ID624 Edoxaban STA Addendum

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Edoxaban tosylate for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation

ID 624
Addendum
Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 14/14/01

Completed 22nd May 2015

DOES NOTCONTAIN CIC/AIC

Brunel University London

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 BACKGROUND

Following submission of the ERG report and factual accuracy check, the company submitted a query to NICE regarding the ERG's critique of the economic model; specifically the large impact on the incremental cost-effectiveness ratios (ICERs) from amending the age-related utility adjustment in the submitted model (letter from Daiichi Sankyo, 12 May 2015). Upon further review, the ERG has identified an additional error in the company's model that was not previously highlighted in the ERG report.

The ERG has now corrected this error in the company's model and has rerun the additional analyses presented in the ERG report. In addition, the ERG has noted that Table 47 of the ERG report incorrectly reports some results of the probabilistic analysis as results of the deterministic analyses.

This addendum details the company's modelling error and the impact this has on the cost-effectiveness results. Corrections to the relevant sections of the ERG report are also provided.

2 ERG RESPONSE

2.1 Correction of error in age-adjusted utility

The company model includes an adjustment to reflect a decrease in health-related quality of life with age. The company uses an estimate (-0.00029 per annum) based on a survey of a US population to which UK utility weights have been applied (Sullivan, 2011). The ERG considers it more appropriate to use data from a UK population as the source for this parameter. Therefore, the ERG conducted an analysis of data from the Health Survey for England, previously reported in an ERG report of aflibercept for the treatment of colorectal cancer (Wade, 2013) to obtain a UK specific estimate (-0.00646). The ERG previously reported that inclusion of this estimate in the company's model had a large impact on the magnitude of the quality adjusted life years (QALYs) gained and incremental cost-effectiveness ratios (ICERs).

Upon further examination, the ERG has identified an error in the implementation of the age-related utility decrement in the company's model. The decrement is correctly assumed to apply annually from the age of 71 years (i.e. when patients enter the model); however an adjustment is also made which applies the decrement from birth to 71 years. As the baseline utility values in the model already reflect the health-related utility of patients aged an average of 71 years, the inclusion of the additional decrement is double-counting. This has the effect

of exaggerating the impact of changes in the magnitude of the age-related utility adjustment to the ICERs.

2.1.1 Impact on results

The ERG has corrected the error in the company's model and repeated some of the analyses reported in the ERG report.

The ERG's re-analyses have established that the inclusion of the ERG's preferred value for the age-related adjustment does not have a substantial impact on the ICERs following the correction of the error in the company's model. The estimates of QALYs gained for all comparators increase following the correction. In the pairwise comparison of edoxaban with warfarin, the ICERs do not change substantially following correction of the error, either in isolation (Analysis R2 in Tables 49 and 50) or when combined with the ERG's preferred value for the age-adjustment (Analysis R2+R13 in Tables 49 and 50). In the incremental analysis, the correction to the error does not affect the result that edoxaban is dominated (less effective and more costly than at least one other comparator), with or without the amendment to the value of the age-related utility decrement (Analyses R2 and R2+R13 in Tables 47 and 48).

2.1.2 Conclusions

Amendments to the estimate of the age-related utility decrement do not impact on the cost-effectiveness results once the error in the company's model has been rectified. When all of the ERG's preferred values are used in the model the resultant pairwise deterministic (probabilistic) ICERs for the comparison of edoxaban with warfarin are £16,008 (£22,079). Including additional alternative amendments to attempt to reconcile the model survival outputs with the trial data and to reflect the changing age/gender distribution over time changed the deterministic pairwise ICERs to between approximately £15,100 and £15,800, and the probabilistic results to between £21,700 and £23,600 per QALY gained.

REFERENCES

Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. Med Decis Making. 2011;31(6):800-4.

Wade R, Duarte A et al. Aflibercept in combination with irinotecan and fluorouracil-based therapy for the treatment of metastatic colorectal cancer which has progressed following prior oxaliplatin-based chemotherapy, April 2013

Corrections to Greenhalgh et al, *Edoxaban tosylate for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation: A Single Technology Appraisal*. LRiG, 2015.

Summary section 1.6. Retraction of the following paragraph (p13-14)

<u>Age-related utility decrements</u>

The ERG identified a number of inconsistencies in the model and has concerns about some of the sources of data used in the analysis. However, the majority of these were found to have only minor impacts on results in analyses conducted by the ERG using the ERG's preferred values. An important exception was the use of data from a US rather than UK population to reflect a deterioration in HRQoL with age. The use of UK data had a substantial impact on the cost effectiveness results in the pairwise comparison between edoxaban and warfarin, with the ICER increasing to £32,129 per QALY gained in the probabilistic analysis and £34,008 per QALY gained in the deterministic analysis.

Summary section 1.72. Retraction of the following paragraph (p15)

- The economic model uses data from a US population study to inform a deterioration in HRQoL with increasing age. These estimates are significantly lower than those from UK population studies. The use of data from a UK population in the model substantially increases the ICER for edoxaban compared to warfarin.

Summary Section 1.8. Replacement text (p15-16).

1.8 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG has carried out the following alterations to the company's base case model:

R1. Correcting an error in the cell reference for the utility estimate for post-SE

R2. Corrected implementation of age-related disutility

R3. An alternative utility estimate for the SE state

R4. HRs in the incremental analysis for warfarin from the company's NMA rather than HR from the ENGAGE trial data.

