NICE National Institute for Health and Care Excellence

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Single Technology Appraisal (STA)

Everolimus for preventing organ rejection in liver transplantation [ID559]

Dear [redacted]

The Evidence Review Group, Peninsula Technology Assessment Group (PenTAG), and the technical team at NICE have now had an opportunity to take a look at the submission received on the 24 September 2014 by Novartis. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm** on 03 November 2014. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact [redacted], Technical Lead [redacted]. Any procedural questions should be addressed to [redacted] Project Manager [redacted] in the first instance.

Yours sincerely

Janet Robertson
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

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Section A: Clarification on effectiveness data

Decision Problem

The scope of the appraisal described the comparator as standard immunosuppressive therapy with a calcinerium inhibitor (such as tacrolimus or ciclosporin) and a corticosteroid in combination with azathioprine or mycophenolic acid.

A1. **Priority Question**: The Company submission has excluded ciclosporin from the analysis as "clinical practice for post-liver transplant immunosuppression in the UK is based on tacrolimus combination regimens". However, this is not consistent throughout the submission. For example, both sets of PICOS criteria in Table 14 and Table 15 include ciclosporin. Therefore please clarify your strategy with regards to ciclosporin.

A2. **Priority Question.** The Company submission includes evidence for the other comparator drugs both with and without corticosteroids. However there is limited information about which studies included in the analysis (NMA) used corticosteroids. Please provide details about the use of corticosteroids in the NMA studies and the economic analysis. The results presented (section 7) do not make any references to corticosteroids in the intervention or comparator arms of the model.

A3. **Priority Question.** The Company submission states that 'mycophenolate mofetil is specified in the submission as mycophenolate sodium' but this expression has not been included as a search term. Please confirm why this term has been omitted. If it has been excluded by mistake, please repeat the searches to include this term, highlighting any additional studies which are identified and any additional studies which meet the inclusion criteria.

Clinical evidence

A4. **Priority Question.** On page 41 of the submission, Table 4, it seems that the inclusion criteria for the comparator section is missing from the cell on second column, second row. Please provide this missing information. Also please confirm if the decision to exclude graft function/fibrosis and time to recurrence of hepatocellular carcinoma was solely based on expert opinion or if any searches regarding these outcomes were undertaken beforehand.

A5. Table 7 on page 48 of the Company submission presents the excluded studies. It would be useful to have a brief summary of study results (in terms of efficacy and adverse events for example), particularly the ones with relevance to the decision problem like T2304, which considers everolimus with reduced dose of tacrolimus.

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A6. **Priority Question.** On page 49 of the Company submission it states that "*The patients in the Tacrolimus elimination arm who had not reached Day 180 post-randomisation were discontinued from the assigned study treatment and switched to local standard treatment".* On page 59, the submission subsequently states that these patients "*were expected to be converted to local standard treatment and to enter the follow-up phase".* Please provide more detail as to how these patients (n=231) were dealt with in the analysis. Have they joined the comparator arm of the trial (tacrolimus/prednisolone) and if so, were there any statistical analyses/adjustments to account for this? Also, what is the period referred to as follow-up phase?

A7. **Priority Question.** Page 51 of the Company submission states that patients were randomised into the H2304 study 30 days after transplantation. Please confirm whether this in line with other trials included in the NMA as this could bias the results.

A8. **Priority Question.** For Tables 9 and 10 on pages 66-69 of the submission, please explain why the numbers for deaths and graft losses do not match the numbers in Figures 4 and 5 respectively (pages 61-62) for either of the treatment arms. Please also explain why the reporting of adverse events in Figures 4 and 5 is not consistent with Table 43. In addition, the face validity of the p-value<0.001 for the Kaplan–Meier composite efficacy survival probabilities in Table 9 is questionable when confidence intervals (CIs) include 0. Please explain this.

A9. **Priority Question.** On page 68 of the submission there is no information on the availability of the p-value for severity of rejection, HCC outcome and HCV recurrence. Please clarify this.

A10. **Priority Question.** On page 70, the Company submission presents the subgroup baseline results Please provide some clinical interpretation of the results.

Network Meta-analysis (NMA)

A11. **Priority Question.** The ERG believes that Section 6.7 would benefit from the inclusion of summary tables to synthesise raw data, further description of the methods used to undertake NMA and more detailed interpretation of results. Please provide this information. More specifically, we would like to make reference to Jansen et al, 2011 (submitted by the Company) and the simplified checklist of items to be included in a report of meta-analysis presented in the paper (Table 1) as a reference of what should be included/updated in the manufacturer submission.

