Forest

[redacted] Tel: [redacted]

2 May 2012

Mr R Fernley
National Institute for Health and Clinical Excellence
Level 1A, City Tower
Piccadilly Plaza
Manchester
M1 4BD

Forest Laboratories response to NICE Assessment Report

Colistimethate sodium powder and tobramycin powder for inhalation for the treatment of pseudomonas lung infection in cystic fibrosis [ID342]

Dear Mr Fernley,

This document addresses the request to provide comments on the Assessment Report developed by the Assessment Group, School of Health and Related Research (ScHARR) Sheffield on behalf of NICE.

The economic analysis submitted by Forest Laboratories to NICE was not intended to be a full and comprehensive economic analysis, principally because Forest Laboratories were aware of the difficulties associated with the development of health economic evaluations for cystic fibrosis interventions – difficulties highlighted in the Evidence Review Group (ERG) report. We expected that the analysis developed by the ERG during the review process, reflecting their greater resources and expertise, would take advantage of the analysis provided by Forest Laboratories in building a more sophisticated assessment. Our intention was to contribute to the review process where Forest Laboratories could add insight (for example through the utility mapping study), rather than present an exhaustive analysis.

Our review of the analysis conducted by the ERG has highlighted the following areas of potential weakness:

Treatment pathway

- There was no comprehensive pathway analysis that would illustrate the context in which cystic fibrosis (CF) treatments are used in practice (e.g. Tobi off-months where other antibiotic treatments may be required)[1]
- Use of Colobreathe has not been shown to lead to resistance in the COLO/DPI/02/06 trial, whereas TOBI leads to an increase in minimum inhibitory concentration (MIC). The analysis provided by the ERG report does not include the cost implications of increased IV antibiotic use.

Decision population

- The model that was developed appears to provide a simulation of a cohort of patients aged 21 and above, which we believe inaccurately reflects the population to which the reviewed interventions are intended. Therefore we believe that:
    - The model should have included the younger population, reflecting both the clinical trial population and the patient profile in clinical practice
        - The assumptions used by the assessment group exclude over 40% of the patients population enrolled in the Colobreathe trial. Furthermore, the excluded group also represents those in whom Colobreathe similarly shows clinical benefit
    - Despite patient level data being requested by the assessment group, it would appear that no patient level analysis was performed. A patient level simulation rather than a cohort analysis may have been a better approach, given the heterogeneous patient population, in age and other characteristics

Trial design

- The TOBI population in the Colobreathe trial only included TOBI tolerant patients, resulting in an inaccurate representation of the cohorts compared in the analysis.

Clinical benefit

- The use of absolute FEV_1 values may not provide an accurate estimation of clinical benefit. Rather, we suggest that the relative value of FEV_1% also be considered to take into account differences in patient characteristics, and the effect of aging – in cystic fibrosis there is much debate about the relevant endpoint, which we do not feel this review has clarified
- It appears that mortality has not been built into the model, despite the existence of several published studies linking FEV_1 to mortality:
    - The assessment appears to deny a link between FEV_1 and mortality, which was first demonstrated in the Kerem *et al.* study.[2]
    - A more recent study by Goerge *et al.* (2011)[3] highlights the correlation between FEV_1 and mortality. *"On the basis of work by Kerem et al in 1992, a forced expiratory volume in one second (FEV_1) of less than 30% predicted has been generally accepted as the level of lung function at which median mortality within two years is greater than 50%."* Furthermore, this study compared mortality of patients with <30% of predicted FEV_1 between two datasets (1990 and 2003). *"Median survival for patients who entered the cohort most recently (2002-3) was 5.3 years, more than twice that for those who entered the study in the early 1990s, when median survival was less than two years, similar to the value published by Kerem et al. in 1992."*

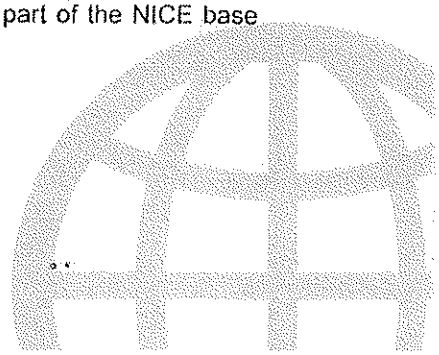
      Although the available data and FEV_1-mortality correlation may have changed over time (reflecting improvements in the clinical management of CF), there is still a clear link between FEV_1 and mortality.
    - A disease model developed by Buzzetti et al.[4] also used the correlation between FEV_1 and death, to accurately predict mortality rates in their validation sample.

