12th September 2011

NHS
National Institute for Health and Clinical Excellence

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[redacted]

Re: Single Technology Appraisal – Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation

The Evidence Review Group (BMJ Technology Assessment Group) and the technical team at NICE have now had an opportunity to take a look at submission received on the 16th August 2011 by Bayer. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **17:30, 26th September 2011**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments, or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact [redacted]

Yours sincerely

[redacted]
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

A1. **Priority request:** Please provide the WinBUGs working code for each outcome reported in the network meta-analysis in the submission (i.e. including the appropriate parameter data for priors and trials included in the analysis).

A2. **Priority request**: Please complete the following table to provide the results for each of the outcomes assessed in the network meta-analysis using the ROCKET-AF ITT data and the restricted set of comparators, i.e. odds ratios for rivaroxaban compared with selected comparators.

	Adj dose warfarin		Acetylsalicylic Acid		Dabigatran 110mg		Dabigatran 150mg		Placebo	
	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI
Composite (ischaemic stroke & systemic embolism)										
Total stroke										
Ischaemic stroke										
Haemorrhagic stroke / ICH										
Systemic embolism										
MI										
Cardiovascular death										
Mortality										
Major haemorrhage										
Minor bleed										
Gastrointestinal bleed										
Transient ischaemic attack										

A3. **Priority request**: Please complete the table below to provide details on the number of people in the ROCKET-AF trial who switched to open label warfarin in the ITT population (i.e. before site notification ITT population).

	Rivaroxaban			Warfarin		
	n	N	Event rate (100 pt-year)	n	N	Event rate (100 pt-year)
Number of people who switched to open label warfarin						
Number remaining on randomised blinded study drug						
Other (please provide further details below)						

A4. **Priority request**: Please provide table 21 for the ITT and safety on treatment populations (% INR values in therapeutic range for warfarin by region).

A5. **Priority request**: Please provide a rationale for why there were more major gastrointestinal bleeding events in the rivaroxaban group than in the warfarin group of ROCKET-AF (224 bleeds [3.15%] with rivaroxaban vs. 154 bleeds [2.16%] with warfarin).

A6. **Priority request**: Please complete the table below to provide details on the rates of dyspepsia in the rivaroxaban and warfarin groups of ROCKET-AF.

	Rivaroxaban			Warfarin			Rivaroxaban vs. Warfarin	
	n	N	Event rate (100 pt-year)	n	N	Event rate (100 pt-year)	Hazard Ratio (95% CI)	p-value
Dyspepsia (ITT population)								
Dyspepsia (per protocol population)								
Dyspepsia (safety on treatment population)								

A7. **Priority request**: Please provide a PRISMA flow diagram for the network meta-analysis and explain any discrepancies in numbers between the PRISMA diagram and the details provided in the Oxford Outcomes systematic review and network meta-analysis reports provided with the submission.

A8. **Priority request**: For each outcome assessed in the network meta-analysis please provide:

a. the quantification of heterogeneity (i.e. the value for tau).

b. the number of unconstrained data points and the residual deviance.

A9. Please provide the number of UK centres that were there in ROCKET-AF and the number of patients from the UK that were randomised.

A10. In the network meta-analysis, please clarify why the ROCKET-AF safety on treatment data set was chosen rather than the ITT data set, which was used for all other trials included in the network meta-analysis (page 18 Oxford Outcomes network meta-analysis report).

A11. Please confirm whether in ROCKET-AF the coatings of the "matching oral warfarin placebo" and matching oral rivaroxaban placebo" were the same as those used in the corresponding "active" tablets.

A12. Please clarify whether patients randomly assigned to warfarin with moderate renal impairment (i.e. a baseline creatinine clearance 30-49ml/min) were treated any differently to those with baseline creatinine clearance >49ml/min (outlined on page 41 of the manufacturer's submission).