R5. An alternative utility estimate for the MI state

R6. An alternative utility estimate for the TIA state

R7. Utility values for the three stroke states unadjusted for respondents' own health

R8. An alternative utility values for stroke states

R9. Patients receiving dabigatran 150mg switch to dabigatran 110mg at age 80 years

R10. All patients discontinue treatment following HS

R11. Applying the acute stroke fatality rate to all stroke events (16.8% for IS and 31.6% for HS)

R12. Case fatality rates for the three stroke states sourced from ENGAGE trial data

R13. Amended age adjusted utility decrement per year

R14. Warfarin daily cost estimated using data from the eMIT database

R15. Amendments to reflect a distribution of different starting ages, each with different gender distribution

R16. ENGAGE trial hazard rates for HS

R17. Reconciliation of OS estimates

The ERG also carried out a number of analyses in which multiple parameters were changed.

- Analysis C: Combining alternative utility data (R2, R3, R5, R6, R8) and warfarin hazard ratios from NMA (R4) (in the incremental analysis only).
- Analysis D: As for analysis C plus the age-adjustment to utilities, the costs of warfarin, the HR for HS and assumptions regarding dose reduction for dabigatran treatment discontinuation after HS (R9, R10, R13, R14, R16).
- Analysis E: All the amendments introduced in analysis D plus applying the amendment to the probabilities of acute stroke fatality from the trial (R12)
- Analysis F: All the amendments introduced in analysis D plus applying the amendment to reconcile the model and ENGAGE trial OS estimates (R17) and the age/gender distribution over time (R15).

Individually, most of the ERG amendments to the company model had only minor impacts on the ICERs per QALY gained in the pairwise analyses with warfarin. Cumulatively, the corrections and amendments without the adjustments to the fatality rates or survival data (Analysis D) increased the ICERs for edoxaban compared to warfarin to £22,079 (probabilistic analysis) and £16,008 (deterministic analysis) per QALY gained. Two approaches to reconciling the trial and model data for OS were undertaken (analyses E and F). These increased the ICERs per QALY gained for edoxaban compared to warfarin to £21,725 and £23,634 in the probabilistic analysis (£15,176 and £15,807 in the deterministic analysis).

In the incremental analyses, the result that edoxaban was dominated (more costly and less effective) by at least one other NOAC was consistent across all ERG amendments, and consistent between the probabilistic and deterministic analyses.

Summary Section 1.9. Replacement text (p17).

1.9 ERG conclusions

The company has presented direct clinical evidence to support the use of edoxaban for preventing stroke and SE in people with NVAF from the ENGAGE trial. The ERG considers this trial, which is complete, to be robust and of good quality. Results from the ENGAGE trial suggest that, based on the primary composite endpoint of stroke and SE, edoxaban is non-inferior, but not superior, to warfarin.

The cost effectiveness analysis presented by the company shows that edoxaban is dominated (more costly and less effective) by at least one other treatment option in both the deterministic and probabilistic analyses. These results are robust to a range of alternative assumptions and sources of data.

However, the ERG has concerns about the reliability of the company's estimates. Firstly the results of the incremental analyses are driven by the HRs estimated by the company's NMA; the ERG notes that the assumption of proportionality underpinning this analysis is violated. Secondly, the difference between the OS predicted by the model and the ENGAGE trial raises some concerns as to the validity of the model.

The ERG carried out a number of amendments to the company's model. Analyses using the ERG's preferred input values increases the deterministic pairwise ICER per QALY gained for the comparison of edoxaban with warfarin (Analysis D) from £12,881 to £16,008 (probabilistic analysis: £16,269 to £22,079). Further amendments to address the differences in OS estimates, and the age/gender distribution increase the ICERs per QALY gained to between approximately £21,700 and £23,600 in the probabilistic analysis and between £15,100 and £15,800 in the deterministic analysis.

Amendment to Section 5.6.6. Replacement text, 3rd paragraph under the sub-heading 'Age-related utility decrement' (p112).

Data from a UK population have previously been used to estimate an age-related utility decrement in a NICE appraisal of aflibercept for the treatment of metastatic colorectal cancer (TA307[83]). In this STA[83], the ERG used EQ-5D data from the Health Survey for England[84] and an analysis using these data yielded an estimated annual utility decrement of -0.00646. However, including this estimate in the analyses using the company's model does not affect the cost-effectiveness results.

Amendment to Section 5.6.10. Additional bullet point to be added (p119).

8. The ERG identified an error in the implementation of the age-adjusted utility decrement. The decrement is correctly assumed to apply annually from the age of 71 years (i.e. when patients enter the model); however an adjustment is also made which applies the decrement from birth to 71 years. As the baseline utility values in the model already reflect the health-related utility of patients aged an average of 71 years, the inclusion of the additional decrement is double-counting. Correction of this error had minimal impact on the ICERs.

Amendment to Section 5. 7.

5.7 Conclusions of the cost effectiveness section

Retraction of the following bullet point

- The source of data used to adjust utilities to reflect a reduction of HRQoL with increasing age are based on data from a US population and significantly underestimate this impact when compared with data from a UK population.

