Apixaban for the prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation

ERRATUM

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This document contains erratum in respect of the ERG report in response to the manufacturer's factual inaccuracy check.

The table below lists the page to be replaced in the original document and the nature of the change:

Page No.	Change
27	The text in row 4, column 3 of table 4 has been amended from suitable to unsuitable.
65	The text relating to the manufacturers provision of residual deviance data has been amended.
120	The parameters for apixaban and warfarin in Table 56 have been marked as commercial in confidence and the reference for these parameters amended to AVERROES Case Study Report.
122	Within the sentence "Furthermore, apixaban extendedly dominated (i.e. resulted in a lower ICER versus warfarin despite having higher total costs) rivaroxaban and dabigatran blend", the word QALYs has been exchanged for the word costs.
139	Appendix 9.7 has been amended to Appendix 9.6
145	The percentage of recurrent strokes that are mild has been marked as commercial in confidence.
151	Within the sentence "rivaroxaban and dabigatran blend were extendedly dominated (i.e. resulted in a lower incremental cost-effectiveness ratio (ICER) versus warfarin despite having higher total QALYs) by apixaban", the word QALYs has been exchanged for the word costs.

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

The manufacturer provided a summary of the final decision problem issued by the National Institute for Health and Clinical Excellence[30] (NICE; MS, pg 32), together with the rationale for any deviation from the decision problem (Table 4).

Table 4. Summary of decision problem as outlined in the manufacturer's submission (reproduced from MS; Section 5; pg 32)

Key parameter	Final scope issued by NICE[30]	Decision problem addressed in the submission	Rationale if different from the scope
Population	Adults with NVAF who are at risk of stroke or systemic embolism	As per the final scope	
Intervention	Apixaban	As per the final scope	
Comparator(s)	Warfarin (in people for whom warfarin is suitable) Dabigatran etexilate Rivaroxaban	As per the final scope plus aspirin for people for whom warfarin is unsuitable	As outlined in Sections 2.3 and 2.5 above, aspirin is currently recommended for patients unsuitable for warfarin or those at low risk of strokes, and is also still widely used in clinical practice in England and Wales. Aspirin remains therefore, a relevant comparator in this submission.
Outcomes	Stroke non-CNS systemic embolism Myocardial infarction Mortality Transient ischaemic attacks Adverse effects of treatment including haemorrhage Health-related quality of life	As per the final scope with the exception of TIAs	TIAs were not recorded in the ARISTOTLE trial[28]
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As per the final scope	

assessed. The manufacturer reported that there was little difference in model fit between the fixed and random effects models and all outcomes were reported using a fixed effects model. The manufacturer's rationale for the use of a fixed rather than random effects model was built around the small number of studies in the network (three studies). The manufacturer considered that as a result of the small number of included studies, a random effects model would produce poor estimates of the variation in between-study treatment effects. The manufacturer also cites text from the Cochrane Systematic Review Handbook[41] that recommends that at least 10 studies are used in the calculations to investigate heterogeneity. The ERG notes that while a random effects model incorporates heterogeneity it does not investigate heterogeneity. Consequently, the ERG does not consider the number of studies in the network to be sufficient reason to choose a fixed effects model over a random effects model. Rather, the ERG considers that the best fitting model should be chosen. However, the ERG acknowledges that NMA 1 is a "star-shaped" network; i.e. it has a single "common comparator" that links the five treatments of interest together. The between study heterogeneity generated using the random effects model reflects the prior value inputted into the model as there are insufficient trial data to further inform this estimate. The ERG thus considers the manufacturer's use of a fixed effects model to be a reasonable choice given the limited data set.

The ERG notes that within the MS, the manufacturer did not report the DIC or residual deviance values for either the fixed or random effects models. However, upon request, the manufacturer supplied the residual deviance values for NMA 1 during the clarification stage. Based on these, the ERG agrees with the manufacturer's assessment that both the fixed and random effects models fit the data well.

