Appendix 2

Correspondence from Novartis to NICE dated 17 August 2010

From: karen

Sent: 17 August 2010 13:46
To: Frances Sutcliffe
Cc: Helen Tucker; Lori Farrar; 'nicola.redfern@novartis.com'; Rebecca Trowman
Subject: RE: Everolimus for the second-line treatment of advanced metastatic renal cell carcinoma

Dear Frances

Thank you very much for your email and confirmation of the requested additional analysis.

If we were able to provide the additional analyses by the 29th September would this allow sufficient time for it to be considered at the 13th October Appraisal Committee meeting?

In order to do the work it would be helpful for us to understand some technical points regarding PenTAG's adjustments to our model. If at all possible I would be very grateful if you could provide us with the following.

1) The Weibull curve from PenTAG's adjusted model appears to have an increasing hazard rate which would lead to steadily increasing TPs; however, the TPs in the model appear to fluctuate up and down over time. Would it be possible please to provide an explanation of how these TP's were calculated and hence the reason for this fluctuation?

2) It appears that the there's been some sort of calibration; however, would it not be preferable to use TPs derived directly from the Weibull cumulative density function?

3) Would it be possible please to have the 95% CI's for the two Weibull curves?

4) Would it be sufficient to obtain the estimates of the median survivals implied by the 95% CI RPSFT estimate and vary the TPs in the PSA so that the median survival estimates fall within that boundary?

Many thanks for your help with this.

Kind regards

Karen

ERG Response to Novartis Email dated 17th August 2010

STA 08/208/01: Everolimus for the second-line treatment of advanced and/or metastatic renal cell carcinoma.

PenTAG responses to Manufacturer's Queries (email :18 August 10)

MANUFACTURE QUERY	PENTAG RESPONSE
The Weibull curve from PenTAG's adjusted model appears to have an increasing hazard rate which would lead to steadily increasing TPs; however, the TPs in the model appear to fluctuate up and down over time. Would it be possible please to provide an explanation of how these TP's were calculated and hence the reason for this fluctuation?	For this re-calibration, the key aspect is that the overall survival in the model follows the overall survival represented by the Weibull curves. To do this the transition probabilities have been set such that the modelled survival curves follow as closely as possible the Weibull curves derived from the regression analysis.
It appears that the there's been some sort of calibration; however, would it not be preferable to use TPs derived directly from the Weibull cumulative density function?	In general, we believe a preferable (and much simpler) way to have constructed the model would be to use an 'area under the curve' type model to drive the state populations. Such an approach could have used the curves directly to calculate the state occupancy at each cycle. However given that a Markov approach has been adopted the important thing is that the transition probabilities in the model faithfully represent the correct state populations given the assumed survival curves.
Would it be possible please to have the 95% CI's for the two Weibull curves?	Unfortunately we could not locate our original workings. The curves represent the best fit to the data using regression analysis which can easily be repeated to obtain these values
Would it be sufficient to obtain the estimates of the median survivals implied by the 95% CI RPSFT estimate and vary the TPs in the PSA so that the median survival estimates fall within that boundary?	The important uncertainty to represent in the sensitivity analysis is the hazard ratio for overall survival between Everolimus treatment and BSC. To do this the uncertainty calculated within the RPSFT analysis needs to be represented in the probabilistic sensitivity analysis.