National Institute for Health and Clinical Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Axitinib for the treatment of advanced renal cell carcinoma after failure of prior systematic treatment

Please find enclosed the ERG report prepared for this appraisal.

You are asked to check the ERG report from *Kleijnen Systematic Reviews Ltd in collaboration with Erasmus University Rotterdam and Maastricht University* to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 5pm, *24th October 2012* using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The attached proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

24th October 2012

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Table 1.1, page 11, second column, eighth row The correct proportion of any AEs (grade 3-4) for sorafenib is 52.4%	Please replace 52.2% with 52.4%	Typographical error	Agree

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Table 1.1, page 11, fourth column, fifth row The correct number of sunitinib refractory patients for AEs dataset is N=190/190	Please replace N=126/123 with N=190/190	Typographical error	Agree

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 1.2, page 11, first and second paragraph, 3rd bullet point and page 20, section 3.4, first paragraph, 3rd sentence: The ERG incorrectly state that other outcomes, such as response, quality of life and adverse events were not reported.	Please amend as follows *"Treatment response, quality of life and adverse events were reported for Axitinib in the AXIS study and assumptions were made when axitinib was compared with best supportive care"*	It is not accurate to state that these outcomes were not reported in the manufacturer submission	We do not agree. These outcomes were not reported for the comparison of axitinib versus BSC.

Response, quality of life and adverse events were reported for Axitinib as these outcomes were included in the AXIS study and assumptions were made for best supportive care			

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 1.3, page 12, first paragraph ERG states: "For the sunitinib refractory population, the evidence relies on a simulated treatment comparison, this comparison is not based on randomised treatment allocation, but on a comparison of two single treatment arms; therefore there is considerable potential for bias in the outcomes of this analysis." (Similar observation made in section 1.6.2, page 15; section 1.7, page 16; section 4.2.6, page 57; section 4.3, page 58) It is important to recognize that the STC methodology involves adjusting for differences between the populations in the arms of the two studies. This is a fundamental component of STC which reduces	Please amend the final clause of the sentence to read: "*the STC method adjusts for differences between the studies, reducing the potential for bias, though some potential remains due to limitations in terms of comparability of the studies.*"	The current text does not acknowledge the explicit adjustments included in the STC to reduce bias where comparison of single arms is necessary.	We do not agree. There is no way to assess whether or not the final result is biased.

the potential for bias. This method also relies on the general comparability of the studies being compared, but this is the case for all indirect comparisons. Limitations in terms of comparability of studies (particularly in terms of prior lines of treatments received) have been acknowledged.			

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 1.5, page 13, last paragraph and section 5.3.1, page 101, last paragraph, last sentence: The ERG states that "The manufacturer performed the univariate sensitivity analysis by varying all parameters between plus and minus 20%. This is often not very informative, since this 20% may be either a under- or over-estimate of the true uncertainty. Thus, the ERG performed a univariate sensitivity analysis in which parameters were varied between the limits of their 95% confidence interval (as defined for the PSA). This revealed that for the cytokine	Please acknowledge that this scenario might be clinically implausible and to balance the argument please add the ICER at the lower limit of the 95% confidence interval. More generally, please acknowledge that *"whilst univariate sensitivity analysis using the 95% CIs is useful to understand the impact of this variation to the results, the results of these extreme scenarios should be interpreted with caution as some univariate scenarios could be clinically implausible."*	The current text is not balanced and does not acknowledge that the scenario might be clinically implausible	We do not agree. First, it is not uncommon in oncology to observe a significant change in PFS with no gain in OS. In addition, the upper limit of the 95% confidence interval is not an extreme scenario, it is a possible scenario given the statistical uncertainty about the outcome. Also, we see no reason to make this sort of disclaimers for univariate sensitivity analyses when they were not made for the probabilistic sensitivity analysis.

refractory subgroup, the ICER is extremely sensitive to changes in the HR for the overall survival. At the upper limit of the 95% confidence interval, the ICER would amount to almost £400,000 (with PAS)" As stated in our clarification question response document, the results of the univariate sensitivity analysis with parameter variation based on 95% confidence intervals (as used in the PSA) should be interpreted with caution as some univariate scenarios could be clinically implausible. More specifically, the scenario where the upper limit of the 95% confidence interval for the HR for the overall survival is used in the univariate analysis might be clinically implausible as it would require assuming that the axitinib treatment would have 75% reduction in the hazard of progression with no reduction in the hazard of death.			

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 1.5, page 13, last	Please replace STA with STC	Typographical error	Agree

paragraph, last sentence: The ERG states that "*This is related to the fact that no measures of uncertainty were provided for the STA adjustment factor for the BSC arm*" We assume that ERG refers to the simulated treatment comparison (STC) adjustment factors.			

