18 August 2010

NHS
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By email only

Dear Martin,

Re: Single Technology Appraisal – Vinflunine for the second line treatment of transitional cell carcinoma of the urothelial tract

The Evidence Review Group Southampton Health Technology Assessment Centre and the technical team at NICE have now had an opportunity to take a look at submission received on the 23 July 2010 by Pierre Fabre. 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 **17:00, 2 September 2010**. 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 Sally Gallaugher – Technical Lead (sally.gallaugher@nice.org.uk) Any procedural questions should be addressed to Kate Moore – Project Manager Kate.Moore@nice.org.uk in the first instance.

Yours sincerely

Helen Chung
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

A1. (Page 21: Table A3, decision problem). Please explain asterisk in outcomes box.

A2. (Page 24). Please explain why non-inferiority trials were explicitly stated as an exclusion criterion whereas equivalence trials were not.

A3. (Page 25). Please supply a list of the 77 excluded references grouped by reason for exclusion, plus any other excluded references that relate to second line therapy.

A4. (Page 30: Table B6) Was the difference in performance status between the VFL+BSC arm and the control arm statistically significant?

A5. (Page 30: Table B6). Were the differences in prior cisplatin therapy and prior carboplatin therapy between the vinflunine plus BSC arm and the control arm statistically significant?

A6. (Page 30: Table B6). Please clarify sample size for prior CTx.

A7. (Page 31). Response rates are listed as secondary outcomes. This appears inconsistent with an earlier statement in the manufacturer submission (MS; p. 21) that there would be no comparative data for response rates in this end of life population with a heavy tumour burden. Please clarify.

A8. (Page 31). Quality of life and clinical benefit are included as outcomes but are not classified either as primary or secondary outcomes – instead they are referred to as “other criteria”. What does this mean and how does it influence their analysis and interpretation?

A9. (Page 31-32). Please clarify the relationship between the independent review committee (IRC), independent review panel (IRP), independent response review panel (IRRC) and Synarc. It is stated later in the MS that the IRC was blinded to the intervention received. Does this blinding apply to IRP, and IRRC and Synarc?

A10. (Page 32). Please explain the rationale for the superiority hypothesis. Only two publications referred to on page 32 (von der Maase 2000; Sternberg 1988) and two different publications are referred to on page 38 (Culine et al. 2006; von der Maase et al. 2006 – the latter not in the reference list).

A11. (Page 32). Please clarify the meaning of the bullet point stating “A follow up time of 6 months after randomisation of the last topic”.

A12. (Pages 32-33). The MS reports that data were censored at the start date of further chemotherapy or the date of last news but it is unclear what this means. Please provide further explanation of the method of censoring used and the implications of these censored data when interpreting the statistical analyses.

A13. (Page 33). The MS refers to prognostic factors including “the presence of lymph nodes”. Please clarify whether this means the involvement of lymph nodes/presence of metastases rather than just presence of lymph nodes.

A14. (Page 38: Table B8). Results for vinflunine plus BSC are exactly the same for all 3 analyses (ITT, eligible ITT and per protocol) even though the groups have different numbers of patients. Please confirm if these are the correct data.

A15. (Page 39). Please provide rationale (and give reference if applicable) for the choice of prognostic factors in the planned multivariate analysis. Please also explain why the involvement of lymph nodes/presence of metastases is not included in this analysis.

A16. (Pages 41 & 42: Table B10). Please clarify what is meant by an extended multivariate analysis and why the results for this analysis in the ITT population differ from the results for the pre-specified multivariate analysis in the same population presented table B9 (page 40).

A17. (Page 43). It is not clear why results of a per protocol (PP) analysis are reported, as this is not the analysis population used to test superiority. Although PP may be used to support results from an ITT analysis no discussion of this is given. Please clarify.

A18. (Pages 44 & 46). Missing footnote. Please clarify whether the footnote “a” in Figures B5 and B6 refers to the stratified log rank test, as in the preceding figures.

A19. (Page 45). Please clarify why the results for disease control rate (DCR) but not for progression-free survival (PFS) are different to those reported in the primary publication (Bellmunt et al., J Clinical Oncology 2009; 27: p. 4456). DCR values in the primary publication are 41.1% and 24.8% for the two study groups whereas in the MS (p. 45) DCR values of 55.1% and 27.1% are given.

A20. (Pages 59 & 60). The MS reports the median overall survival as 7.9 months (95% CI 6.67 to 9.69 months). However, in the primary publication (Vaughn et al., Cancer, 2009; 115: p. 4113) the corresponding data are 8.2 months (95% CI 6.8 to 9.6 months). Please explain the discrepancy.

A21. (Pages 59 & 60). The rate of disease control, duration of disease control, response duration, and progression-free survival are not reported in the primary publication (Vaughn et al.). Please clarify the source of these data.

A22. (Page 124). The question “Were there any unexpected imbalances in drop-outs between groups?” is answered “yes”. This appears inconsistent with the text, which states there were no differences in drop out rates. Please clarify.

A23. The vesicant nature of vinflunine is not mentioned in the MS. Please explain whether there would be clinical, safety or cost implications of using a vesicant.

Section B: Clarification on cost-effectiveness data

B1. (Page 69; section 6.2.1). The MS states that the population modelled consists of advanced or metastatic TCCU patients who failed a prior platinum-containing regimen. Bellmunt et al. 2009 describe the trial participants as patients with locally advanced or metastatic TCCU with documented progression after first-line platinum. Please confirm whether trial participants correspond to patients who stopped responding to a platinum-containing regimen?

B2. (Page 76; table B31). The hazard ratio for overall survival (OS) shown in the table is 0.70. The text states this is based on the data from study 302 for the eligible ITT patient population. However, in Figure B4 (page 40), the hazard ratio is shown as 0.78. Please confirm the actual value used in the model. If this differs from 0.78, please explain the reason for this discrepancy.

B3. (Page 76; table B31) The hazard ratio for progression-free survival (PFS) in the eligible ITT population shown in the table is 0.47. However, only the hazard ratio for the ITT population is provided in the clinical effectiveness section (Fig B6, p 46, HR 0.68). Please supply the equivalent PFS curve as that in figure B6 for the eligible ITT population.

B4. (Page 76; table B31). The mean values and standard errors for OS and PFS hazard ratios presented in this table do not match those in table B32 (p78). Please explain the reason for this discrepancy.

B5. (Page 78; table B32). Please provide the source of the estimates (mean and SE) used for the risk of adverse events with vinflunine plus BSC. Please explain the differences between these values and those presented in Table B34 (page 86).

B6. (Page 96; table B39). Please explain the methodology for calculating the cost for palliative radiation therapy and how the other costs shown in the table have been derived.

B7. Please state when a reference for the current price of vinflunine, for example BNF / MIMS, will be available.