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A12. **Priority Question.** Please provide further justification regarding the choice of the clinical endpoints/outcomes considered for the NMA.

A13. **Priority Question.** The Company submission identified potential treatment modifiers (described in Table 18). Please explain why these covariates were not taken into account with treatment-by-covariate interactions in a meta-regression model to try to reduce the impact of bias.

A14. **Priority Question.** Please summarise the information provided on pages 87 – 92 in a table. As indicated in Jansen et al 2011, the ERG considers that the key study and patient characteristics of each study included in the NMA should be provided in a Table format. This is essential to judge whether there are differences across trials that might act as effect modifiers, causing bias in the analysis. Furthermore, point estimates and the corresponding measures of uncertainty should be reported for each treatment arm of the individual trials, as well as the relative treatment effects for each of the RCTs included in the NMA. This allows comparisons between the pooled results of the NMA and the individual study results. Please ensure that data on the number of UK patients in the trial, dose of tacrolimus and the baseline estimated glomerular filtration rate (eGFR) are included as these will be crucial for the generalisability of results?

A15. **Priority Question.** Please explain the rationale behind the selection of the uniform parameters (0 and 5) for the prior distribution selected for the heterogeneity parameters.

A16. **Priority Question.** Please provide further justification as to why the fixed effects model was chosen over the random effects one (beside the DIC scores). NICE DSU guidance (Dias et al, 2014) suggests that the posterior mean of the deviance is presented with the DIC statistics to ensure that the model chosen provides the best fit to the data. Leverage plots would also be useful.

A17. **Priority Question.** Please provide the following information relating to Tables 23 to 37: 1) present the probability of being the best treatment for each treatment as a ranking of the drugs' effectiveness; 2) explain the similarity of the results for the inconsistency and consistency models - for example, on Table 23 all point estimates (with the exception of one) are <u>exactly the same</u>, with credible intervals (CrI) following the same pattern; 3) provide further interpretation of the results from a clinical and biological point of view <u>on all tables</u>, for example, Table 28 presents CrI between 0 and 267900 for everolimus + reduced tacrolimus compared with azathioprine + standard tacrolimus. What is the clinical relevance of such high values?

A18. **Priority Question.** On page 104 the Company submission reports that at 12 months everolimus+reduced tacrolimus is more efficacious than mycophenolate mofetil (MMF) +reduced tacrolimus (Table 32). Please provide a clinical

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interpretation for these results since the benefit of improved renal function is thought to come from reduced dosages of tacrolimus (which both everolimus and MMF present in this case). Please also explain from a clinical point of view why in Table 33 everolimus+reduced tacrolimus is comparable (and not more efficacious as in Table 32) than MMF+reduced tacrolimus. Please also explain why everolimus+reduced tacrolimus is so much more effective than standard tacrolimus, In addition, why are MMF+reduced tacrolimus and azathioprine+ciclosporin comparable and more effective than standard tacrolimus respectively, when everolimus+reduced tacrolimus is supposed to be comparable to both MMF+reduced tacrolimus and azathioprine+ciclosporin in terms of relative effectiveness?

Section B: Clarification on cost-effectiveness data

B1. **Priority Question.** The ERG is not convinced that 3 month cycles can capture all the relevant outcomes for the disease modelled. For example, on page 153 the Company submission states that *"Three days of high dose steroids are used to treat detected acute rejection (for example, 1000mg of methylprednisolone) with around 85 to 90 percent success rates of therapy. If this therapy fails, it is repeated again 3 days later with the same success rate."* This suggests people should be able to progress through the states in the model much faster than is currently allowed. Please clarify whether all the clinical outcomes which take place in shorter periods of times are captured in the model, and if so, please demonstrate this.

B2. **Priority Question.** On page 142, Table 46, please clarify the renal related death estimation process. The probability of death in this state should be related with renal functioning.

B3. **Priority Question.** For Table 55, on page 159 please clarify how the tacrolimus dosages used in each treatment regimen compare with the UK standard practice (in terms of tacrolimus dosage).

B4. **Priority Question.** It is important for the ERG to understand why the ICERs in the Company submission are so high. Please include some rationale for this and (if deemed relevant) compare the ICERs in this submission with ones previously presented in the appraisal process for any of the comparator drugs.

B5. **Priority Question.** Please provide the calculations used to derive the parameters in Tables 53 and 54 for all treatment arms, with regards to taking the NMA odds ratios (ORs) presented in Tables 23 to 37 (section 6) and estimating

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the probabilities used in the model. Please also explain the rationale behind the sources selected for the model parameters presented in these tables.