A13. The ERG note that there is a large difference between the ITT (to site notification) analysis results and the safety on treatment analysis results for primary endpoint of ROCKET-AF in the North America subgroup (Hazard ratio 0.95 vs. 0.58, as summarised in the table below; taken from Figures 11 and 12 in the submission). Please can you explain the potential reasons for this apparent discrepancy?

Population	**Event rate**		**Hazard ratio Rivaroxaban vs Warfarin**
	Rivaroxaban	**Warfarin**	
ITT to site notification	47/1339 (3.51%)	50/1342 (3.73%)	0.95 0.64 to 1.42
Safety population/on treatment	20/1334 (1.5%)	36/1339 (2.69%)	0.58 0.34 to 1.01

A14. Please provide the numbers of people in each of the ROCKET AF trial arms who had a temporary disruption to treatment and the mean length (and range) and reasons for the interruptions.

A15. Please provide the numbers of people who received the 15mg dose of rivaroxaban in the ITT and per protocol populations

A16. In the submission it states that over 50% of people in ROCKET-AF received treatment for >18 months, but no further details are provided. Please complete the table below to provide details on the number of people who discontinued their randomised study drug at each of the time periods listed

below. Please also provide the overall mean, median and range of treatment duration for the ITT, per protocol and safety on treatment populations.

	ITT population				**Per protocol population**				**Safety on treatment population**			
	Rivaroxaban		**Warfarin**		**Rivaroxaban**		**Warfarin**		**Rivaroxaban**		**Warfarin**	
	n	**N**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
Mean treatment duration												
Median treatment duration												
Range of treatment duration												
0 to <3 months												
≥3 to <6 months												
≥6 to <9 months												
≥9 to <12 months												
≥12 to <15 months												
≥15 to <18 months												
≥18 to <21 months												
≥21 to <24 months												
≥ 24 months												

A17. Please provide details of the ITT treatment discontinuation rates in ROCKET-AF for each of the region subgroups in each of the trial arms, along with an itemised breakdown of the reasons for treatment discontinuation.

A18. Please complete the table below to provide a breakdown by the types and frequency of adverse event that led to treatment discontinuation in each of the ROCKET-AF trial arms for the ITT population. Please complete similar tables for the per protocol and safety on treatment populations.

	ITT Population					
	Rivaroxaban			Warfarin		
	n	N	Event rate (100 pt-year)	n	N	Event rate (100 pt-year)
Adverse event (please specify [add additional table rows below as necessary]):						
Adverse event:						

A19. Please expand on the reasons for protocol violations that led to exclusion of the data from one site (the GCP violating site) from all the analyses in ROCKET AF.

A20. Please expand on the decision to use the total ROCKET AF population in the submission rather than the data from the Western Europe and North America subgroups, given that the TTR for the whole trial population is lower than that typically reported for the UK and seen in other clinical trials, for example, e.g. RE-LY.

A21. Please complete the table below to provide details of bleeding adverse events in each trial arm in ROCKET AF by age using the following subgroups for the ITT population:

a. <65;

b. ≥65 and <75;

c. ≥75 and <85;

d. ≥85.

Please complete similar tables for the per protocol on treatment and safety on treatment populations.

Age (years)	Bleeding outcome	ITT Population					
		Rivaroxaban			Warfarin		
		n	N	Event rate (100 pt-year)	n	N	Event rate (100 pt-year)
<65	Composite of all major and non-major clinically relevant bleeding events						
	Major bleed						
	Non-major clinically relevant bleeding						
	Minor bleed						
	Gastrointestinal bleed						
≥65 and <75	Composite of all major and non-major clinically relevant bleeding events						
	Major bleed						
	Non-major clinically relevant bleeding						
	Minor bleed						
	Gastrointestinal bleed						
≥75 and <85	Composite of all major and non-major clinically relevant bleeding events						
	Major bleed						
	Non-major clinically relevant bleeding						
	Minor bleed						
	Gastrointestinal bleed						
≥85	Composite of all major and non-major clinically relevant bleeding events						
	Major bleed						

Age (years)	Bleeding outcome	ITT Population					
		Rivaroxaban			Warfarin		
		n	N	Event rate (100 pt-year)	n	N	Event rate (100 pt-year)
	Non-major clinically relevant bleeding						
	Minor bleed						
	Gastrointestinal bleed						

A22. Please provide the definition used in ROCKET AF for no prior VKA use (i.e. were they warfarin naïve patients?).