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 1.6.2, page 15, 3rd paragraph, 2nd sentence. The ERG incorrectly states that "*the submission did not provide a more appropriate analysis and used the overall survival benefit of sorafenib versus BSC from the analysis presented in the TARGET study which censored patients at the point of cross-over*" As explained in our submission *"a more appropriate method of adjusting for cross-over such as Rank-Preserving Structural Failure Time (RPSFT) was not available to reduce the uncertainty introduced by this*	Please replace the second sentence in the relevant paragraph with the wording from the submission: "*A more appropriate method of adjusting for cross-over such as Rank-Preserving Structural Failure Time (RPSFT) was not available to reduce the uncertainty introduced by this bias*"	The current text does not acknowledge that a more appropriate method of adjusting for cross-over was not available	We understand that it was not possible to provide a more appropriate method to correct for cross-over. However, the statement in the report is correct.

bias". As we don't have access to the patient level from the TARGET study we couldn't provide a more appropriate method to correct for cross-over.			

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 1.7, page 16 and comment section, bottom of page 44 The ERG state that they found "one error in the indirect comparison" for the analysis of PFS in the prior cytokine group. They recalculated the HR with what was believed to be the correct HR for PFS (0.44) from the TARGET study and reported a 'corrected' median HR for PFS axitinib vs. placebo of 0.203 (95% CrI 0.132–0.318). However, the value of 0.44 (0.35–0.55) used by the ERG is that reported for the overall population regardless of first-line treatment received in the TARGET study and not the cytokine-refractory population The relevant HR from the TARGET study for the sorafenib vs. placebo comparison in the	Please add statement as per TARGET publication (Negrier 2010[†]): "Progression-free survival was significantly prolonged with sorafenib therapy compared with placebo among patients with and without prior cytokine therapy (respectively 5.5 vs. 2.7 months; hazard ratio, 0.54; 95% confidence interval, 0.45–0.64 and 5.8 vs. 2.8 months; hazard ratio, 0.48; 95% confidence interval, 0.32–0.73)." The value used in the manufacturer's submission was HR 0.54 (as calculated by the ERG) and 95% CI 0.45-0.64, which gives ln 0.54 = -0.616186139 and SE lnHR = (ln0.64 – ln0.45)/3.92 = 0.090 to input to the model. [†]Negrier S, Jager E, Porta C, McDermott D, Moore M, Bellmunt J, et al. Efficacy and safety of sorafenib in patients with advanced renal cell carcinoma with and without prior cytokine therapy, a subanalysis of TARGET. Med Oncol. 2010 Sep;27(3):899-906	The statement is incorrect as there was not an error in the indirect comparison for the cytokine refractory group.	We agree that there was not an error in the indirect comparison for the cytokine refractory group. The error was in Table 17, page 93 of the MS, which specifies the input data for the indirect comparison. This table only mentions the PSF for the ITT population in the TARGET trial. The PFS as report in Negrier et al. (2010) was not reported in the MS.

cytokine-refractory population is 0.54 (0.45–0.64) and this was used in the indirect comparison in our submission. Therefore the correct median HR for axitinib vs placebo is 0.251 (95% CrI 0.165–0.379) as reported in the submission.			

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 1.7, page 16, first paragraph in the section ERG states: "The main issue with this submission is whether a simulated treatment comparison (STC) presents a valid and reliable estimate of the clinical effectiveness of axitinib versus BSC in a sunitinib refractory population. As there is no direct trial evidence it is not possible to compare the results of the STC to any existing evidence so the accuracy and reliability of the results cannot be ascertained." The same may be said about the difficulty of assessing the accuracy and reliability of results from other indirect comparisons when there are no reference results from direct head-to-head trials. Use of	Please amend the final sentence to read "As with any indirect comparison where there is no direct trial evidence, it is not possible to compare the results of the STC to any existing evidence."	The current text does not reflect that the limitations highlighted are common to all indirect analytical methods.	No factual error. We think our text is accurate.

randomization-based methods has the benefit of relying on relative measures of effect, which ensure internal validity, but do not guarantee generalizability, making their use in indirect comparison prone to bias.			