B6. **Priority Question.** On page 149 the Company submission states that *"The expected decrease (as displayed in Table 53) was then applied to the patient in the first year post transplant and their eGFR level after 12 months was then calculated and a patient was assigned to the appropriate CKD [chronic kidney disease] state as per the model schematic (section 7.2.2)."* Please confirm that the expected decrease in eGFR for each treatment arm is the same irrespective of the eGFR starting value. Please provide the calculations undertaken to estimate the absolute eGFR decrease and the respective relative effectiveness of the drugs between treatment arms presented in Table 53.

B7. **Priority Question.** Please clarify if any searches were undertaken on utility data used for the renal sub-model. If not, please provide the rationale for this and for selection of the values presented. Also for Table 58, for the disutility data sources, please provide the same details as for the utility data (Table 57). Some disutility values were based on assumptions. Was there any clinical input informing these assumptions? Were any searches done for disutility data?

B8. **Priority Question.** On page 180 the Company submission states that ***"the baseline time point was immediately (one day) post-transplant***. *These patients entered in the model state Stable Post-Transplant. Thus, the baseline HRQL score was equalled to the score in the first cycle. However, disutility was applied upon entry if the patient experienced an adverse event upon entering the mode*l". However throughout the submission it is mentioned that baseline period was considered 30 days post-transplantation. Please clarify this.

B9. **Priority Question.** Please provide more detail on how the 'utility values adjusted for informative dropout' (Table 60) were obtained.

B10. Please confirm whether the resources presented in Table 63 represent the resource use per 3-month cycle.

B11. **Priority Question.** Table 64 is based on a patient average body weight of 73.9kg. Please provide the rationale for choosing this value and explain why some of the unit costs were taken from sources other than BNF.

B12. **Priority Question.** Please provide the calculations used to derive the parameters in Table 67. More specifically, please explain how the survival probabilities were obtained and why survival and hepatic graft survival include 24 month probabilities?

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B13. In table 65, the cost of testing eGFR (estimated glomerular filtration rate) has been referenced as the cost for EGFR-TK mutation testing, which is a test undertaken for people with non-small-cell lung cancer. Please provide the correct reference for this cost and provide an updated cost if this is incorrect.

Section C: Textual clarifications and additional points

C1. **Priority Question.** Please clarify how the MEDLINE C/E searches have been combined. Page 271 of the submission, line 40, refers to the action 'or/40-43' but there are no lines 42 or 43. Please confirm that line 40 should read '4 AND 7 AND 39' and that line 41 should be a date limit (1990-Current)?

C2. **Priority Question.** In the effectiveness searches (page 252) please confirm that line 10 of the MEDLINE search (line 11 of the EMBASE search, line 10 of the CENTRAL/CDSR search, and Line 3 of the DARE search) is correctly presented. Is the ERG correct in its interpretation that the line should read: (cellcept or mycophenolic acid or morpholinoethyl ester…)? Otherwise the concern is that mycophenolic acid is not being searched as a free-text term and this might impact on the identification of studies.

C3. **Priority Question.** Please clarify why the Company submission has not used free text search terms for the 'transplantation' concept in their search of CENTRAL and CDSR.

C4. **Priority Question.** Please confirm the data parameters of the resources searched (i.e. OVID MEDINE 1946 to September Week 4 2014).

C5. Please confirm precisely how the searches were limited to human only populations (taking the MEDLINE clinical effectiveness searches as an example, line 22, p252 of the submission).

C6. **Priority Question.** In the first paragraph of page 159, the Company submission states that "no further changes in this clinical outcome were assumed". Please clarify which outcome you are referring to?

C7. Please explain the rationale behind the selection of interval ranges used for probabilistic sensitivity analyses (PSA).

C8. **Priority Question.** Throughout the submission 12 month, 24 and 36 month data are referred to. However, only 12 month data are included in the economic analysis. 24 and 36 month data could have been used on different occasions, for example to validate model estimates or to obtain adverse events data. Please

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explain why these longer-term data have not been used at all and also why they are not consistently presented in the clinical section.

C9. **Priority Question.** The Company submission highlights that one of the limitations of the evidence base is the UK comparator dose. It also states that a blood concentration of <5ng/mL would be considered low-dose tacrolimus in the UK. The H2304 12 month study reports a blood concentration between 3 and 5 ng/ml however. Please clarify whether the submission is referring to the comparator studies. Please also clarify the implications of this limitation for the results presented in terms of everolimus cost-effectiveness.