Dabigatran – Comments to the new information provided by manufacturer

From Section 1.2. of the Appraisal Committee's preliminary recommendations:

1. *A cost-effectiveness analysis of the sequential regimen outlined above, comparing dabigatran etexilate with warfarin* ***using relative risks from the whole RE-LY trial population*** *rather than from the post hoc subgroup analysis. The analysis should include* ***sensitivity analyses*** *using a range of assumptions of* ***international normalised ratio (INR) monitoring costs*** *such as those used by the Evidence Review Group (ERG)* ***(£279.36, £241.54*** *and* ***£115.14****) in addition to the cost stated in the manufacturer's submission* ***(£414.90****).*

Initially three separate models were submitted to the ERG for evaluation. These were:

1. 150 Single dose model

2. 110 Single dose model

3. Sequence model with subgroup data (initial)

At the ACD the committee requested the manufacturer's resubmit the Sequence model with data from the complete population (revised). The following refers to the ERG's evaluation of the revised sequence model.

The ERG compared the inputs in the revised sequence model with the inputs used for the original single dose model and sequence dose model (revised versions submitted with the response for points of clarification). There was one difference between the inputs of the revised sequence model and the inputs used for the single dose model, which had been checked previously for the initial ERG report. The values for ischaemic stroke disability and mortality rates by treatment used in the revised sequence model were the same as those used in the initial sequence model rather than those from the single dose model. Table 1 compares the disability and mortality rates by treatment used in the single dose model and in the sequence dose models (initial and revised).

Table 1 - Comparison of ischaemic stroke disability and mortality rates by treatment used in the single dose model and in the revised sequence dose models

Relative risk vs trial warfarin	Intervention	Single dose model	Sequence dose models
Mortality	Dabigatran 150mg	1.13 (0.73; 1.74)	1.0338 (0.5839; 1.8305)
	Dabigatran 110mg	0.95 (0.63; 1.45)	1.2333 (0.6510; 2.3367)
Independent state	Dabigatran 150mg	1.07 (0.90; 1.28)	1.0767 (0.9065; 1.2788)
	Dabigatran 110mg	0.89 (0.74; 1.07)	0.6044 (0.3369; 1.0843)
Moderate disability	Dabigatran 150mg	0.80 (0.46; 1.38)	0.7586 (0.4247; 1.3550)
	Dabigatran 110mg	1.23 (0.81; 1.88)	2.0308 (0.8961; 4.6021)

The ERG used the ischaemic stroke disability and mortality rates by treatment used in the single dose model and re-ran the model. Table 2 summarises the results of the incremental analysis of dabigatran sequential dose compared with trial-like warfarin for the four alternative INR monitoring costs.

Table 2 - Incremental analysis for the alternative INR monitoring costs

Population	INR monitoring cost	Intervention	Mean Costs	Mean QALYs	Inc. Cost	Inc. QALY	ICER	MS revised ICER
Full sequence	£115.14	Warfarin	£14,873	7.8147	Baseline			
		Dabigatran	£18,726	8.0310	£3,853	0.2163	£17,813	£18,987
	£241.54	Warfarin	£15,800	7.8147	Baseline			
		Dabigatran	£18,726	8.0310	£2,926	0.2163	£13,528	£14,518
	£279.36	Warfarin	£16,077	7.8147	Baseline			
		Dabigatran	£18,726	8.0310	£2,649	0.2163	£12,246	£13,181
	£414.90	Warfarin	£17,071	7.8147	Baseline			
		Dabigatran	£18,726	8.0310	£1,655	0.2163	£7,651	£8,388
Over 80 only	£115.14	Warfarin	£6,796	4.1535	Baseline			
		Dabigatran	£9,333	4.2804	£2,536	0.1269	£19,983	£22,350
	£241.54	Warfarin	£7,239	4.1535	Baseline			
		Dabigatran	£9,333	4.2804	£2,094	0.1269	£16,497	£18,269
	£279.36	Warfarin	£7,371	4.1535	Baseline			
		Dabigatran	£9,333	4.2804	£1,962	0.1269	£15,454	£17,048
	£414.90	Warfarin	£7,846	4.1535	Baseline			
		Dabigatran	£9,333	4.2804	£1,487	0.1269	£11,717	£12,671

The ERG analysis is broadly in line with the results presented by the manufacturer. Using the treatment disability and mortality risks from the whole RE-LY trial population lowered the ICER of dabigatran by a small extent.

