15 March 2011

NHS
National Institute for Health and Clinical Excellence

NICE
Midcity Place
71 High Holborn
London
WC1V 6NA

Tel: 0161 870 3154
Fax: 020 7061 9792

Email: Kate.Moore@nice.org.uk

www.nice.org.uk

Dear [redacted],

Re: Single Technology Appraisal – Mannitol dry powder for inhalation for the treatment of cystic fibrosis

The Evidence Review Group *Kleijnen Systematic Reviews* and the technical team at NICE have now had an opportunity to take a look at the submission received on the 11th February 2010 by Pharmaxis. 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. Clarification questions which are considered a priority are indicated within the document.

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 NICE by **5pm, 29 March 2011.** 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 Pall Jonsson – Technical Lead (Pall.Jonsson@nice.org.uk) or Rebecca Trowman – Technical Adviser (Rebecca.Trowman@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,

Janet Robertson
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: PRIORITY QUESTIONS

A1. Please provide the complete clinical study reports for the trials 301 and 302.

A2. Please also provide complete clinical study reports for the trials 201, 202 and Robinson 1999.

A3. Please provide the latest information regarding the license indication that you have available

A4. According to the expected license indication, there are two interventions for two different populations:

- Mannitol with rhDNase for all adult CF patients; and
- Mannitol alone for adult CF patients who are ineligible, intolerant or inadequately responsive to rhDNase.

Please could you clarify:

- Why are there no separate data/analyses for mannitol alone in CF patients who are ineligible, intolerant or inadequately responsive to rhDNase?
- Why is there no separate attempt to perform an indirect comparison (versus hypertonic saline) for these two populations/comparisons?
- Why the economic model is not separately focussed on these two populations/comparisons?
- Please could you run the economic model for these two populations separately (mannitol plus rhDNase versus rhDNase plus BSC in all adult CF patients; and mannitol alone versus BSC for CF patients who are ineligible, intolerant or inadequately responsive to rhDNase) and please provide all the necessary data for the ERG to replicate the economic model in these two populations?

A5. There seem to be a number of inconsistent assumptions in the MS:

- On page 14, it is assumed that low dose mannitol has no adverse events ("the safety profile of Bronchitol, [mannitol 400 mg] BD can be assessed in the adult population as compared with the control group [50 mg mannitol]")

- On page 26, it is assumed that low dose mannitol can be considered similar in effectiveness to BSC ("Best supportive care will reflect the control arm from the two phase III studies")

- On page 81, it is assumed that low dose mannitol may show some degree of clinical activity ("The low dose formulation of Bronchitol (control as used in DPM-CF-301 and DPM-CF-302) may show some degree of clinical activity which would preclude its use as a common link to the hypertonic sale RCTs (control reported to be 0.9% saline [isotonic saline] as in 7/8 studies)").

Please provide an explanation for these apparent inconsistencies and, preferably, provide some evidence to support the assumptions.

A6. The ERG note that the current report does not assess the cost-effectiveness of mannitol compared with hypertonic saline as outlined in the scope. Please could you consider providing additional economic analysis of mannitol as a replacement for hypertonic saline (Chapter 6.2)?

A7. Please explain why the probability to switch to control in the model is only based on the response rate found in the trial, not including the withdrawal rate. Please could you conduct an additional analysis including withdrawal rate for switching to control treatment. (Chapter 6.3)

A8. Please could you provide data (per trial and the trials combined) regarding unacceptability of mannitol to patients, drop-out rate, non compliance due to side effects both for mono-therapies and combination treatments?

A9. The ERG note that the analyses in appendix 15 indicate that treatment is not a significant covariate in predicting HUI2 utility score. (Chapter 6.4 and 6.5). Please could you clarify why costs and utilities in the model are treatment dependent?

A10. Please explain why probability of hospitalisation due to exacerbation is treatment independent, but length of stay in a hospital is treatment dependent (Chapter 6.4 and 6.5)?

A11. Please could you provide a sensitivity analysis with treatment independent costs and utilities (Chapter 6.4 and 6.5)?

A12. In the model there is an implicit assumption that best supportive care is equal to best supportive care + rhDNase in terms of effectiveness. Please could you provide

details of any evidence for this assumption; the ERG note that there is a Cochrane review showing effects of rhDNase (Wark et al. CD001506)?

Section B - Clarification on clinical and cost effectiveness

B1. Please could you clarify how many patients in trials 301 and 302 did not pass the mannitol tolerance test (MTT)? Please could you also clarify which adverse events were reported during the screening period?

