Colistimethate sodium powder for inhalation for the treatment of *Pseudomonas* lung infection in cystic fibrosis

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1. EXECUTIVE SUMMARY

Overview of the Colobreathe® technology

Colobreathe® (colistimethate sodium dry powder inhaler (DPI)), which is currently being reviewed by the European Medicines Agency, was granted an orphan indication in February 2002 (EU/3/02/088) with the designated orphan indication: treatment of *Pseudomonas aeruginosa* lung infection (including colonisation) in cystic fibrosis (CF). The designation was granted on the assumption of significant benefit "in particular with regards to improved efficacy compared to tobramycin based on the low potential for resistance induction for colistin and with regards to the contribution to patient care based on the ease of use and the reduced duration of treatment compared to the nebulised form."

The Colobreathe® System comprising Colobreathe® capsules and the Turbospin® DPI should be straightforward for the patient/carer to learn, understand and use. The system is also much more portable than a nebuliser and does not necessarily require the use of a spacer device. Colobreathe® has a much more rapid administration time, compared to a nebuliser. This could potentially increase treatment compliance and offer improved quality of life (QoL) for CF patients and/or carers compared to nebulised treatment. Colobreathe® does not require the use of nebuliser equipment (which has a higher risk of bacterial contamination).

Colobreathe® also has advantages in terms of cost savings (no complex nebuliser equipment required), decreased used of services (as a result of the reduction in support needed for regular nebulised treatment), reduction in environmental contamination (by nebuliser output) and greatly reduced incidence of resistance developing when compared to tobramycin.

Clinical effectiveness

In a pivotal Phase III randomised, controlled efficacy study, Colobreathe® was shown to be non-inferior to tobramycin nebuliser solution for inhalation (TOBI®) with respect to the primary efficacy endpoint of change in forced expiratory volume in 1 second (FEV_1) % predicted.

The change in FEV_1 % predicted after 24 weeks of treatment was similar following Colobreathe® and TOBI® treatment. Following logarithmic transformation and non-parametric analysis, the primary objective to show that Colobreathe® was non-inferior to nebulised TOBI® with respect to the change of FEV_1 % predicted after 24 weeks of treatment was demonstrated.

Colobreathe® was more favourable compared to TOBI® with respect to antimicrobial sensitivity of respiratory tract isolates of *P. aeruginosa* as resistance against colistin was not observed, whereas resistance against tobramycin developed, particularly in TOBI®-treated 6 to 17 year old children (most pronounced in 6 to 12 year olds).

Colobreathe® was more favourable than TOBI® with respect to HRQoL (Health Related Quality of Life), ease of inhaler device use, treatment preference and treatment burden.

Colobreathe® was similar to TOBI® with respect to change in FEV_1 % predicted after 20 weeks of treatment, other pulmonary function tests, patient compliance, weight, investigator's global assessment and use of concomitant medication including bronchodilators.

A reduction in number of exacerbations for Colobreathe® patients was calculated from patient level data in the pivotal trial 'Time to exacerbation' in Colobreathe® arm was 63.6 days and for TOBI® arm was 59.4 days. In addition the mean duration of use of additional anti-pseudomonal agents administered for the management of acute respiratory exacerbation was slightly lower in the Colobreathe® group compared to the TOBI® group.

Safety
Colistimethate sodium as an injectable or aerosol inhalation (nebulisation) formulation has been marketed as Colomycin® powder for solution for injection/inhalation for the treatment of severe systemic infections caused by Gram-negative bacteria and in particular, *P. aeruginosa*, for over 40 years and has an established safety profile. This clinical experience is sufficient and relevant with regard to carcinogenic potential, reproductive toxicity and local tolerance of an inhaled product in that no issues have been identified despite wide usage in the target population. The dose of colistimethate delivered by DPI will be of the same order as that delivered by nebulisation. Minimal, if any, systemic absorption of drug is anticipated when given by DPI.

In summary, the clinical safety of Colobreathe® has been assessed in three open-label Phase I and II studies, (n=40 subjects) conducted in the UK, and the efficacy and safety of Colobreathe® confirmed in the pivotal Phase III open-label active comparator study versus nebulised tobramycin (n=380; 187 randomised to Colobreathe® and 193 randomised to tobramycin). An exploratory pilot deposition study was also conducted.

Cost-effectiveness
Although there is a lack of data regarding the cost-effectiveness of managing patients with chronic *Pseudomonas aeruginosa,* a simple cost-effectiveness model has been created comparing Colobreathe® to TOBI®.

The Colobreathe® pivotal trial collected health related quality of life (HRQoL) data using a disease specific questionnaire (the CFQ-R) and the data from this was mapped by Prof. John Brazier's team (1).

There has been a suggestion that in the literature (Kerem *et al.* (2)) that there is a link between the percentage of predicted FEV_1 and the mortality of CF patients. We therefore investigated the key trial data and found that over one year, Colobreathe® shows a QALY gain compared to TOBI®.

The model demonstrates that at a similar price to TOBI®, Colobreathe® provides a net monetary benefit to the NHS. However, the model does not capture some additional benefits of Colobreathe®:

- The more favourable performance of Colobreathe® with respect to antimicrobial sensitivity of respiratory tract isolates of *P. aeruginosa.* This will have impact both on costs and patient quality of life.
- The costs of devices and consumables required for nebulisation
- Carer time in relation to nebulisation by a predominantly young patient population.
- The benefit of the patient experience (ease of use) that is not adequately captured by the quality of life instrument.

Budget impact
A number of assumptions regarding the number of CF patients, the proportion of these with *Pseudomonas aeruginosa* infection and the cost and number of patients using various different currently available treatment options have been made in order to create a budget impact model. On the assumptions used the estimated net budget impact will be £4,766,945.