From Section 1.2. of the Appraisal Committee's preliminary recommendations:

2. *A cost-effectiveness analysis of the sequential regimen outlined above,* ***comparing dabigatran etexilate with warfarin*** *and including sensitivity analyses using a* ***range of assumptions of INR monitoring costs*** *and the* ***assumptions suggested by the ERG****:*

- *a patient cohort representing people with atrial fibrillation in the UK, using the data reported by Gallagher et al. (2008)*
- *a variable (per patient) cost of £115.14 for anticoagulant monitoring*
- *people have dyspepsia throughout dabigatran etexilate treatment, not just in the first 3 months of treatment*
- *disability and mortality risks after stroke are treatment-independent*
- *disutility associated with dabigatran etexilate during the first 12 months of treatment as used in the RE-LY quality of life sub-study (the details are academic-in-confidence).*

The Committee requested a cost-effectiveness analysis of the sequential regimen using the data reported by Gallagher et al. (2008) (1) to inform on the average age and $CHADS_2$ score of the UK AF patient population. The ERG agrees with the manufacturer that the data presented by Gallagher et al. (2008) is not easily adapted to the model, and welcomes the analysis performed using GPRD data for 2010. The data presented by the manufacturer has two additional advantages; first, it is more recent hence more reflective of the current AF population in the UK; second, it refers solely to the AF patients for which dabigatran would be licensed. Table 3 compares the characteristics of the AF population in the UK according to the manufacturer's GRPD analysis with the RE-LY trial population. The $CHADS_2$ score for the AF population in the UK is similar to the distribution observed in the RE-LY trial. However, the average age of the AF population in the UK is older than the average age in the RE-LY trial population.

Table 3 - Comparison of $CHADS_2$ score and average age between the AF population in the UK according to the manufacturer's analysis of the GPRD data for 2010 and the RE-LY trial population in which the economic model is based (adapted from Table 2 of Manufacturer's New Information Requested by the Committee and from the economic model).

	GPRD analysis ("Pradaxa score" of at least 1)		RE-LY trial population	
	Aged under 80 years	Aged 80 years or over	Aged under 80 years	Aged 80 years or over
Average age of cohort	[redacted]	[redacted]	69.1	82.9
% Male	[redacted]	[redacted]	65.0%	57.1%
$CHADS_2$=0	[redacted]	[redacted]	3.0%	0.0%
$CHADS_2$=1	[redacted]	[redacted]	32.6%	13.5%
$CHADS_2$=2	[redacted]	[redacted]	34.4%	41.7%
$CHADS_2$=3	[redacted]	[redacted]	19.5%	23.3%
$CHADS_2$=4	[redacted]	[redacted]	7.7%	15.0%
$CHADS_2$=5	[redacted]	[redacted]	2.4%	5.3%
$CHADS_2$=6	[redacted]	[redacted]	3.0%	1.1%
$CHADS_2$ = 2 and previous stroke	[redacted]	[redacted]	7.3%	0.0%
$CHADS_2$ = 3 and previous stroke	[redacted]	[redacted]	43.1%	11.2%
$CHADS_2$ = 4 and previous stroke	[redacted]	[redacted]	83.6%	69.7%

Table 4 compares the results of the incremental analysis presented by the manufacturer with the results obtained by the ERG after undertaking the corrections described in point 1 (using disability risks post-stroke from whole RE-LY). The results are broadly in line with the ones presented by the manufacturer. As seen in Table 2, using the disability and mortality risks by treatment from the whole RE-LY trial slightly reduces the ICER. The population average age and $CHADS_2$ score were the parameters that most influenced the ICER; the ICER increased from £13,528 per additional QALY to £16,046 per additional QALY. This effect is likely to be due to the higher average age of the AF population in the UK compared to the population in the RE-LY trial. The ICER increases above £20,000 per additional QALY only for the most conservative scenario, i.e. INR monitoring costs of £115.14 and AF population according to the GPRD data.

