Dear [redacted]

The ERG has gone through the updated rivaroxaban model and some apparent errors and omissions in the model have been brought to our attention (see the attachment with a description of the issues). We would like to give the manufacturer the opportunity to address these issues and provide us with an updated model. The ERG indicated to us that most of the errors to be addressed may not be time consuming save for a few. As you may be aware, the ERG report is due on the 8th of December and thus we will be very grateful if we get the updated model by end of day on 27th of November at the latest. We are very keen on staying with the current timelines so your prompt response on this matter will be greatly appreciated. Please feel free to contact me if you have any queries.

Kind regards
David. S. Chandiwana
Technical Analyst
[redacted]

Comments on the PSA model

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 [redacted]. This has little effects on the PSA results as these parameters are not key drivers.
2) The model is driven by the [redacted]. (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]
Delta C [redacted]
Delta Q [redacted]

Record 4: Adjusting VTE

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

Record 4: Adjusting symptomatic VTE

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

Record 4: Adjusting non-fatal PE (RD)

Record 4: Adjusting Fatal PE (RD)

3) In the psa output sheet AV515 and AW515 are blank, rather than the formulae used in surrounding cells. This can easily be rectified.
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)
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
6) There is inappropriate rounding of input parameters (often to 2 decimal places or 1 significant figure). More accurate values should be used.
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.
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.
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.

Dear [redacted]

Further to the e-mail I sent to you last week, I just received a minor comment from the ERG that 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.

Regards
David. S. Chandiwana
Technical Analyst
[redacted]

Delivered via MessageLabs