Amended text for final paragraph

The ERG has reviewed the decision model submitted by the company and notes that it appears robust to any sensitivity analysis carried out by the company and most of the analyses carried out by the ERG. None of the ERG's amendments to the company's model changed the result that edoxaban is more expensive and less effective that at least one of the alternative treatments when full incremental analyses are carried out. When all of the ERG's preferred values are used in the model the resultant pairwise deterministic (probabilistic) ICERs for the comparison of edoxaban with warfarin are £16,008 (£22,079). Including additional alternative amendments to attempt to reconcile the model survival outputs with the trial data and to reflect the changing age/gender distribution over time

changed the deterministic pairwise ICERs to between approximately £15,100 and £15,800, and the probabilistic results to between £21,700 and £23,600 per QALY gained.

Replacement text for Section 6 (p120-130)

6 IMPACT ON THE ICER OF ADDITIONAL ANALYSES UNDERTAKEN BY THE ERG

The cost-effectiveness results generated as a result of model amendments and corrections implemented by the ERG to examine issues described in section 5 of this report are displayed in Table 47 (deterministic incremental analysis) and Table 48 (probabilistic incremental analysis). The changes feature up to 17 revisions which use the ERG's preferred alternative parameter values or formulae.

The changes carried out by the ERG are listed below and further details of their implementation are reported in Appendix 8 of this ERG report. Further details on the costs and QALY estimates for each comparator following the amendments are provided in Appendix 9.

The analyses are detailed in Appendix 8 and include:

R1. Correcting an error in the cell reference for the utility estimate for post-SE (change estimate from 0.74 to 0.68)

R2. Correcting an error in the implementation of the age-adjusted utility in the model

R3. Employing an alternative utility estimate for the SE state based on regression coefficients from a single regression model (Updated value = 0.69)[72]

R4. Using HRs in the incremental analysis for warfarin from the company's NMA rather than HR from the ENGAGE trial data.

R5. Using an alternative utility estimate for the MI state based on UK data reported by Sullivan (updated value = 0.663)[72]

R6. Using an alternative utility estimate for the TIA state based on the study by Luengo-Fernandez[85] (updated decrement = -0.086)[85]

R7. Using the company's utility values for mild, moderate and severe stroke states without the adjustment for respondents' own health (updated values: 0.76, 0.39, 0.11 respectively)[73]

R8. Using alternative utility values for stroke states based on the study by Luengo-Fernandez[75] (updated values for acute mild, moderate and severe stroke states: 0.63, 0.40, and 0.03 respectively. Post-event mild, moderate and severe stroke states: 0.63, 0.46 and 0.28)[85]

R9. Assuming all patients receiving dabigatran 150mg switch treatment at age 80 years to dabigatran 110mg

R10. Assuming all patients discontinue treatment following HS

R11. Applying the acute stroke fatality rate to all stroke events (mild stroke change to 16.8% (IS) and 31.6% (HS) from 0%)

R12. Use case fatality rates for mild, moderate and severe acute stroke sourced from ENGAGE trial data

R13. Amend age adjusted utility decrement per year (change from -0.00029 to -0.00646). An analysis presenting this amendment with the correction to the implementation of the age-adjusted utility (R2) is also presented

R14. Warfarin daily cost sourced from eMIT as per NICE reference case (change from 0.11 to 0.04 per day)

R15. Amendments to reflect a distribution of different starting ages, each with different gender distribution

R16. Applying ENGAGE trial hazard rates for HS

R17. Reconcile OS estimates by adjusting other cause mortality adjustment factor and using trial data for acute stroke case fatality rates for mild, moderate and severe stroke

The ERG also carried out four analyses in which multiple parameters were changed. The pairwise analysis excluded the amendment to use the warfarin hazard ratios from the NMA. The amendments are labelled C, D, E and F and results presented in Table 47 to Table 50:

- Analysis C: corrected implementation of age-related utility adjustment (R2), ERG sourced utility values for SE (R3), warfarin hazard ratios from NMA (R4), alternative utility values for MI (R5), TIA (R6) and ERG sourced utility values for acute and post stroke health states (R8).
- Analysis D: corrected implementation of age-related utility adjustment (R2), ERG sourced utility values for SE (R3), warfarin hazard ratios from NMA (R4), alternative utility values for MI (R5), TIA (R6) and ERG sourced utility values for acute and post stroke health states (R8), assumption regarding method used to switch patient medication from dabigatran 150mg to 110mg at age 80 (R9), assumption regarding treatment discontinuation after HS (R10), amendment to age adjusted utility decrement per year (R13), change in daily cost warfarin (R14), plus applying the ENGAGE trial HR for HS (R16).
- Analysis E: All the amendments introduced in analysis D plus applying an amendment to the probabilities of acute stroke fatality from the trial (R12)
- Analysis F: All the amendments introduced in analysis D plus applying the amendment to reconcile the model and ENGAGE trial OS estimates (R17) and the age/gender distribution over time (R15).