Table 4 - Incremental analysis using the range of assumptions suggested by the ACD and comparison with the manufacturer's results

Analysis	Parameter changes	Intervention	Mean Costs	Mean QALYs	Inc. Cost	Inc. QALY	ICER	MS ICER
1.	Assumptions as per Point 1 in ACD INR monitoring costs = £241.54	Warfarin	£15,800	7.8147	Baseline			
		Dabigatran	£18,726	8.0310	£2,926	0.2163	£13,528	£14,518
2.	Assumptions as per Point 1 in ACD INR monitoring costs = £414.90	Warfarin	£17,071	7.8147	Baseline			
		Dabigatran	£18,726	8.0310	£1,654.81	0.2163	£7,651	£8,388
3.	Assumptions as per Point 1 in ACD INR monitoring costs = £279.36	Warfarin	£16,077	7.8147	Baseline			
		Dabigatran	£18,726	8.0310	£2,648.60	0.2163	£12,245	£13,181
4.	Assumptions as per Point 1 in ACD INR monitoring costs = £115.14	Warfarin	£14,873	7.8147	Baseline			
		Dabigatran	£18,726	8.0310	£3,852.67	0.2163	£17,812	£18,987
5.	Patient population from MS for GPRD data for 2010	Warfarin	£13,238	7.0128	Baseline			
		Dabigatran	£16,035	7.1871	£2,797	0.1743	£16,046	£17,373
6.	Dyspepsia throughout the dabigatran treatment	Warfarin	£15,800	7.8147	Baseline			
		Dabigatran	£18,817	8.0310	£3,017	0.2163	£13,949	£14,957
7.	Disability and mortality risks treatment independent	Warfarin	£15,800	7.8147	Baseline			
		Dabigatran	£18,967	8.0275	£3,168	0.2128	**£14,884**	£14,071
8.	Disutility associated with dabigatran treatment for 12 months	Warfarin	£15,800	7.8147	Baseline			
		Dabigatran	£18,817	0.2022	£2,926	0.2022	£14,472	£15,578
9.	Analysis 4 combined with 5 to 8. (INR monitoring costs = £115.14)	Warfarin	£12,400	7.0128	Baseline			
		Dabigatran	£16,245	7.1722	£3,845	0.1594	**£24,120**	£22,593
10.	Analysis 1 combined with analysed 5 to 8 (INR monitoring costs = £241.54)	Warfarin	£13,238	7.0128	Baseline			
		Dabigatran	£16,245	7.1722	£3,007	0.1594	**£18,863**	£17,660
11.	Analysis 4 combined with 5, 6 and 8. (INR monitoring costs = £115.14)	Warfarin	£12,400	7.0128	Baseline			
		Dabigatran	£16,117	7.1731	£3,717	0.1603	£23,187	N/A
12.	Analysis 1 combined with 5, 6 and 8. (INR monitoring costs = £241.54)	Warfarin	£13,238	7.0128	Baseline			
		Dabigatran	£16,117	7.1731	£2,879	0.1603	£17,959	N/A

Note:
Analysis 5 to 8 correspond to the analysis 5 to 8 of presented by the manufacturer but using the disability and mortality rates per treatment from the whole population of the RE-LY trial. The INR monitoring costs used were £241.54 per year.

3. *Further comment and consideration of the cost effectiveness of dabigatran etexilate in the **subgroup of people who are already well controlled on warfarin**.*

