National Institute for Health and Clinical Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Venous thromboembolism (knees and hips) - apixaban

Please find enclosed the ERG report prepared for this appraisal.

You are asked to check the ERG report from *KSR* to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 5pm, *30th September 2011*, using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The attached proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

September 2011

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 1.2, page 7, second bullet point. AND. Section 4.3, p.32, first bullet point. In the following sentence, the ERG omit to comment on the rarity of the PE endpoint: "These results were the same for TKR, except for PE, which showed a significant difference favouring rivaroxaban."	Please add: "All PE results from the adjusted indirect comparisons are limited by the very small number of events in each treatment arm. None of the trials included in the adjusted indirect comparisons were powered to evaluate the PE outcome."	The statement on p.7 is incomplete and potentially misleading without a note indicating that the PE outcome was based on very small numbers of events and that the NOAC trials were not powered to assess this outcome.	Not a factual error. The fact that the outcome is rare and that the studies were not powered to find a difference makes it unlikely that a significant difference would be found. The fact that there was still a statistically significant difference shows that the difference must have been very substantial. This seems to be the opposite of what the manufacturer is stating.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 1.4.2, page 9, (and page 70) last sentence: The ERG report incorrectly states that "The effectiveness and safety of apixaban, and therefore its cost-effectiveness, are based on a single trial.…". Although we suspect the ERG	Please edit as follows: "The effectiveness and safety of apixaban, and therefore its cost-effectiveness are based on the two trials most relevant to the UK population. There was one trial for each of the orthopaedic surgery populations (TKR and THR)."	The original sentence is factually inaccurate as there are two apixaban trials comparing against the UK licensed dose of enoxaparin, viz. ADVANCE 2 focusing on the TKR population, and ADVANCE 3 focusing on	Not a factual error. We were asked to assess the different within each population separately. Within each population there was one trial for apixaban.

are referring to one trial being available per population, it is unclear from this sentence. It is also not correct to state that the trials are not representative of the UK TKR and THR populations.		the THR population. The UK was the 3rd largest recruiting country in the Advance 2 and 3 trials. The Advance programme included 73% of patients from Europe in TKR and 55% in THR. The enrolment versus randomisation rate was 95% for TKR and 94% for THR implying that very few patients from the population seeking a THR or TKR were excluded. The inclusion criteria were very wide with patients able to have unilateral or bilateral procedures (at one sitting) as well as including revision surgery, which closely reflects practice in the UK. The averages ages of patients in Advance 2 and 3 (66 and 61 respectively) were similar to 2010 data from the National Joint Registry population (68 and 66/69 respectively).	

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 4.1.3, page 18, first sentence: The ERG refers to APROPOS as a phase III trial, whereas it is phase II: "MS identifies four direct head-to-head, phase III, randomised, blinded, trials of apixaban versus enoxaparin (ADVANCE-1,[14, 15] ADVANCE-2,[16, 17] ADVANCE-3[18, 19] and APROPOS[20])."	Please edit as follows: "The MS identifies one phase II (APROPOS[20]) and three phase III (ADVANCE-1,[14, 15] ADVANCE-2,[16, 17] ADVANCE-3[18, 19]) direct head-to-head, randomised, blinded, trials of apixaban versus enoxaparin."	APROPOS is a phase II trial.	APROPOS is described as a phase II trial in table 4.2. Therefore, we think it is not necessary to correct the text.

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 4.1.4, page 20, last paragraph: The ERG report has misinterpreted information in the BMS/Pfizer submission in the following sentence: "MS reported that "there is no	Please revise to: "there is no additional apixaban evidence concerning the indication being appraised for this submission anticipated to be available in the next 12 months". Delete: 'However, it is not clear whether this statement relates to apixaban trials	To clarify, the statement related only to apixaban trials.	<u>Not a factual error.</u> It was not clear for the ERG when reading the MS. We thank the manufacturer for clarifying this point.

additional evidence concerning the indication being appraised for this submission anticipated to be available in the next 12 months". However, it is not clear whether this statement relates to apixaban trials only, or comparator trials as well."	only, or comparator trials as well.'		