Table 47 ERG analyses: incremental deterministic results (incremental cost per QALY gained)

Scenario/revision		Comparator					
		Edoxaban	**Apixaban**	**Rivaroxaban**	**Dabigatran 110mg**	**Dabigatran 150mg**	**Warfarin**
A	**CS deterministic base case**	**Dominated**	**Dominated**	**Dominated**	**Dominated**	**£7,645**	**-**
B	**CS probabilistic base case**	**Dominated**	**£13,036**	**Dominated**	**Dominated**	**Extendedly Dominated**	**-**
R1	CS base case-corrected utility for SE*	Dominated	Dominated	Dominated	Dominated	£7,631	-
R2	CS base case – corrected implementation of age-related disutility	Dominated	Dominated	Dominated	Dominated	£7,416	-
R3	CS base case - alternative utility value for SE	Dominated	Dominated	Dominated	Dominated	£7,633	-
R4	Hazard ratio for Warfarin from NMA	Dominated	Dominated	Dominated	Dominated	£7,837	-
R5	Alternative utility value for MI	Dominated	Dominated	Dominated	Dominated	£7,662	-
R6	Alternative utility value for TIA	Dominated	Dominated	Dominated	Dominated	£7,631	
R7	Corrected utility values for mild, moderate and severe stroke	Dominated	Dominated	Dominated	Dominated	£7,780	-
R8	Alternative utility values for acute mild, moderate and severe stroke and post stroke states	Dominated	Dominated	Dominated	Dominated	£7,595	-
R9	Alternative method for switch in dabigatran 150mg to 110mg at 80 years	Dominated	Dominated	Dominated	Dominated	£6,865	-
R10	Discontinuation rate medication following HS 100%	Dominated	Dominated	Dominated	Dominated	£7,683	-
R11	Amend acute mild stroke case fatality rate to 16.8% (IS) and 31.6% (HS) from 0%	Dominated	Dominated	Dominated	Dominated	£7,604	-
R12	Use trial data on acute stroke case fatality rates for mild, moderate and severe stroke	Dominated	Dominated	Dominated	Dominated	£7,757	-
R13	Age-adjusted utility decrement per year changed from -0.00029 to -0.00646	Dominated	Dominated	Dominated	Dominated	£19,428	-

Table 47 ERG analyses: incremental deterministic results (incremental cost per QALY gained) continued

Scenario/revision		Comparator					
		Edoxaban	**Apixaban**	**Rivaroxaban**	**Dabigatran 110mg**	**Dabigatran 150mg**	**Warfarin**
R2 +R13	Correct implementation of age-adjusted utility and age-adjusted utility decrement per year changed from -0.00029 to -0.00646	Dominated	Dominated	Dominated	Dominated	£7,475	-
R14	Warfarin daily cost sourced from eMIT as per NICE reference case	Dominated	Dominated	Dominated	Dominated	£8,377	-
R15	Change in age and gender distribution over time	Dominated	Dominated	Dominated	Dominated	£4,976	-
R16	Apply ENGAGE trial hazard rates for HS	Dominated	Dominated	Dominated	Dominated	£9,885	-
R17	Reconcile OS estimates- amend other cause mortality adjustment factor value to 1.54165	Dominated	Dominated	Dominated	Dominated	£8,080	-
C	R2+R3+R4+R5+R6+R8	Dominated	Dominated	Dominated	Dominated	£7,625	-
D	**R2+R3+R4+R5+R6+R8+R9+R10+R13+R14+R16**	**Dominated**	**Dominated**	**Dominated**	**Dominated**	**£8,583**	**-**
E	**R2+R3+R4+R5+R6+R8+R9+R10+R12+R13+R14+ R16**	**Dominated**	**Dominated**	**Dominated**	**Dominated**	**£8,620**	**-**
F	**R2+R3+R4+R5+R6+R8+R9+R10+R13+R14+R15+ R16+R17**	**Dominated**	**Dominated**	**Dominated**	**Dominated**	**£7,016**	**-**

*Base case used for model amendments R2-R17

Table 48 ERG analyses: incremental probabilistic results

Scenario/revision		Comparator					
		Edoxaban	Apixaban	Rivaroxaban	Dabigatran 110mg	Dabigatran 150mg	Warfarin
A	**CS deterministic base case**	**Dominated**	**Dominated**	**Dominated**	**Dominated**	**£7,645**	**-**
B	**CS probabilistic base case**	**Dominated**	**£13,036**	**Dominated**	**Dominated**	**Extendedly Dominated**	**-**
R1	CS base case-corrected utility for SE*	Dominated	£15,275	Dominated	Dominated	£12,210	-
R2	CS base case – corrected implementation of age-related disutility	Dominated	£12,681	Dominated	Dominated	Extendedly Dominated	-
R3	CS base case - alternative utility value for SE	Dominated	£15,531	Dominated	Dominated	£13,365	-
R4	Hazard ratio for Warfarin from NMA	Dominated	£14,960	Dominated	Dominated	£14,273	-
R5	Alternative utility value for MI	Dominated	£21,363	Dominated	Dominated	£12,052	-
R6	Alternative utility value for TIA	Dominated	£23,933	Dominated	Dominated	£11,565	
R7	Corrected utility values for mild, moderate and severe stroke	Dominated	£15,275	Dominated	Dominated	£12,210	-
R8	Alternative utility values for acute mild, moderate and severe stroke and post stroke states	Dominated	£16,132	Dominated	Dominated	£12,691	-
R9	Alternative method for switch in dabigatran 150mg to 110mg at 80 years	Dominated	Dominated	Dominated	Dominated	£10,570	-
R10	Discontinuation rate medication following HS 100%	Dominated	£12,543	Dominated	Dominated	Extendedly Dominated	-
R11	Amend acute mild stroke case fatality rate to 16.8% (IS) and 31.6% (HS) from 0%	Dominated	£15,050	Dominated	Dominated	£12,756	-
R12	Use trial data on acute stroke case fatality rates for mild, moderate and severe stroke	Dominated	£15,793	Dominated	Dominated	£13,486	-
R13	Age-adjusted utility decrement per year changed from -0.00029 to -0.00646	Dominated	£33,313	Dominated	Dominated	£28,308	-

