Bayer HealthCare
Bayer Schering Pharma

Single Technology Appraisal (STA) of rivaroxaban (Xarelto®) for the prevention of venous thromboemobolism (VTE) in adult patients undergoing elective hip or knee replacement surgery

Clarification on cost effectiveness data in response to Evidence Review Group second queries

27th November 2008

Please note commercial in confidence data have been removed from this version

Comments on the PSA model

All changes described below have been made in file: Xarelto VTE Prevention_Cost Effectiveness Model_Confidential_E&S_PSA_211108.xls

1. ***In the psa input sheet. Cells K123 and K124. There seems to be confusion regarding standard error and standard deviation. The data in E123-G123 have come from a meta-analysis, which will have calculated the standard error of the mean. Therefore assuming the number of patients within a trial is not needed and assuming n=100 will reduce the true uncertainty by 10 (the square root of 100). This can be rectified by setting cells K123 and K124 to 1. This has little effects on the PSA results as these parameters are not key drivers.***

This has been changed in the model.

2. ***The model is driven by the Fatal PE parameter. (see table below comparing the results using Record 4 between Rivaroxaban and Enoxaparin when using univariate sensitivity analyses and a deterministic approach). The model does not change this parameter in the PSA, despite confidence intervals being provided in the main document. This should be amended.***

Record 4: Adjusting bleed

value	[redacted]	[redacted]	[redacted]
Delta C	[redacted]	[redacted]	[redacted]
Delta Q	[redacted]	[redacted]	[redacted]

Record 4: Adjusting VTE

value	[redacted]	[redacted]	[redacted]
Delta C	[redacted]	[redacted]	[redacted]
Delta Q	[redacted]	[redacted]	[redacted]

Record 4: Adjusting symptomatic VTE

value	[redacted]	[redacted]	[redacted]
Delta C	[redacted]	[redacted]	[redacted]
Delta Q	[redacted]	[redacted]	[redacted]

Record 4: Adjusting non-fatal PE (RD)

value	[redacted]	[redacted]	[redacted]
Delta C	[redacted]	[redacted]	[redacted]
Delta Q	[redacted]	[redacted]	[redacted]

Record 4: Adjusting Fatal PE (RD)

value	[redacted]	[redacted]	[redacted]
Delta C	[redacted]	[redacted]	[redacted]
Delta Q	[redacted]	[redacted]	[redacted]

This has been changed in the model.

Please note however that assuming a RD of [redacted] for fatal and non-fatal PE (upper limit of the RD in the Table generated by the ERG review group above) will result in negative rates of PE in the enoxaparin arm since the risk difference ([redacted]%) is much higher than the probability of an event in the rivaroxaban arm. Using the RECORD 4 data (as in the example above) and assuming the largest possible risk difference (0 events in the enoxaparin arm) gives the following results:

Record 4: Adjusting non-fatal PE (RD)

value	[redacted]	[redacted]	[redacted]
Delta C	[redacted]	[redacted]	[redacted]
Delta Q	[redacted]	[redacted]	[redacted]

Record 4: Adjusting Fatal PE (RD)

value	[redacted]	[redacted]	[redacted]
Delta C	[redacted]	[redacted]	[redacted]
Delta Q	[redacted]	[redacted]	[redacted]

* differs from base case at 5th significant figure.

3. In the psa output sheet AV515 and AW515 are blank, rather than the formulae used in surrounding cells. This can easily be rectified.

This has been corrected in the model.

4. The event rates for comparators can become negative. This occurs when the trials are pooled (see symptomatic DVT for hip replacement and fatal PE for knee replacement)

This was due to an error in the RD in the probability of fatal PE in the pooled THR analysis. The number was entered as a percentage ([redacted]%) instead of a decimal ([redacted]). This has been corrected.

In the TKR analysis the negative probability was due to rounding which has also been corrected in response to comment 6.

5. There is no uncertainty in the event probabilities assumed for Rivaroxaban (see cells C68, C70-C75 of the prophylaxis model). In the model these values are held constant (rather than sampling from the confidence intervals), with the RR of the comparators applied to this value. This will underestimate the true uncertainty in the results, as a constant RR (that isn't 1) will have a different effect determined by the baseline probability

This limitation is acknowledged. Given the large sample size in the RECORD studies (n>10,000 treated) we assume that the magnitude of any additional uncertainty introduced by variation in the true rate of with rivaroxaban is likely to be modest.

One way sensitivity analysis considering variation in the event rates with rivaroxaban give the results below. Note that increasing event rates in the rivaroxaban arm in these tests in general improves the economic profile as relative risks are maintained: higher underlying risk results in larger incremental benefit.