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 4.2.1, page 21, first paragraph, sentences 2-4: The ERG incorrectly state that the APROPOS trial was excluded in the manufacturer submission, whereas it was included but just summarised instead of a full description. The intention behind this was to minimise the length of the submission. "According to the manufacturer "APROPOS is a phase II dose finding study and as such is not presented in full in this submission. However, a brief overview is provided in Appendix 14" (MS, page 38).	Please delete the following: 'The inclusion criteria clearly state that phase II-IV trials are included and no reference is made to dose-finding studies being excluded. Therefore it is unclear why this study is treated differently.'	It is incorrect to say this study was excluded from the submission. We did not think the study was as relevant as the other ADVANCE trials to the main part of the submission, but it is included in summary form in the appendices and in the indirect comparison and MTC sensitivity analyses.	Not a factual error. We stated that the study was treated differently. This seems to be confirmed here. It is commendable that the manufacturer tried to minimise the length of the submission. However, with 850 pages in total this was the largest MS we have seen so far.

The inclusion criteria clearly state that phase II-IV trials are included and no reference is made to dose-finding studies being excluded. Therefore it is unclear why this study is treated differently."			

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 4.2.1, page 21, third paragraph: The ERG incorrectly state that duration of hospital stay was not reported in the apixaban trials. Duration of hospital stay for patients undergoing knee and hip replacements was reported in the trials and in the submission, however, the decision problem section does state that these data was not available. So this error in the ERG report may stem from this error in the MS.	Please remove "duration of hospital stay" from this sentence.	It is incorrect to say that duration of hospital is not reported either in the Advance 2 and 3 trials in the MS.	We agree, this has been corrected.

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Table 4.4, page 22: The Table contains a typographical error.	All DVT in the enoxaparin arm should read **68**/1911 and not 86/1911.	The Table contains a typographical error.	We agree, this has been corrected, together with the corresponding RR.

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Table 4.4, page 22: The Table reports intended follow up results for PEs for Advance 3 but this is inconsistent with Table 4.3 where intended treatment results for PE are reported.	Please replace intended follow up results for PE in Advance 3 with intended treatment figures of: 3/2708 – apixaban 5/2699 - enoxaparin	The reporting of PE results in Table 4.4 for Advance 3 should be consistent with that in Table 4.3 for Advance 2.	We agree, this has been corrected, together with the corresponding RR.

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 4.2.1, page 22, last paragraph, first and second sentences: "The ADVANCE-1 and the APROPOS studies employed the American dosing regimen for enoxaparin (30 mg bid), and both trials were in patients with total knee replacement. Both trials reported no significant differences for any of the outcomes reported."	Please amend to: "Both trials reported no significant differences for most of the outcomes reported. However, ADVANCE-1 found that for the composite outcome of adjudicated major or clinically relevant non-major bleeding there was a statistically significant lower incidence of such events in the apixaban (2.9%) compared to the enoxaparin (4.3%) treatment arm (p=0.03)."	It is incorrect and misleading to state there were no statistically significant differences for any of the outcomes reported in the ADVANCE-1 trial when the composite of major or clinically relevant non-major bleeding was reported in the MS on page 113, Table 52, and in the relevant publication: Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Portman RJ. N Engl J Med. 2009 Aug 6;361(6):594-604..	We have amended this sentence to: "Both trials reported no significant differences for nearly all of the outcomes reported."

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 4.2.1, page 22, last paragraph, last sentence: "Follow-up for 60 days after the last dose of study medication was completed in	Please add "In Advance 1…" to the front of this sentence.	This sentence does not make clear which study the results relate to.	Not a factual error. This is obvious when looking at the numbers of patients (1600 per arm in ADVANCE-1, and 100 per arm in APROPOS).