Table 48 ERG analyses: incremental probabilistic results continued

	Scenario/revision	Comparator					
		Edoxaban	**Apixaban**	**Rivaroxaban**	**Dabigatran 110mg**	**Dabigatran 150mg**	**Warfarin**
R2+ R13	Amendments to age-adjusted utility: implementation and value (0.00646)	Dominated	£13,130	Dominated	Dominated	Extendedly Dominated	-
R14	Warfarin daily cost sourced from eMIT as per NICE reference case	Dominated	£12,902	Dominated	Dominated	Extendedly Dominated	-
R15	Change in age and gender distribution over time	Dominated	Dominated	Dominated	Dominated	£8,045	-
R16	Apply ENGAGE trial hazard rates for HS	Dominated	Dominated	Dominated	Dominated	£10,323	-
R17	Reconcile OS estimates- amend other cause mortality adjustment factor value to 1.54165	Dominated	£20,549	Dominated	Dominated	£13,763	-
C	R2+R3+R4+R5+R6+R8	Dominated	£12,553	Dominated	Dominated	£12,461	-
D	**R2+R3+R4+R5+R6+R8+R9+R10+R13+R14+R16**	**Dominated**	**Dominated**	**Dominated**	**Dominated**	**£14,902**	**-**
E	**R2+R3+R4+R5+R6+R8+R9+R10+R12+R13+R14+R16**	**Dominated**	**Dominated**	**Dominated**	**Dominated**	**£15,783**	**-**
F	**R2+R3+R4+R5+R6+R8+R9+R10+R13+R14+R15+R16 +R17**	**Dominated**	**Dominated**	**Dominated**	**Dominated**	**£11,975**	**-**

*Base case used for model amendments R2-R17

Table 49 ERG analyses: pairwise deterministic results (edoxaban versus warfarin)

Scenario/revision		Edoxaban		Warfarin		Incremental		
		Cost	QALYs	Cost	QALYs	Cost	QALYs	ICER
A	**CS deterministic base case**	£15,957	6.52	£13,413	6.32	£2,544	0.20	£12,881
R1	CS base case-corrected utility for SE*	£15,957	6.51	£13,413	6.32	£2,544	0.20	£12,823
R2	CS base case – corrected implementation of age-related disutility	£15,957	6.71	£13,413	6.51	£2,544	0.20	£12,454
R3	Alternative utility value for SE	£15,957	6.51	£13,413	6.32	£2,544	0.20	£12,823
R4	HR for warfarin from NMA	£15,957	6.51	£13,403	6.32	£2,554	0.19	£13,287
R5	Alternative utility value for MI	£15,957	6.51	£13,413	6.31	£2,554	0.20	£12,818
R6	Alternative utility value for TIA	£15,957	6.51	£13,413	6.32	£2,554	0.20	£12,823
R7	Corrected utility values for mild, moderate and severe stroke	£15,957	6.53	£13,413	6.34	£2,554	0.20	£12,951
R8	Alternative utility values for acute mild, moderate and severe stroke and post stroke states	£15,957	6.51	£13,413	6.32	£2,544	0.20	£12,809
R9	Alternative method for switch in dabigatran 150mg to 110mg at 80 years	£15,957	6.51	£13,413	6.32	£2,544	0.20	£12,823
R10	Discontinuation rate medication following HS 100%	£15,927	6.51	£13,385	6.32	£2,542	0.20	£12,813
R11	Amend acute mild stroke case fatality rate to 16.8% (IS) and 31.6% (HS) from 0%	£15,726	6.47	£13,110	6.27	£2,616	0.21	£12,644
R12	Use trial data on acute stroke case fatality rates for mild, moderate and severe stroke	£15,556	6.46	£12,871	6.25	£2,685	0.21	£12,649
R13	Age-adjusted utility decrement per year changed from -0.00029 to -0.00646	£15,957	2.34	£13,413	2.27	£2,544	0.07	£34,008
R2+R13	Amendments to age-adjusted utility: implementation and value (0.00646)	£15,957	6.65	£13,413	6.45	£2,544	0.20	£12,555
R14	Warfarin daily cost sourced from eMIT as per NICE reference case	£15,957	6.51	£13,203	6.32	£2,754	0.20	£13,883
R15	Change in age and gender distribution over time	£18,365	6.92	£15,806	6.66	£2,558	0.26	£10,010

Table 49 ERG analyses: pairwise deterministic results (edoxaban versus warfarin) continued

Scenario/revision		Edoxaban		Warfarin		Incremental		
		Cost	QALYs	Cost	QALYs	Cost	QALYs	ICER
R16	Apply ENGAGE trial hazard rates for HS	£15,957	6.51	£13,078	6.35	£2,879	0.17	£17,137
R17	Reconcile OS estimates- amend other cause mortality adjustment factor value to 1.54165	£15,335	6.24	£12,904	6.06	£2,430	0.18	£13,735
C	R2+R3+R4+R5+R8	£15,957	6.70	£13,403	6.51	£2,544	0.20	£12,912
D	**R2+R3+R4+R5+R6+R8+R9+R10+R13+R14+R16**	**£15,927**	**6.65**	**£13,010**	**6.47**	**£2,917**	**0.18**	**£16,008**
E	**R2+R3+R4+R5+R6+R8+R9+R10+R12+R13+R14+R16**	**£15,539**	**6.60**	**£12,520**	**6.41**	**£3,019**	**0.19**	**£15,807**
F	**R2+R3+R4+R5+R6+R8+R9+R10+R13+R14+R15+R16+R17**	**£17,735**	**6.77**	**£14,675**	**6.56**	**£3,060**	**0.20**	**£15,176**