4.4.2 Outcomes reported in network meta-analysis

The following safety and efficacy outcomes were reported in NMA 1:

- stroke + SE;
- any stroke;
- SE;
- haemorrhagic stroke;
- ischaemic stroke;
- MI;
- all-cause mortality;
- fatal stroke;
- disabling stroke;

associated with CRNM bleeds (apixaban submission, £1,133.93; dabigatran submission, £84; rivaroxaban submission, £126).[43][44] However, the ERG considers that the codes included in the calculation of each temporary event were reasonable and accepts the costs used in the manufacturer's submission.

Adverse event costs

Dyspepsia was the only adverse event that was not explicitly modelled as a health state (permanent or temporary). An additional cost of dyspepsia management was applied to all patients who experienced this adverse event. Table 56 summarises the proportion of patients assumed to experience dyspepsia for each considered intervention.

Table 56. Treatment specific proportions of patients experiencing dyspepsia

Treatment	Proportion of patients assumed to experience dyspepsia (%)	Source
Apixaban	[redacted]	AVERROES Case Study Report.
Warfarin	[redacted]	AVERROES Case Study Report.
Dabigatran (110 mg)	3.69	RE-LY
Dabigatran (150 mg)	3.53	RE-LY
Rivaroxaban	1.67	Assumption*
*[redacted]		

The yearly cost of dyspepsia management was assumed to be £27.60 and was comprised of:

- endoscopy costs – £6.12 based on a cost of £612 (HRG code FZ42Z]) applied to 1% of patients (NICE CG17);[83]
- GP visits – £1.80 based on a cost of £36 (personal social services research unit costs)[77] applied to 5% of patients (NICE CG17);[83]
- the weighted average cost of treatment with omeprazole and lansoprazole (omeprazole and lansoprazole accounted for 95.7% of all proton pump inhibitors prescribed);[81] costs were taken from Electronic Drug Tariff[80] and weighted by the proportion of patients receiving each available dose; weights were taken from national prescribing data.[81]

5.3.12 Model validation and face validity check

Within the MS, the manufacturer stated that the model was assessed for internal (verification) and external (validation) validity. Verification was carried out by two independent economists and used extreme value analysis to identify any flawed algorithms or irregularities. Validation was carried out by assessment of the face validity of the model with clinicians and comparison of the model results against published results.

Model results were compared with the cost-effectiveness results reported in the dabigatran and rivaroxaban submissions.(43)(44) A higher ICER (£13,648 versus £6,264) was estimated for

Table 57. Base case incremental results – VKA suitable population (adapted from MS; Table 79; pg 146)

Treatment	Total			Incremental†			ICER (£/QALY)	
	Costs (£)	LYG	QALY	Costs (£)	LYG	QALY	Versus warfarin	Incremental
Deterministic								
Warfarin	7,188	7.469	5.696	–	–	–	–	–
Dabigatran (150/110 mg)	8,437	7.537	5.788	1,248	0.068	0.091	13,648	Extendedly dominated
Dabigatran (110 mg)	8,684	7.503	5.756	247	-0.034	-0.032	25,308	Strictly Dominated
Rivaroxaban	8,778	7.553	5.809	95	0.050	0.054	14,071	Extendedly dominated
Apixaban	8,983	7.614	5.860	205	0.06	0.05	11,008	11,008
Probabilistic								
Warfarin	5,331	6.869	5.303	–	–	–	–	–
Dabigatran (150/110 mg)	6,737	6.921	5.342	1,406	0.05	0.04	36,450	Extendedly dominated
Dabigatran (110 mg)	6,832	6.899	5.321	95	-0.02	-0.02	83,628	Strictly Dominated
Rivaroxaban	7,070	6.943	5.366	237	0.04	0.05	27,565	Extendedly dominated
Apixaban	7,228	7.002	5.416	159	0.06	0.05	16,852	16,852

Abbreviations used in table: LYG, life year gained; mg, milligram; QALY, quality adjusted life year; VKA, vitamin K antagonist.
†Versus the next least costly technology.

