Comment From Dr R I Ketchell. Clinical Expert

Re Multiple Technology Appraisal (MTA)

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

Dear NICE:

Having already provided to you an expert written personal statement with regard to the ongoing multiple technology assessment for colistimethate sodium and tobramycin powder for inhalation for the treatment of pseudomonas lung infection in cystic fibrosis patients, I would now like to take this opportunity to provide my personal comments on the draft assessment report prepared and publicised by NICE on October 24th 2012 (ID342).

As an employee of the Cardiff and Vale University Health Board, I am specifically responsible for the care of 238 adult cystic fibrosis patients across Wales. As recognised, the subset of CF patients with chronic pseudomonas aeruginosa infection have a significantly worse prognosis and quality of life than those with intermittent infection as the chronic nature leads to and accelerates the progressive decline in lung function characteristic of CF and is central to the respiratory related morbidity and mortality. The advantages of inhaled antibiotic therapy for PsA infection in CF has been recognised for nearly 40 years. The hypothesis is that an antibiotic delivered directly to the site of infection will be maximally effective, achieving sputum antibiotic levels far in excess of those achievable by intravenous administration without the risks of systemic toxicity. With this in mind, I am delighted NICE have recommended the approval of the tobramycin dry powder inhaler for these patients. However, the decision NOT to recommend the approval of the colistin DPI (Colobreathe) as well gives me significant cause for concern as a prescribing physician.

This concern is driven by the way tobramycin and colistin (nebulised forms) are currently used in clinical practice, where we have seen a move AWAY from the historical norm (colistin as a first line therapy followed by tobramycin for those patients who cannot tolerate colistin or require additional clinical efficacy) TOWARD a treatment regimen of alternating therapy between these two agents on a monthly basis. The reality of this decision therefore, is to provide an individual patient with a DPI treatment in Month 1 and ask that they return to a nebulised formulation in Month 2 – a situation the patient will find totally unacceptable and one which will lead to high rates on non-compliance and poor quality of life in Month 2 which will ultimately result in faster disease progression.

Although several guidelines exist when considering antibiotic management in CF patients with cystic fibrosis - typically those issued by the CF Trust (May 2009) and those prepared by The British Thoracic Society Cystic Fibrosis Special Advisory Group – these are focussed on historical prescribing practices given the arbitrary use of 1st and 2nd line recommendations for colistin and tobramycin respectively. Current prescribing, as described above, now tends

to focus on an alternating treatment regime in the majority of specialist centres. Perhaps the time has come to reflect the current clinical practise with a revision to these guidelines.

As a clinical expert in the UK, I also had the opportunity to participate in the pivotal Colobreathe study (COLO/DPI/02/06) which is described in the ARD. There is no doubt the design and logistics of the study were complex, particularly when a study requiring such large patient numbers can only achieve this by selecting sites from across the whole of Europe. Whilst the statistical aspects of the trial are not something on which I can comment, the choice of comparator most definitely is and although nebulised colistin may have been the preferred choice, I can understand the legal, scientific and regulatory rational for not moving forward with this. Specifically, in 2002 at the start of this study, Forest had only 3 actual choices for the comparator arm – placebo, nebulised colistin or nebulised tobramycin. Ethically, the clinical community would not support a placebo arm given the 24 week duration of the trial, nebulised colistin was not registered / approved in several of the countries identified for patient recruitment (given the orphan nature of the disease, recruitment was never going to occur solely in the UK) and thus nebulised tobramycin was the only choice the company could move forward with. Indeed, by using tobramycin as the comparator, one could conclude that Colobreathe is as effective as the current evidence based 'gold standard' since previous studies have demonstrated that nebulised tobramycin is superior to nebulised colistin.

In conclusion, if the price of Colobreathe can be moderated to ensure similar alignment to tobramycin podhaler or promixin, then I believe Colobreathe would be a welcome addition to the physician's armamentarium, the patients choice of medication and would ultimately, improve compliance in this patient population. Although I welcome the decision to approve TIP; as an expert in cystic fibrosis with many years experience and looking after a large number of patients I feel that the decision not to approve Colobreathe on the evidence given is a retrograde step in the future care of my patients. I therefore urge NICE to reconsider their decision.

Yours Faithfully

Dr R I Ketchell, FRCP, PhD

Consultant Physician and Director of the Adult Cystic Fibrosis Centre