*Base case used for model amendments R2-R17

Table 50 ERG analyses: pairwise probabilistic results (edoxaban versus warfarin)

Scenario/revision		Edoxaban		Warfarin		Incremental		
		Cost	QALYs	Cost	QALYs	Cost	QALYs	ICER
A	**CS deterministic base case**	**£15,957**	**6.52**	**£13,413**	**6.32**	**£2,544**	**0.20**	**£12,881**
B	**CS probabilistic base case**	**£15,471**	**6.72**	**£12,868**	**6.56**	**£2,603**	**0.16**	**£16,269**
R1	CS base case-corrected utility for SE*	£15,404	6.74	£12,825	6.57	£2,579	0.17	£15,171
R2	CS base case – corrected implementation of age-related disutility	£15,360	6.97	£12,741	6.81	£2,619	0.16	£16,369
R3	Alternative utility value for SE	£15,462	6.73	£12,832	6.58	£2,630	0.15	£17,533
R4	HR for warfarin from NMA	£15,389	6.76	£12,753	6.62	£2,636	0.14	£18,829
R5	Alternative utility value for MI	£15,432	6.75	£12,862	6.59	£2,570	0.16	£16,063
R6	Alternative utility value for TIA	£15,474	6.75	£12,916	6.58	£2,558	0.17	£15,047
R7	Corrected utility values for mild, moderate and severe stroke	£15,476	6.73	£12,975	6.56	£2,501	0.17	£14,712
R8	Alternative utility values for acute mild, moderate and severe stroke and post stroke states	£15,397	6.76	£12,784	6.6	£2,613	0.16	£16,331
R9	Alternative method for switch in dabigatran 150mg to 110mg at 80 years	£15,382	6.75	£12,807	6.58	£2,575	0.17	£15,147
R10	Discontinuation rate medication following HS 100%	£15,428	6.74	£12,844	6.58	£2,584	0.16	£16,150
R11	Apply acute stroke fatality rates to all IS and HS strokes in the model	£15,466	6.74	£12,873	6.58	£2,593	0.16	£16,206
R12	Use trial data on acute stroke case fatality rates for all IS and HS stroke	£15,317	6.73	£12,643	6.58	£2,674	0.15	£17,827
R13	Age adjusted utility decrement per year changed from -0.00029 to -0.00646	£15,478	2.42	£12,879	2.35	£2,599	0.07	£37,129
R2+ R13	Amendments to age-adjusted utility: implementation and value (0.00646)	£15,370	6.90	£12,708	6.74	£2,662	0.16	£17,012
R14	Warfarin daily cost sourced from eMIT as per NICE reference cost	£15,557	6.74	£12,810	6.57	£2,747	0.17	£16,159
R15	Change in age and gender split over time	£17,794	7.20	£15,233	7.00	£2,561	0.20	£12,805

Table 50 ERG analyses: pairwise probabilistic results (edoxaban versus warfarin) continued

Scenario/revision		Edoxaban		Warfarin		Incremental		
		Cost	QALYs	Cost	QALYs	Cost	QALYs	ICER
R16	Apply ENGAGE trial hazard rates for HS	£15,532	6.73	£12,587	6.60	£2,945	0.13	£22,654
R17	Reconcile OS estimates- amend other cause mortality adjustment factor value to 1.54165	£14,717	6.43	£12,201	6.29	£2,516	0.14	£17,971
C	R2+R3+R4+R5+R8	£15,431	6.93	£12,892	6.77	£2,540	0.16	£15,780
D	**R2+R3+R4+R5+R6+R8+R9+R10+R13+R14+R16**	**£15,502**	**6.87**	**£12,502**	**6.74**	**£2,999**	**0.14**	**£22,079**
E	**R2+R3+R4+R5+R6+R8+R9+R10+R12+R13+R14+R16**	**£15,319**	**6.87**	**£12,242**	**6.74**	**£3,077**	**0.13**	**£23,634**
F	**R2+R3+R4+R5+R6+R8+R9+R10+R13+R14+R15+R16+R17**	**£17,138**	**7.04**	**£14,012**	**6.90**	**£3,126**	**0.14**	**£21,728**

*Base case used for model amendments R2-R17

Amendment to Section 8.2. Replacement text for 3rd paragraph p132

The ERG had concerns about some of the data inputs included in the economic model; however the results were robust to most sensitivity analyses exploring the impact of many alternative data sources and assumptions. Including these amendments increased the ICER for edoxaban in the deterministic (probabilistic) pairwise comparison with warfarin to £16,008 (£22,079). Additional analyses conducted by the ERG to explore alternative approaches to reconciling the model outputs with the ENGAGE trial (Analyses E and F) and the age/gender distribution over time led to ICERs of approximately between £15,100 and £23,600. The results of the incremental analyses did not change, in that edoxaban remained dominated (was more costly and less effective) by other treatments included in the model.