1562/1599 (97.7%) patients assigned to apixaban and in 1554/1596 (97.4%) assigned to enoxaparin.”			Therefore, it seems unnecessary to amend this.

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Table 4.5, page 23: Table states that data for “Major VTE/All-cause death” is NR or not reported from APROPOS. This is incorrect as the composite (proximal DVT + PE + death) was reported in the Lassen et al. 2007 paper. This is the same definition as the equivalent data reported for Advance 1.	Please add proximal DVT + PE + death figures of ‘2’ for the Apixaban 2.5mg bid and ‘5’ for the enoxaparin 30mg bid arms.	It is not correct to say that these results were not reported.	We agree, this has been corrected, together with the corresponding RR.

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 4.2.2, page 24, second paragraph, last sentence:	Please delete the following: ‘It was not clear if any of the procedures for	This is the factually correct information.	Not a factual error. We thank the manufacturer for clarifying this. However,

The ERG state that 'It was not clear if any of the procedures for searching, screening, assessing validity, extraction and synthesis were undertaken by a single reviewer and independently checked by a second reviewer or using a consensus of multiple reviewers.' The description of these methods were not complete in the submission and so for completeness the detail should be added.	searching, screening, assessing validity, extraction and synthesis were undertaken by a single reviewer and independently checked by a second reviewer or using a consensus of multiple reviewers.' Please add the following: 'Screening on the basis of title and abstract was conducted by a single reviewer, with a 25% random sample of citations screened by a second reviewer to check that the inclusion/exclusion criteria were being properly applied. No discrepancies were recorded. Screening on the basis of full paper, validity assessment of relevant full papers, and data extraction were all conducted by two independent reviewers with any discrepancies referred to a third party. For data synthesis, data that went into Winbugs or STATA were independently checked by two reviewers and any discrepancies referred to a third party.'		our statement was correct at the time we wrote our report. Therefore, there is no need to change the text of the report.

Issue 13

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 4.2.2, page 25, last paragraph:	Please delete the following paragraph:	The paragraph contains an error and is misleading, as just one	We agree. We meant one-third, and

The ERG incorrectly state that the two-thirds of patients had missing data in the Advance 2 and 3 trials, where it was 28-36% of patients at most. "Nevertheless, the large amount of missing data is problematic. The most appropriate way to assess whether missing data are likely to have an effect on the results is by performing a sensitive analysis in which all missing data are treated as negative events. However, with two-thirds of respondents having missing data there is no possibility to do any kind of sensitivity analysis."	'Nevertheless, the large amount of missing data is problematic. The most appropriate way to assess whether missing data are likely to have an effect on the results is by performing a sensitive analysis in which all missing data are treated as negative events. However, with two-thirds of respondents having missing data there is no possibility to do any kind of sensitivity analysis.' Please replace with: 'The number of participants included in the primary efficacy analysis in proportion to those randomised was 64.5% for ADVANCE 2, and 71.5% for ADVANCE 3. Approximately one-third of respondents had missing data from these trials. The main reason for the difference between the randomised and primary efficacy analysis populations is that assessment by venograph was not always possible or of sufficient quality, as the primary endpoint included venographically detected events (burden of VTE). This study design is consistent with the trials for rivaroxaban and dabigatran and consistent with numerous trials including LMWH in the past. However, for the key secondary endpoint of major VTE, or symptomatic VTE or VTE related death, these events were clinically detected or symptomatic and	third of participants have missing data, not two thirds as stated in the ERG report. In ADVANCE 2 the primary efficacy analysis statistics are as follows: Apixaban: 976/1528 (64%) Enoxaparin: 997/1528 (65%) In ADVANCE 3 the primary efficacy analysis statistics are as follows: Apixaban: 1949/2708 (72%) Enoxaparin: 1917/2699 (71%)	will correct this as follows: "However, with one-third of respondents having missing data there is no possibility to do any kind of sensitivity analysis". This does not change any conclusions.

	therefore included the whole population and this is reflected in the results table.‘		

Issue 14

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Table 4.8, page 28 Duration of hospital stay is reported for the Advance trials and PE is reported for APROPOS (see Table 2 in Lassen et al. 2007 paper), whereas Table 4.8 in the ERG report states that these data are not reported, which is incorrect.	Please replace crosses for ticks for Duration of hospital stay for all Advance trials and PE for apropos.	The Table incorrectly summarises the availability of data from the apixaban trials.	We agree, this has been corrected.