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 1.7, page 16, first paragraph in the section, 3rd sentence and second paragraph in the section, last sentence and section 5.2.10.3, page 99, second paragraph, third sentence ERG states that *"As there is no direct trial evidence it is not possible to compare the results of the STC to any existing evidence so the accuracy and reliability of the results cannot be ascertained"* This is not correct as the submission reported the results of a systematic review to identify clinical studies (RCTs and non-RCTs) reporting efficacy data in patients with advanced/mRCC who received BSC following progression with first-line sunitinib treatment. The results of the	Please acknowledge that the submission reported the results of a systematic review to identify clinical studies (RCTs and non-RCTs) reporting efficacy data in patients with advanced/mRCC who received BSC following progression with first-line sunitinib treatment. The results of these studies identified potentially can be used to ascertain the accuracy and reliability of the results. The model estimates using the STC method for overall survival of BSC were generally higher than those reported in these studies and as result the STC method might underestimate the OS benefit of axitinib versus BSC.	The current text does not acknowledge that the results of the STC could be compared with the existing evidence for the overall survival of sunitinib refractory patients receiving best supportive care	We do not agree. The systematic review found only non-RCT evidence; this cannot be used to ascertain the accuracy and reliability of the results.

studies identified can be used to ascertain the accuracy and reliability of the results. More specifically, the model estimates using the STC method for overall survival of BSC was generally higher than those reported in these studies and as result might underestimate the OS benefit of axitinib versus BSC.			

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 57, second paragraph The paragraph has been misplaced. Also, the same paragraph has been included correctly in page 54	Please delete paragraph	The paragraph has been misplaced	Agree, the same paragraph appears on pages 53 and 56. We have removed the paragraph on page 56.

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 60, last paragraph The ERG has omitted to mention that the STC method was used in the SMC approval of everolimus in pancreatic neuroendocrine tumour.	Please insert additional sentence: “In addition, STC method was used in the SMC approval of everolimus in pancreatic neuroendocrine tumour”	The current text does not acknowledge that the STC method was used in the SMC approval of everolimus in pancreatic neuroendocrine tumour.	We have only discussed previous use of the method in NICE appraisals.

Issue 13

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 5.2.7, second paragraph, last sentence, page 78 The ERG stated that "Note that all these estimates were based on the axitinib and sorafenib groups together". However, this statement applies only to the end-of-treatment utility estimates.	Please amend as follows: "Note that end-of-treatment utility estimates were based on the axitinib and sorafenib groups together"	Statement is incorrect	Agree

Issue 14

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 5.2.10.3, page 99, second paragraph, fourth and fifth sentence ERG states "*The ERG does not agree this conclusion since Table 5.20 shows that exactly half of the scenarios are below the base case ICER. Therefore, it remains uncertain whether the base case ICER represents a conservative choice or not."* In the submission, it is stated that *A recent study carried out by UK health economists including*	Please delete two sentences	Statement is incorrect	We do not agree. Our statement follows directly from the statement made in the submission, last paragraph section 7.7.11: "The scenario analyses examined for the cytokine refractory population indicate that the model base case can be viewed as a reasonably conservative estimate, with the majority of ICERs lower than the base case estimate."

members of the NICE Decision Support Unit (91) which examined different methods for correcting for crossover concluded that this methodology potentially underestimates the true measurement of incremental OS benefit in both simulated and RCT datasets. As the TARGET study data has never been analysed with a more appropriate methodology for dealing with treatment switching in randomised clinical trials (such as a Rank Preserving Structural Failure Time Model, a NICE-validated methodology for correcting for crossover (78)), the overall survival benefit of sorafenib vs. BSC in the TARGET study is uncertain and potentially biased. As a result, the ICER is conservative due to biases introduced by using the HR from the TARGET study which is present in all scenarios and not based on the number of scenarios above or below the base case ICER.			

Issue 15

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 5.2.10.3, page 100, last paragraph, second sentence ERG states that *"current estimates for BSC are conservative*" This statement is clear. Overall survival for BSC is overestimated and therefore the OS benefit for axitinib is conservative	Please amend sentence as follows "*This would indeed imply that overall survival for BSC is overestimated and therefore the OS benefit for axitinib is conservative"*	Wording might be difficult to interpret	We agree that our sentence was a bit condensed, it has been changed.

Issue 16

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
5.3.1, page 108, first paragraph, first sentence: ERG incorrectly states that *"Similar remarks to those made for the situation with PAS regarding the overall distribution of the uncertainty also apply in this case"* This is incorrect as probability of being cost-effective improved for sunitinib refractory patients.	Please delete statement and include specific remarks for the sunitinib refractory patients to reflect that probability being cost-effective improved for sunitinib refractory patients.	Statement is incorrect	This sentence was meant to convey that the remark made about the shape of the distribution with PAS would also apply to the without PAS situation. The suggestion made by the manufacturer, relating to the probability of being cost-effective relate to the location of the distribution. We realize that our statement may not be very clear, and we have opted to delete this statement

Issue 17

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 5.3.2 , page 110, fourth paragraph, first sentence: ICER difference without PAS should be marked as commercial in confidence	Please mark ICER difference without PAS commercial in confidence	Unmarked commercial in confidence information	Agree

Issue 18

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Appendix 1B, page 136, second-paragraph, title Axitinib is referred as Apixaban	Please replace Apixaban with Axitinib	Typographical error	Agree