Replacement text for Appendix 9 (p169-172)

ERG probabilistic sensitivity analyses results (Mean costs and QALYs)

Scenario/revision		Edoxaban		Apixaban		Rivaroxaban		Dabigatran 110mg		Dabigatran 150mg		Warfarin	
		Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs
A	**CS deterministic base case**	**15,957**	**6.52**	**15,940**	**6.59**	**16,744**	**6.44**	**16,074**	**6.51**	**15,563**	**6.60**	**13,413**	**6.32**
B	**CS probabilistic base case**	**15,471**	**6.72**	**15,531**	**6.77**	**16,313**	**6.65**	**15,732**	**6.66**	**15,293**	**6.75**	**12,868**	**6.56**
R1	CS base case-corrected utility for SE*	15,404	6.74	15,489	6.79	16,274	6.68	15,723	6.68	15,261	6.77	12,825	6.57
R2	CS base case – corrected implementation of age-related disutility	15,360	6.97	15,447	7.02	16,222	6.91	15,626	6.92	15,208	7.01	12,741	6.81
R3	CS base case - alternative utility value for SE	15,462	6.73	15,557	6.78	16,342	6.67	15,741	6.68	15,292	6.77	12,832	6.58
R4	Hazard ratio for Warfarin from NMA	15,389	6.76	15,480	6.81	16,260	6.70	15,672	6.71	15,231	6.79	12,753	6.62
R5	Alternative utility value for MI	15,432	6.75	15,525	6.80	16,316	6.69	15,652	6.70	15,244	6.79	12,862	6.59
R6	Alternative utility value for TIA	15,474	6.75	15,547	6.80	16,367	6.68	15,731	6.69	15,279	6.79	12,916	6.58
R7	Corrected utility values for mild, moderate and severe stroke	15,476	6.73	15,565	6.77	16,377	6.66	15,769	6.68	15,305	6.76	12,975	6.56
R8	Alternative utility values for acute mild, moderate and severe stroke and post stroke states	15,397	6.76	15,482	6.81	16,250	6.70	15,252	6.80	15,252	6.80	12,784	6.60
R9	Alternative method for switch in dabigatran 150mg to 110mg at 80 years	15,382	6.75	15,477	6.80	16,252	6.68	15,609	6.71	15,138	6.81	12,807	6.58
R10	Discontinuation rate medication following HS set at 100%	15,428	6.74	15,509	6.79	16,271	6.68	15,762	6.68	15,312	6.77	12,844	6.58

ERG probabilistic sensitivity analyses results (Mean costs and QALYs) continued

Scenario/revision		Edoxaban		Apixaban		Rivaroxaban		Dabigatran 110mg		Dabigatran 150mg		Warfarin	
		Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs
R11	Amend acute mild stroke case fatality rate to 16.8% (IS) and 31.6% (HS) from 0%	15,466	6.74	15,552	6.79	16,363	6.67	15,753	6.69	15,333	6.77	12,873	6.58
R12	Use trial data on acute stroke case fatality rates for mild, moderate and severe stroke	15,317	6.73	15,401	6.78	16,176	6.67	15,578	6.69	15,177	6.77	12,643	6.58
R13	Age adjusted utility decrement per year changed from -0.00029 to -0.00646	15,478	2.42	15,568	2.44	16,384	2.39	15,805	2.39	15,350	2.43	12,879	2.35
R2+ R13	Amendments to age-adjusted utility: implementation and value (0.00646)	15,370	6.90	15,443	6.95	16,240	6.83	15,707	6.84	15,258	6.93	12,708	6.74
R14	Warfarin daily cost sourced from eMIT as per NICE reference cost	15,557	6.74	15,619	6.79	16,450	6.67	15,818	6.68	15,377	6.77	12,810	6.57
R15	Change in age and gender split over time	17,794	7.20	17,852	7.26	18,851	7.12	18,087	7.15	17,447	7.27	15,233	7.00
R16	Apply ENGAGE trial hazard rates for HS	15,532	6.73	15,602	6.78	16,433	6.66	15,807	6.68	15,340	6.77	12,587	6.60

ERG probabilistic sensitivity analyses results (Mean costs and QALYs) continued

Scenario/revision		Edoxaban		Apixaban		Rivaroxaban		Dabigatran 110mg		Dabigatran 150mg		Warfarin	
		Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs
R17	Reconcile OS estimates-amend other cause mortality adjustment factor value to 1.54165	14,717	6.43	14,789	6.48	15,548	6.38	15,031	6.39	14,568	6.47	12,201	6.29
C	R2+R3+R4+R5+R6+R8	15,431	6.93	15,529	6.98	16,308	6.86	15,749	6.87	15,296	6.96	12,892	6.77
D	**R2+R3+R4+R5+R6+R8+ R9+R10+R13+R14+R16**	**15,502**	**6.87**	**15,583**	**6.92**	**16,379**	**6.81**	**15,820**	**6.82**	**15,296**	**6.93**	**12,502**	**6.74**
E	**R2+R3+R4+R5+R6+R8+ R9+R10+R12+R13+R14+ R16**	**15,319**	**6.87**	**15,401**	**6.92**	**16,206**	**6.80**	**15,669**	**6.81**	**15,141**	**6.92**	**12,242**	**6.74**
F	**R2+R3+R4+R5+R6+R8+ R9+R10+R13+R14+R15+ R16+R17**	**17,138**	**7.04**	**17,178**	**7.10**	**18,523**	**6.97**	**17,465**	**7.00**	**16,781**	**7.13**	**14,012**	**6.90**