B2. Please explain the rationale for the health state definitions in the economic model. The ERG note that the relative definition of the health states 'CF' and 'improved CF' implies a very heterogeneous patient population in each health state (with respect to FEV1, and exacerbation rate; utility and costs can be expected to differ due to variation in absolute FEV1).

B3. Please explain the role of categorising FEV1-predicted in the model (>80; 60-79; 40-59; <40) in relation to age and BMI.

B4. Table 67. Please explain why no interaction terms were included in the BioGrid analysis of survival (Adults only). Please also clarify why the analysis excluded people aged over 47 years when there is a model that includes all ages? (Chapter 6.3.7)

B5. Please explain how the hazard ratio for FEV1 (Table 69) was used (transformed) for transition probability 'pDie' in the model. Please could you clarify which baseline function or baseline probability was used when applying the hazard ratio. (Chapter 6.3.7)

B6. Please explain why BMI is included in the regression model if it is not included in the health economics model? If BMI is excluded because of non-significance, the Cox model should be rerun with only ppFEV1 as a covariate (6.3.7)

B7. Please explain the reason why in bullet point 2 of the description of how the utility scores were estimated, the change from baseline is calculated separately for V3 and V4. It is not clear how this is used to fill table 74. (Chapter 6.4.9)

B8. Table 74: please explain why only the paper by Anyanwu was used to estimate utility pre- and post-lung treatment when 3 relevant references were found. (Chapter 6.4.9)

B9. Please explain how the utilities at the various time points post-treatment were combined to in one utility estimate of 0.8. (Chapter 6.4.9)

B10. In Table 82, please provide a column for the total population (i.e. mannitol plus control). Additionally, please provide the numbers on which each mean total cost is based, and the standard errors of these means. (Chapter 6.5)

B11. In Table 85, please explain why an exponential distribution was assumed for the cost of pulmonary exacerbation, cost of lung transplant and cost post-lung treatment. (Chapter 6.5)

B12. Table 95 Results PSA – Monotherapy: Please provide 2 separate tables instead of table 95, one giving the results for the patient population for which mannitol is second line treatment and/or contraindicated and one giving the results for the patient population for which mannitol is add-on drug. (Chapter 6.7.6)

B13. Please clarify the mean ICER of £43,703 per QALY gained and its confidence intervals, how has this been obtained? Also please clarify to which population this ICER applies. (Chapter 6.7.8)

B14. Please clarify for figure 25 to which population each curve applies. (Chapter 6.7.8)

B15. Please provide scenario analysis on the percentage of compliance / adherence to treatment. (Chapter 6.7.9)

B16. Please provide life years in specific health states for the comparators as basic outcome of the modeling exercise. (Chapter 6.7.9)

Section C – Clarification on literature searches

C1. Please provide further details regarding the search strategy presented in 9.4.4 (pg 220) in order for the ERG to replicate it. Section 9.4.1 states that Medline, Medline In-Process and Embase were searched via the Ovid host, however the strategy presented in 9.4.4 does not appear to be Ovid search syntax and did not work when put into Ovid Medline. Please clarify whether a PubMed search strategy was utilised, which databases were searched and which database hosts were used.

C2. Please provide complete search strategies for each of the databases searched (e.g. Medline, Medline In-Process, Embase, Cochrane Library etc.), including all search terms.

C3. Appendix 10 (page 227)

- Please clarify why the databases, Embase and EconLit were not searched.
- Please clarify why the PubMed searches were limited to English language only?

C4. Appendix 12 (page 233-4)

- Please clarify why the databases, Please clarify why, Embase, NHS EED and EconLit were not searched
- Please clarify why the PubMed searches were limited to English language only?
- Please clarify why the PubMed search strategy reported as retrieving 177 references on page 234 but 119 references on page 148.

C5. Appendix 13 section 6.5 (pg 234-235).

- Please clarify why the databases, Embase and EconLit were not searched.
- Please clarify why the PubMed searches were limited to English language only?

Section D: Textual clarifications and additional points

D1. In Table 62, the relative risk of an exacerbation with mannitol (responders) is 0.66. In Table 56 the RR is 0.65, please clarify. (Chapter 6.3.6)

D2. In Table 71, please clarify whether the Standard Deviations presented are Standard Errors of the mean or observed standard deviations? (Chapter 6.4.3)

D3. Please clarify what is meant by “(0)” and “section 0” on page 32

D4. Please provide references for the studies identified in Appendix 4 and 5.