A23. Please provide details of any protocol amendments made in ROCKET AF and give the reasons for any amendments.

A24. Please explain the nature of the protocol violations leading to exclusion of people from the per protocol analysis in ROCKET-AF.

A25. The NICE final scope lists transient ischaemic attacks and health-related quality of life as important outcome measures to be considered in the STA. Please can you clarify your reasons for not including data on these outcomes within the submission and where possible provide any available data.

A26. Please complete the following table to provide data for all outcomes reported in ROCKET AF for each of the patient subgroups in the ITT, per protocol and safety on treatment populations:

a. Patients with and without prior use of vitamin K antagonists at baseline.

b. North America region.

c. Western Europe region.

d. INR control as measured by percentage time in therapeutic range (TTR) for people in the warfarin group with TTR <60% and ≥60% compared with the rivaroxaban total population.

	Rivaroxaban			Warfarin			Rivaroxaban vs. Warfarin	
	n	N	Event rate (100 pt-year)	n	N	Event rate (100 pt-year)	Hazard Ratio (95% CI)	p-value
Composite (ischaemic stroke & systemic embolism)								
Total stroke								

Ischaemic stroke								
Haemorrhagic stroke / ICH								
Non-CNS Systemic Embolism								
Myocardial Infarction								
Vascular death								
Mortality (all cause)								
Composite of all major and non-major clinically relevant bleeding events								
Major bleed								
Non-major clinically relevant bleeding								
Minor bleed								
Gastrointestinal bleed								
Minimal bleeding								

A27. On page 21 of the submission please clarify:

a. whether the proportion of patients with a CHADS2 score of zero is 12.6% of the total AF population or if this is specific to the non-valvular AF population.

b. why the estimated number of patients eligible for rivaroxaban is different in the text to that reported in table 8 (662,747 and 669,003).

A28. In table 9 on page 32 of the MS, please confirm the criteria for determining whether people had chronic non-valvular AF for inclusion in the systematic review.

A29. Please provide network meta-analysis diagrams for the primary outcome using:

a. the ROCKET-AF ITT data and restricted set of comparator.

b. the ROCKET-AF ITT data and full set of comparators.

A30. Please provide the data/risk of bias tables for RE-LY and Pengo 2010, as provided in the Appendices of the Oxford Outcomes report on the systematic review, for the other trials included in the systematic review and network meta-analysis.

A31. Please provide the following sensitivity analyses for all the outcomes reported in the network meta-analysis using the ITT restricted comparator data set:

a. restricting the VKA trial data included in the analysis to warfarin;

b. restricting the aspirin trial data included in the analysis to a mean daily aspirin dose of 150mg.

A32. :Please provide details of any differences in the methods and trial inclusion/exclusion criteria between J-ROCKET and ROCKET-AF.

A33. Please provide the ITT, per protocol and safety on treatment data for each of the primary, secondary and safety outcomes in J-ROCKET.

A34. The NICE final scope lists antiplatelet agents and dabigatran as comparators for rivaroxaban in people for whom warfarin is unsuitable. Please can you clarify your reasons for not covering these comparisons in this population within the submission?

A35. Please comment on the generalisability of the ROCKET AF trial to the UK population, including:

a. How similar are the event rates from the ROCKET AF trial to those in the UK atrial fibrillation patient population;

b. How similar are the characteristics of the patients in the ROCKET-AF trial to the atrial fibrillation patients of the UK.

