with many other drugs including 'over the counter' medicines – the adjustments required to stay with INR targets can be challenging and can cause anxiety for the individual and impose additional resources on carers and NHS resources. Importantly, The Committee has acknowledged the variations in the frequency of INR monitoring in clinical practice in the UK and have accepted that 6 visits in the first three months and 2/3 in the three months thereafter are reasonable. Stabilising on warfarin varies from individual to individual and some people despite frequent testing do not increase their TTR and could be tested far more frequently than the figures presented in the ACD.[1] 1. Rose P, James R, Chapman O, Marshall S. A real world evaluation to describe the characteristics, outcomes and resource use associated with patients being managed by a secondary care based anticoagulation service. Accepted for poster presentation at 14th Annual European Congress of ISPOR(International Society of Pharmacoeconomics and Outcomes Research)2011	Comment noted.

Comments received from members of the public

Role*	Section	Comment	Response
NHS Professional	Preliminary Recommendation	At present we wish to consider the following patients: patients who present with their first DVT we would consider rivaroxaban in patients who have an allergy/intolerance to warfarin (and those who have poor access to INR monitoring) access to rivaroxaban. Rivaroxaban will also be considered in patients indicated for long-term anticoagulation, and in addition to the above criteria, will have poor INR control defined as time within range of less than 60% following a 6 month trial.	Comment noted. The Committee considered additional information on the patient population for whom up to 12 months of treatment is intended and additional evidence on long term use and concluded that rivaroxaban should be recommended as an option for treatment of DVT and PE after a diagnosis of acute DVT.
	Manufacturer's submission	I agree with the evidence that clearly supports the use of rivaroxaban for the treatment of DVT but further evidence is required for long-term anticoagulation in high risk patients. I agree that quoted cost of INR monitoring is an overestimate.	Comment noted. See above response to CSAS and the Royal College of Nursing.
	Consideration of the evidence	It should be noted within our experience most patients are treated for 6 months then a decision is taken at that point to decide whether to continue with long-term anticoagulation. This would include patients with recurrent DVTs/PEs, patients with significant thrombophilia, patients with significant risk factors and patients who wish to continue long-term anticoagulation due to concerns of recurrence. Evidence does support the use of rivaroxaban in this indication and consideration to compliance in an elderly population.	Comment noted. The Committee agreed that 6 months is currently the average treatment duration for anticoagulation in the UK, and a decision to continue further anticoagulation is done after taking into account the individual's risk factors such as risk of bleeding. See 4.2 of the FAD for further details.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.