In both the deterministic and probabilistic incremental results, dabigatran 110 mg is strictly dominated by (i.e. was less costly and less effective than) dabigatran blend (150 mg/110 mg) and may therefore be excluded from the analysis. Furthermore, apixaban extendedly dominated (i.e. resulted in a lower ICER versus warfarin despite having higher total QALYs) rivaroxaban and dabigatran blend. Apixaban had an ICER versus warfarin of £11,008 and £16,852 in the deterministic and probabilistic incremental analyses, respectively.

Tables 58 and 59 summarise the QALYs and costs gained for each treatment disaggregated by health state. In addition, Table 60 presents model outcomes compared with the clinical results of ARISTOTLE.

- apixaban, dabigatran blend (150 mg BD switching to 110 mg at the age of 80 years), dabigatran 110 mg and rivaroxaban: using warfarin as second-line treatment;
- apixaban, dabigatran blend (150 mg BD switching to 110 mg at the age of 80 years), dabigatran 110 mg and warfarin: using rivaroxaban as second-line treatment;
- apixaban, rivaroxaban and warfarin using dabigatran blend as second-line treatment.

The results of these analyses are presented in Appendix 9.6

To summarise, when second-line treatment was assumed to be warfarin, dabigatran 110 mg and rivaroxaban were strictly dominated by dabigatran blend. The ICER of apixaban versus dabigatran blend was £28,695. When rivaroxaban was used as second-line therapy, dabigatran 110 mg was strictly dominated by warfarin treatment, the ICERs of dabigatran blend and apixaban versus warfarin were £9,923 and £11,637, respectively. An incremental ICER of apixaban versus dabigatran blend was £60,366. When second-line treatment was assumed to be dabigatran 110 mg, rivaroxaban was extendedly dominated by apixaban and the ICER of rivaroxaban versus warfarin was £287.

The ERG considers it important to note that the risks patients were exposed to on second-line treatment were constant (see Section 5.3.7 and 5.4.5). Therefore, caution should be used when interpreting these results. However, the main driver of the higher ICERs seen in the analyses around second-line treatment choice (e.g. apixaban versus dabigatran blend) was discontinuation. That is, patients who discontinued treatment fared far better than in the base case. Therefore, treatments with higher discontinuation rates (e.g. dabigatran) appeared more effective than in the manufacturer's base case.

In addition, based on expert clinical advice, the ERG notes that there is some uncertainty regarding the relative other-cause discontinuation rates of apixaban and dabigatran. This is because, by contrast to ARISTOTLE, RE-LY was an open label trial. Expert clinical advice was that within open label trials, unexplained new symptoms may be associated with the novel therapeutic and treatment stopped. Therefore, it is possible that some of the higher level of discontinuation observed with dabigatran versus warfarin in RE-LY may be attributable to this phenomenon. The ERG carried out an exploratory analysis to investigate the impact of other-cause discontinuation on the manufacturer's cost-effectiveness results. In the exploratory analysis, the ERG assumed there was no difference in other-cause discontinuation between apixaban and dabigatran (both doses). The results of this exploratory analysis are presented in Appendix 9.7. To summarise, rivaroxaban and dabigatran 110 mg were strictly dominated by dabigatran blend. However, apixaban no longer extendedly dominated dabigatran blend, rather the ICER for the comparison of apixaban with dabigatran blend became £14,456.

dabigatran versus warfarin, whereas a lower ICER (£14,071 versus £18,883) was estimated for rivaroxaban

of recurrent stroke severity; assumed to be equivalent to that observed in ARISTOTLE for patients treated with apixaban for both scenario analyses is (i.e. ~[redacted]% of recurrent strokes will be mild).