Section B: Clarification on cost-effectiveness data

B1 **Priority request**: The model engine sheets show that the manufacturer intended to model different subgroups of patients within, below and above TTR ranges but ultimately presented results assuming all patients were within TTR ranges. The ERG requests a scenario analysis (including sensitivity analysis) incorporating the different proportions of patients in each TTR range observed in ROCKET AF.

Within TTR	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Warfarin based on the ROCKET AF trial SoT data								
Rivaroxaban based on the ROCKET AF trial SoT data								

B2 **Priority request**: The ERG requests that the manufacturer populates the following table with the different proportions of patients who are within, below and above TTR ranges in ROCKET AF trial.

Proportions of people	ITT population	Per protocol population	SoT population
Within range (2-3)			
Below range <2			

B3 **Priority request**: For consistency across all comparisons the ERG requests that point estimates from the network meta-analysis should be used in the dabigatran deterministic analysis and that probabilistic sensitivity analysis be conducted i.e. present the cost effectiveness plane and the CEACs.

Within TTR	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Dabigatran based on NMA data								
Rivaroxaban based on NMA data								

B4 **Priority request**: Based on the evidence from the SAFE study (see table below) the ERG requests that bleeding risk is age adjusted in a similar manner to stroke and SE.

Age	Gastrointestinal bleed (rate at age)
65	1
70	1.2
80	1.6
90	1.9

Source: Hobbs et al 2005 *A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study*

B5 **Priority request**: The ERG requests a revised model in which dyspepsia is included as a side effect.

B6 **Priority request**: The ERG requests a scenario analysis which incorporates a cost of INR monitoring of £279.36 as recommended by the Appraisal Committee undertaking the appraisal of dabigatran *(The cost was taken from the CG 36, assumed that the new drugs will not totally replace warfarin, includes variable costs in primary care and total costs in secondary care, replaced 2004/05 reference costs with 2008/09 reference costs and inflated to 2009/10 prices*.).

B7 **Priority request**: The ERG requests that the manufacturer updates the main analysis with age adjusted utilities.

B8 Please explain the clinical rationale for each of the transitions in the table below, with particular reference to how and why patients are moving between on and off treatment health states.

From	To	Rationale

Post minor stroke (on treatment)	Minor stroke (off treatment)	
Post minor stroke (on treatment)	Major stroke (off treatment)	
Post minor stroke (on treatment)	IC bleed - untreated	
Post major stroke (on treatment)	Minor stroke (off treatment)	
Post major stroke (on treatment)	Major stroke (off treatment)	
Post major stroke (on treatment)	IC bleed - untreated	
AC initiation	Minor stroke (off treatment)	
AC initiation	Major stroke (off treatment)	
AC initiation	IC - untreated	
AC initiation	SE - untreated	
On Tx Stable	Minor stroke (off treatment)	
On Tx Stable	Major stroke (off treatment)	
On Tx Stable	IC - untreated	
On Tx Stable	SE - untreated	
Post IC bleed (high risk)	Minor stroke (off treatment)	
Post IC bleed (high risk)	Major stroke (off treatment)	
Post IC bleed (high risk)	IC - untreated	
Minor bleed – untreated	AC initiation	
Major bleed - untreated	AC initiation	

B9 The ERG requests that the manufacturer presents the results of the one-way sensitivity analysis of age and time horizon.

B10 Please give the clinical rationale for the absence of a post systemic embolism health state.

B11 The ERG requests that data from England and Wales should be used as far as is applicable. In the post stroke state, independent of therapy, the rates were derived from an Italian study (MS ref 92). Please can the manufacturer explain why UK data sources such as the Oxford Vascular Study (OXVASC) were not used?

B12 Please explain the discrepancy between the number of papers from which data have been extracted and the number of papers identified (as indicated by the flow diagram). For instance, quality-of-life papers retrieved should be 16 but the extraction accounts for 12 papers (MS table 48 pg 173).