*Base case used for model amendments R2-R17

ERG deterministic sensitivity analyses results (Mean costs and QALYs)

Scenario/revision		Edoxaban		Apixaban		Rivaroxaban		Dabigatran 110mg		Dabigatran 150mg		Warfarin	
		Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs
A	**CS deterministic base case**	**15,957**	**6.52**	**15,940**	**6.59**	**16,744**	**6.44**	**16,074**	**6.51**	**15,563**	**6.60**	**13,413**	**6.32**
B	**CS probabilistic base case**	**15,451**	**6.72**	**15,531**	**6.77**	**16,313**	**6.65**	**15,732**	**6.66**	**15,293**	**6.75**	**12,868**	**6.56**
R1	CS base case-corrected utility for SE*	15,957	6.51	15,940	6.59	16,744	6.43	16,074	6.51	15,563	6.60	13,413	6.32
R2	CS base case – corrected implementation of age-related disutility	15,957	6.71	15,940	6.79	16,744	6.63	16,074	6.71	15,563	6.80	13,413	6.51
R3	CS base case - alternative utility value for SE	15,957	6.51	15,940	6.59	16,744	6.43	16,074	6.51	15,563	6.60	13,413	6.32
R4	Hazard ratio for Warfarin from NMA	15,957	6.51	15,940	6.59	16,744	6.43	16,074	6.51	15,563	6.60	13,413	6.32
R5	Alternative utility value for MI	15,957	6.51	15,940	6.58	16,744	6.43	16,074	6.51	15,563	6.59	13,413	6.31
R6	Alternative utility value for TIA	15,957	6.51	15,940	6.59	16,744	6.43	16,074	6.51	15,563	6.60	13,413	6.32
R7	Corrected utility values for mild, moderate and severe stroke	15,957	6.51	15,940	6.59	16,744	6.43	16,074	6.51	15,563	6.60	13,413	6.32
R8	Alternative utility values for acute mild, moderate and severe stroke and post stroke states	15,957	6.51	15,940	6.59	16,744	6.43	16,074	6.51	15,563	6.60	13,413	6.32
R9	Alternative method for switch in dabigatran 150mg to 110mg at 80 years	15,957	6.51	15,940	6.59	16,744	6.43	16,074	6.51	15,469	6.62	13,413	6.32
R10	Discontinuation rate medication following HS set at 100%	15,927	6.51	15,911	6.59	16,711	6.43	16,060	6.51	15,550	6.60	13,385	6.32
R11	Amend acute mild stroke case fatality rate to 16.8% (IS) and 31.6% (HS) from 0%	15,726	6.47	15,724	6.55	16,493	6.39	15,874	6.48	15,398	6.57	13,110	6.27

ERG deterministic sensitivity analyses results (Mean costs and QALYs) continued

Scenario/revision		Edoxaban		Apixaban		Rivaroxaban		Dabigatran 110mg		Dabigatran 150mg		Warfarin	
		Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs
R12	Use trial data on acute stroke case fatality rates for mild, moderate and severe stroke	15,556	6.46	15,566	6.53	16,306	6.37	15,743	6.46	15,287	6.56	12,871	6.25
R13	Age-adjusted utility decrement per year changed from -0.00029 to -0.00646	15,957	2.34	15,940	2.38	16,744	2.31	16,074	2.34	15,563	2.38	13,413	2.27
R2+ R13	Amendments to age-adjusted utility: implementation and value (0.00646)	15,957	6.65	15,940	6.73	16,744	6.57	16,074	6.65	15,563	6.74	13,413	6.45
R14	Warfarin daily cost sourced from eMIT as per NICE reference cost	15,957	6.51	15,940	6.59	16,744	6.43	15,940	6.59	15,563	6.60	13,203	6.32
R15	Change in age and gender distribution over time	18,365	6.92	18,315	7.01	19,275	6.82	18,492	6.93	17,720	7.05	15,806	6.66
R16	Apply ENGAGE trial hazard rates for HS	15,957	6.51	15,940	6.59	16,744	6.43	16,074	6.51	15,563	6.60	13,078	6.35
R17	Reconcile OS estimates- amend other cause mortality adjustment factor value to 1.54165	15,335	6.24	15,309	6.30	16,090	6.17	15,461	6.24	14,948	6.31	12,904	6.06
C	R2+R3+R4+R5+R6+R8	15,957	6.70	15,940	6.78	16,744	6.62	16,074	6.70	15,563	6.79	13,403	6.51
D	**R2+R3+R4+R5+R6+R8+R9+R10+ R13+R14+R16**	**15,927**	**6.65**	**15,911**	**6.72**	**16,711**	**6.57**	**16,711**	**6.57**	**15,456**	**6.75**	**13,010**	**6.47**
E	**R2+R3+R4+R5+R6+R8+R9+R10+ R12+R13+R14+R16**	**15,539**	**6.60**	**15,549**	**6.67**	**16,287**	**6.51**	**15,734**	**6.60**	**15,197**	**6.72**	**12,520**	**6.41**
F	**R2+R3+R4+R5+R6+R8+R9+R10+ R13+R14+R15+R16+R17**	**17,735**	**6.77**	**17,674**	**6.85**	**18,613**	**6.67**	**17,893**	**6.78**	**17,066**	**6.90**	**14,675**	**6.56**

*Base case used for model amendments R2-R17