Table 1 One way sensitivity analysis results: Varying rates of VTE and bleeding for rivaroxaban within study limits

Sensitivity Analysis	Incremental Cost	Incremental QALYs	ICER
Base Case - RECORD 1	-£83.57	0.0072	Rivaroxaban dominates
Riva VTE event rates upper limit – RECORD 1	-£95.41	0.0078	Rivaroxaban dominates
Riva VTE event rates lower limit – RECORD 1	-£76.81	0.0069	Rivaroxaban dominates
Riva major bleeding rates upper limit – RECORD 1	-£81.70	0.0071	Rivaroxaban dominates
Riva major bleeding rates lower limit – RECORD 1	-£84.84	0.0073	Rivaroxaban dominates
Base Case - RECORD 2	-£0.23	0.0145	Rivaroxaban dominates
Riva VTE event rates upper limit – RECORD 2	-£32.98	0.0162	Rivaroxaban dominates
Riva VTE event rates lower limit – RECORD 2	£23.59	0.0132	£1,785
Riva major bleeding rates upper limit – RECORD 2	-£0.23*	0.0145*	Rivaroxaban dominates
Riva major bleeding rates lower limit – RECORD 2	-£0.23*	0.0145*	Rivaroxaban dominates
Base Case - RECORD 3	-£82.20	0.0021	Rivaroxaban dominates
Riva VTE event rates upper limit – RECORD 3	-£91.94	0.0027	Rivaroxaban dominates
Riva VTE event rates lower limit – RECORD 3	-£73.80	0.0017	Rivaroxaban dominates
Riva major bleeding rates upper limit – RECORD 3	-£81.35	0.0021*	Rivaroxaban dominates
Riva major bleeding rates lower limit – RECORD 3	-£82.79	0.0022	Rivaroxaban dominates
Base Case - RECORD 4**	-£50.62	-0.0097	Rivaroxaban dominates
Riva VTE event rates upper limit – RECORD 4	-£54.30	-0.0096	Rivaroxaban dominates
Riva VTE event rates lower limit – RECORD 4	-£47.31	-0.0099	Rivaroxaban dominates
Riva major bleeding rates upper limit – RECORD 4	-£47.59	-0.0100	Rivaroxaban dominates
Riva major bleeding rates lower limit – RECORD 4	-£52.85	-0.0096	Rivaroxaban dominates

*different from base case at 4th significant figure or below

** please note this study uses a non-UK dose of enoxaparin

6. ***There is inappropriate rounding of input parameters (often to 2 decimal places or 1 significant figure). More accurate values should be used.***

This has been amended in the model.

7. ***The cost-effectiveness plane does not work when the expectation in the incremental QALY for Rivaroxaban compared with the comparator is negative. Please correct.***

The scale of the x-axis was set manually for clarity of display. This now changes automatically to fit the data on the graph.

8. ***Whilst use of the mean estimates of effect (irrespective of significance) have been appropriately investigated, it would be beneficial to be able to set some of the variables where there was no statistically significant difference to equal values for Rivaroxaban and the comparator. If possible, amend the model so that radio buttons (or similar) can allow the user to choose between combinations of parameters using the raw data and selecting equivalence. This would allow subjective scenarios to be analysed more easily than at present, allowing prior beliefs of equivalence to be incorporated.***

We believe that the risk of introducing error by redesigning the model inputs at this late stage exceeds the potential convenience benefit. We, of course, remain happy to conduct additional sensitivity analyses at the request of the ERG, as performed to date.

9. ***The long-term effects of bleeding have not been incorporated within the model for those patients who survive. Approximately 5% of all bleeds will be intracranial, which has a marked effect on utility (see Goodacre et al Q J Med 2006 99; 377-388 for details on both of these parameters). The reduction in total cohort utility due to the disutility of bleeds would be beneficial.***

The cost of treating a stroke has been included in the cost of a prophylaxis related major bleed, assuming that 3% of major bleeds lead to stroke (based on NICE, 2007). Increasing this cost does not have a significant impact on the results.

Adding this would require adding further states to the model – it is not practicable to substantially redesign and quality control the model in the time frame available to respond to these questions. The following calculation indicated that this effect is in any case unlikely to alter the interpretation of the analysis.

The largest difference in prophylaxis related major bleeding between rivaroxaban and enoxaparin were observed in the RECORD 1 trial in which the incremental difference in probability was 0.0027 – 0.0009 = 0.0018 (p=ns). If we assume that 5% of these patients have an intracranial bleed (following the ERG reference above), the difference in intracranial bleeds will be 0.0018*0.05 = 0.00009. Taking the most extreme assumption that all these patients die instantly and this have zero utility for 12.8 years (the average LYs in the analysis) this would be equivalent to a loss of (0.00009*12.8) = 0.001 QALYs. In this case rivaroxaban would still be associated with higher QALYs than enoxaparin since the incremental QALYs per patient is estimated to be 0.0072.

10. ***In the model the utility, without a VTE or PTS remains constant at 0.825 regardless of the patient's age (i.e. it remains this when the patient is 100). We thought you may want to consider this when you respond to the previous issues.***

When we reduced the average utility at age >=75 from 0.825 to 0.78, the incremental QALYs per patient in the analysis of RECORD 1 fell from 0.072 to 0.071. We suggest that any inaccuracy introduced is likely to be small.