Utility estimates

- The Assessment Report commented on the low number of patients available in the estimation dataset (93 patients used for utility mapping purposes), yet it appears that the utility data used in the de novo analysis by the ERG was derived from a pool of 75 patients
- Furthermore, the mean age of patients used to derive utilities in the ERG model was 28 years old, compared to an average of 21.1 years in the Colobreathe trial population

Cost of interventions

- It appears that the costs of antibiotics taken during the off months of TOBI treatment have not been captured in the model. In addition, the costs of replacing nebuliser spare parts and other consumables have not been accounted for in the ERG analysis
- Although patients numbers are limited, the proposed model should have included transplantation and associated downstream costs (as well as mortality), which contribute significantly to the economic burden of CF treatment. It should be noted that those patients who received lung transplantation required 56 weeks to regain baseline FEV_1 function
- An attempt to estimate treatment administration time and the effects on carers would have been useful to better quantify the cost of treatment. Reduction in carer and supervision time could have a significant impact on loss of productivity and therefore on the costs attributed to the interventions. A recent paper by Sansgiry et al. commented on the importance of including indirect costs associated with the disease when modelling.[5]
- The impact on carer's health related quality of life and time was not considered in the analysis. This is likely to represent an important cost to carers and potentially in some cases, where paid carers are involved, to Personal Social Services (PSS) – part of the NICE base case.



Sensitivity analyses

- The probabilistic sensitivity analysis conducted by the assessment group model suggests that Colobreathe is not cost effective for the majority of the scenarios investigated. However the COLO/DPI/02/06 trial demonstrated non-inferiority compared to Tobi; the results of the cost-effectiveness analysis should also indicate a similar trend, yet the initial analysis shows differences that we believe do not reflect the outcomes of the Colobreathe trial. Furthermore, the sensitivity analyses performed by the assessment group are unlikely to reflect the uncertainty surrounding the trial since none of the alternative analyses represent non-inferiority (ICER approaching 0).

Overall, the analysis provided by the assessment group and the presentation of key results such as the ICER does not seem sufficiently robust and clear. It is likely that other reviewers of this report may be led to misinterpret the findings. It is our view that the conclusions drawn from this analysis should be considered as speculative.

We hope that the Assessment Committee will take into account the contents of this letter along with the need for better treatments for cystic fibrosis, the clinical evidence in support of Colobreathe, and the wider benefits for both patients and caregivers. We also hope that the Assessment Committee will place less weight on the modelling as the Evidence Review Group has already commented on the difficulties of modelling this condition.

Yours sincerely,
For Forest Laboratories UK Ltd.

[redacted]

References

1Royal Brompton Hospital. Clinical Guidelines: Care of Children with Cystic Fibrosis. Available at: www.rbht.nhs.uk/childrencf. Published January 2011.

2 Kerem E, Reisman J, Corey M, Canny GJ, Levison H. Prediction of mortality in patients with cystic fibrosis; N Engl J Med 1992 Apr 30;326(18):1187-91.

3 George PM et al.; Improved survival at low lung function in cystic fibrosis: cohort study from 1990 to 2007; BMJ 2011;342:d1008.

4 Buzzetti R, Alicandro G, Minicucci L, et al. Validation of a predictive survival model in Italian patients with cystic fibrosis. J Cyst Fibros. 2012 Jan;11(1):24-9.

5 Sansgiry SS, Joish VN, Boklage S, Goyal RK, Chopra P, Sethi S. Economic burden of Pseudomonas aeruginosa infection in patients with cystic fibrosis. J Med Econ. 2012;15(2):219-24.