5.4.7 Resources and costs

As discussed in Section 5.3.12, differences exist between the ICERs estimated by the manufacturer's model and those estimated in the dabigatran and rivaroxaban submissions.(43)(44) The manufacturer attributed these differences to differences in the key parameters such as costs associated with stroke events. Furthermore, the ERG notes that the acute cost of SE is approximately double the acute cost used in other NOAC submissions (apixaban submission, £4,077.98; dabigatran submission, £2,772 [fatal and non-fatal acute costs]; rivaroxaban, £1,658.12). Moreover, the acute cost associated with SE used in the dabigatran and rivaroxaban submissions was derived from NHS reference costs. Therefore, the ERG considers the costs used in the other NOAC submissions to be more plausible than those employed in the manufacturer's model. The ERG carried out sensitivity analyses to assess the impact of using the lower costs for acute SE. The incremental results did not change and dabigatran and rivaroxaban continued to be extendedly dominated by apixaban (Appendix 9.6). However, the ICER of apixaban versus warfarin increased from £11,008 to £11,012 and £11,016 when the costs used in the dabigatran and rivaroxaban submission were used, respectively.

5.4.8 Perspective, time horizon and discounting

The model submitted by the manufacturer adopted a lifetime time horizon where patients were followed for 49 years (from 74 to 123 years of age). Given that the observed life expectancy of the general population was approximately 79 years (MS; pg 271), the ERG considers the maximum modelled age of 123 years to lack face validity. In addition, the ERG notes that within the model 99.7% of patients had died after 26 years (by 100 years of age). Therefore, in line with current good research practices(87) the ERG recommends using a time horizon of 26 years (74 to 100 years of age). As part of the clarification process the ERG requested a revised model with a 26 year time horizon. To which the manufacturer provided a model with a truncated time horizon. Upon implementation of the shorter time horizon the incremental model results remained the same, with dabigatran and rivaroxaban being extendedly dominated (see Appendix 9.6). However, the ICER of apixaban versus warfarin increased by £6, from £11,007 to £11.013.

- dabigatran 110 mg was strictly dominated by (i.e. is less costly and less effective than) dabigatran blend;
- rivaroxaban and dabigatran blend were extendedly dominated (i.e. resulted in a lower incremental cost-effectiveness ratio (ICER) versus warfarin despite having higher total QALYs) by apixaban;
- apixaban had an ICER versus warfarin of £11,008 per quality adjusted life year (QALY).

The ERG carried out several sensitivity analyses to investigate uncertainty around the model's base case assumptions. It is important to note that none of these sensitivity analyses altered the incremental cost effectiveness results. Furthermore, the ICER of apixaban versus warfarin generated by the ERG's revised base case (£12,757) remained relatively consistent with the manufacturer's base case ICER (£11,008).

In addition to sensitivity analyses, the ERG carried out exploratory analyses around the choice of second-line treatment. Exploratory analyses around second-line treatment options were prompted by expert clinical input regarding uncertainty in clinical practice. The results of these analyses were highly variable, with incremental ICERs for apixaban varying between £287 (versus warfarin when dabigatran 110 mg was chosen as second-line treatment) and £60,366 (versus dabigatran blend, when rivaroxaban was chosen as second-line treatment). However, the ERG notes that within the manufacturer's model patients on second-line treatment were exposed to a constant risk of events. Therefore, the results of these analyses should be interpreted with caution as the main driver of the ICERs was discontinuation rates associated with first-line therapy. That is, patients who discontinued treatment fared far better than in the base case. Consequently, treatments with higher discontinuation rates (e.g. dabigatran) appeared more effective than in the manufacturer's base case.

In addition, the ERG carried out exploratory analyses around the level of discontinuation and risk of MI associated with dabigatran. Exploration of the impact of treatment discontinuation associated with dabigatran was prompted by expert clinical input. Clinical opinion was that the manufacturer's analysis of treatment specific discontinuation rates may have been biased by the open-label trial used to inform the treatment effect of dabigatran. Regarding the risk of MI, the manufacturer's first sensitivity analysis of NMA 1 revealed uncertainty in the significance of the reduction of MI risk associated with apixaban versus dabigatran. However, it is important to note that the analyses carried out by the ERG were extreme value analyses which assumed no difference between apixaban and dabigatran for treatment discontinuation and MI risk. These analyses resulted in ICERs of £11,191 and £14,456, respectively.