For the RE-LY trial, time in therapeutic range was calculated for the participants on warfarin. The mean time in therapeutic range was 64.4% (for the analyses excluding interruptions) and 63.4% (for the analyses including interruptions).(2) For the UK centres, the mean time in therapeutic range was 72%.(3) INR control in a controlled setting such as an RCT may not be reflective of clinical practice. An observational study set in Wales focussing on AF patients found that patients treated with warfarin were within therapeutic range 67.9% of the time, 15.4% with INR above 3 and 16.7% with INR below 2. (2)This study was used by the manufacturer in the economic model for the calculation of the risk associated with INR outside target range. We acknowledge that 100% within therapeutic range is equivalent to perfect INR control, which is difficult to achieve in clinical practice. According to the Jones et al (2005), the best controlled patients (as defined by the quartile with best control) were within therapeutic range 83.7% of the time.(2) This value is tested in the sensitivity analysis (see Table 5). For the subgroup of patients whose INR is within range 83.7% of the time, the ICER of dabigatran is £46,989 per additional QALY if their INR monitoring costs are £241.54 per annum. If their INR monitoring costs are £414.90 per annum, then the ICER decreases to £31,386. It is unclear how INR monitoring costs vary by time in therapeutic range. Patients well-controlled on warfarin may require less or more INR monitoring visits. On one hand, more visits may be required to ensure INR remains within target range. On the other hand, good INR control may be intrinsic to the individual, and these particular patients may require fewer visits due to their INR being within range consistently.

Table 5 – Subgroup analysis according to INR control

Analysis	Parameter changes	Intervention	Mean Costs	Mean QALYs	Inc. Cost	Inc. QALY	ICER
10.	Analysis 1 combined with 5 to 8 (INR monitoring costs = £241.54)	Warfarin	£13,238	7.0128			
		Dabigatran	£16,245	7.1722	£3,007	0.1594	**£18,863**
13.	Well-controlled patients TTR = 83.7%[†] & INR costs = £241.54	Warfarin	£12,743	7.0902			
		Dabigatran	£16,310	7.1661	£3,568	0.0759	£46,989
14.	Well-controlled patients TTR = 83.7% & INR costs = £414.90	Warfarin	£13,927	7.0902			
		Dabigatran	£16,310	7.1661	£2,383	0.0759	£31,386

[†]TTR = 83.7% - The ratio between proportion of trial patients with INR below and above target range was applied to the 16.3% (the time outside therapeutic range) to estimate the proportion of patient with INR below 2 and the proportion of patients with INR above 3, in the absence of specific data from Jones et al (2005).(2)

Threshold analysis

According to the manufacturer's analyses, INR would need to be within target range an average of approximately 83-85% of the time for the ICER to be above £30,000 per additional QALY. It is unclear which INR monitoring cost was used for these analyses. Nevertheless, a best-controlled quartile in the study by Jones et al (2005) had INR within target range 83.7% of the time.(2) Therefore, the ICER for this subpopulation would be above £30,000 per additional QALY according to the manufacturer's threshold analysis.

The ERG carried out a threshold analysis to estimate the level of TTR required in order to raise the ICER above £30,000 per additional QALY, assuming an INR monitoring cost of £241.54 per annum and the other ERG changes 5 to 8 from Table 4. INR would need to be within the target range an average of 75-76% of the time for the ICER of dabigatran to be above £30,000 per additional QALY gained.

Comparison between single and sequence dose models

Prior to the ACD the licensing for dabigatran was still to be determined so the ERG followed economic guidelines and performed a full incremental analysis with the treatment strategies submitted by the manufacturer. The multiple models submitted by the manufacturer allow the committee to compare different treatment strategies. Using the MS models, which claim to weigh all the important risks and benefits of treatment, dabigatran 150 mg for patients over 80 years old is more effective than the 110 mg dose in the same age group. The results of the MS models are contradictory to the EMAs preference for the sequence treatment strategy. It is unclear how the MS models differ from the information weighed by the EMA and whether this information would change the cost-effectiveness.

References

1. Gallagher AM, Rietbrock S, Plumb J, van Staa TP. Initiation and persistence of warfarin or aspirin in patients with chronic atrial fibrillation in general practice: do the appropriate patients receive stroke prophylaxis? Journal of Thrombosis and Haemostasis. 2008;6(9):1500-6.
2. Jones M, McEwan P, Morgan CLI, Peters JR, Goodfellow J, Currie CJ. Evaluation of the pattern of treatment, level of anitcoagulation control, and outcome of treatment with warfarin in patients with non-valvar atrial fibrillation: a record linkage study in a large British population. Heart. 2005;91:472-7.
3. Wallentin L, Yusuf S, Ezekowitz MD, Alings M, Flather M, Franzosi MG, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. LANCET. 2010;376(9745):975-83.