Issue 15

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 4.2.6, page 28, third paragraph: The ERG make an incorrect reference to an internal company document as the	Insert correct reference to Prescription Cost Analysis 2010.	This is incorrectly referenced in the MS. The correct reference is Prescription Cost Analysis 2010, not IMS data on file.	Not a factual error. We thank the manufacturer for clarifying this. However, our statement was correct at the time we wrote our

basis for the assumption that enoxaparin is the most widely used LMWH, however, the reference should be PCA data: "The MS does not seem to make any attempt to assess the relative effectiveness of apixaban compared with other LMWHs. And is not clear how enoxaparin compares to other LMWHs. According to the MS (MS, page 25): "Enoxaparin is the most widely used LMWH in the UK (13), and is the most widely studied. Enoxaparin was used as the comparator in the apixaban registrational trials." And in chapter 5.6 describing the meta-analysis (MS, page 70): "Enoxaparin was the only LMWH considered for inclusion, as it is the most widely used LMWH VTE prophylaxis option in the UK (13) for the THR and TKR populations." Unfortunately, reference 13 is an internal company document, which was not part of the manufacturer submission. Therefore the			report. Therefore, there is no need to change the text of the report.

source could not be checked by the ERG.”			

Issue 16

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Table 4.9, p.29 Indirect comparison results based on ITT populations have been reported as based on primary efficacy populations.	Please replace with the correct primary efficacy analysis results. Note that the VTE composite primary efficacy results from MTC1 and MTC2 will require redaction as they are academic in confidence. The following factual errors were identified: 1) VTE composite - apix vs. enox, riva vs. apix, dabi vs. apix, and fond vs. apix - MTC1 and MTC2 results are from the ITT analysis, not the primary efficacy analysis 2) Any DVT - apix vs. enox, riva vs. apix, dabi vs. apix, fond vs. apix - MTC 1 and MTC 2 results are from the ITT analysis, not the primary efficacy analysis; fond vs. apix IC3 results are from the ITT, not the primary efficacy analysis.	The footnote to this table indicates that for the VTE composite, any DVT and major VTE outcomes, results from the primary efficacy population are reported. In light of this, the following factual errors were identified: 1) VTE composite - apix vs. enox, riva vs. apix, dabi vs. apix, and fond vs. apix - MTC1 and MTC2 results are from the ITT analysis, not the primary efficacy analysis 2) Any DVT - apix vs. enox, riva vs. apix, dabi vs. apix, fond vs. apix - MTC 1 and MTC 2 results are from the ITT analysis, not the primary efficacy analysis; fond vs. apix IC3 results are	We agree, this has been corrected. Academic in confidence data have been highlighted and underlined.

		from the ITT, not the primary efficacy analysis.	

Issue 17

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Table 4.10, p.30 Indirect comparison results based on ITT populations have been reported as based on primary efficacy populations.	Please replace with the correct primary efficacy analysis results. Note that VTE composite primary efficacy results from MTC1 and MTC2 will require redaction as they are academic in confidence. The following factual errors were identified: 1) VTE composite - apix vs. enox, riva vs. apix, and dabi vs. apix, - IC2, IC3, MTC1 and MTC2 results are from the ITT analysis not the primary efficacy analysis 2) Any DVT - apix vs. enox, riva vs. apix, dabi vs. apix, fond vs. apix - IC2, IC3, MTC 1 and MTC 2 results are from the ITT analysis, not the primary efficacy analysis. 3) Major VTE - apix vs. enox, riva vs. apix, dabi vs. apix - IC2 and IC3 results are from the ITT analysis, not the primary efficacy analysis.	The footnote to the preceding table indicates that for the VTE composite, any DVT and major VTE outcomes, results from the primary efficacy population are reported. In light of this, the following factual errors were identified: The following factual errors were identified: 1) VTE composite - apix vs. enox, riva vs. apix, and dabi vs. apix, - IC2, IC3, MTC1 and MTC2 results are from the ITT analysis not the primary efficacy analysis 2) Any DVT - apix vs. enox, riva vs. apix, dabi vs. apix, fond vs. apix - IC2, IC3, MTC 1 and MTC 2 results are from the ITT	We agree, this has been corrected.

		analysis, not the primary efficacy analysis. 3) Major VTE - apix vs. enox, riva vs. apix, dabi vs. apix - IC2 and IC3 results are from the ITT analysis, not the primary efficacy analysis.	

Issue 18

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
5.2.3, Page 40 In the headings to Table 5.2 and in comments following this, the ERG incorrectly implies that the assessment of cost effectiveness was based on patient characteristics taken from the apixaban trials. This was not the case. The model used the average age and gender split from the NJR.	Please replace table 5.2 headings "Model" and "Clinical practice" with trial labels ("Advance 2" for TKR; "Advance 3" for THR) and "National Joint Registry" respectively Please remove following text as it is incorrect: "the fact that a younger population was modeled compared to clinical practice favours the more effective treatment, because more life years can be gained".	In the base case patients enter the model at the national average age of having a TKR and THR (National Joint Registry, 2010) and the gender split is set equal to that recorded in the national joint registry (2010). As a result more life years cannot be gained as suggested in the current text.	We agree and have corrected this in the text. However, the baseline and relative risks in the model are based on the trial population.

Issue 19

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 41 The ERG have omitted to clarify in the following sentence that fondaparinux was not included in the indirect comparisons for reasonable methodological reasons: "Fondaparinux was included in the scope, but excluded from the comparison because according to the manufacturer insufficient data were available to allow an indirect comparison. The ERG disagrees with this and asked for inclusion of fondaparinux as a comparator for THR. In reaction, the manufacturer provided additional analyses including fondaparinux for THR"	Please insert additional new sentence: "Fondaparinux was included in the scope, but excluded from the comparison because any VTE and death were reported separately in the relevant trials and therefore could not be combined. The ERG requested that a pragmatic approach be taken and suggested that because the overlap between any VTE and death was likely to be small, that combining these outcomes was reasonable."	The current text does not acknowledge that the manufacturer had a sound methodological reason for excluding fondaparinux and that a pragmatic approach has been applied to incorporate this intervention into the analysis.	We agree and have included the proposed sentence in the text.

Issue 20

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 43 The ERG do not state that the following result was based on the assumption that there was no overlap between the outcomes of Any VTE and Death: "In the indirect comparison group 1, the relative risk of fondaparinux 2.5 mg od versus Enoxaparin 40mg od was found to be 0.430 (95% CI 0.30- 0.62)".	Please add following text to end of this sentence: "assuming no overlap between the outcomes any VTE and death."	It is important that it is clear that this result is not based on a composite VTE and all cause death endpoint and that it is derived by combining two non-mutually exclusive endpoints.	We agree and have added the proposed text. However, we had already shown that assuming complete overlap would have made little difference to the relative risk.

Issue 21

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 48, Table 5.9. "N/A" incorrectly included in the table for duration of utility decrement for NMCR bleed	Use the duration of 0.949 for both NMCR bleed and minor bleed for THR patients	The ERG report is missing data that is available.	We agree and have added this to the Table.

and minor bleed for THR patients			

Issue 22

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Table 5.14 page 53. Per day cost of £6.68	£6.28	Typographical error. Total costs are based on the correct value of £6.28.	We agree and have corrected this typographical error.