

# Colistimethate sodium powder and tobramycin powder for inhalation for the treatment of chronic *Pseudomonas aeruginosa* lung infection in cystic fibrosis: systematic review and economic model

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## Scientific summary

Treatment of chronic *P. aeruginosa* lung infection in cystic fibrosis

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# Scientific summary

## Background

Cystic fibrosis (CF) is an inherited condition that is characterised by the abnormal transport of chloride ions (Cl<sup>-</sup>) across transporting epithelia. This leads to the production of thick sticky mucus in the lungs, pancreas, liver, intestine and reproductive tract, and an increase in the salt content in sweat. Among other problems, people with CF experience recurrent respiratory infections and have difficulties digesting food. CF affects over 9000 children and individuals in the UK. In 2010, CF was recorded as the cause of death in 103 cases in England and Wales. Although CF limits life expectancy, more people with the condition are living longer. More than half of the CF sufferers in the UK are aged > 16 years. People with CF are susceptible to lung infections. This is thought to be because the thick mucus makes it difficult for the body to clear inhaled bacteria, and because people with CF have an increased airway inflammatory response to pathogens. The most common bacterial infection is *Pseudomonas aeruginosa*. In 2010, around 37.5% of UK patients were chronically infected with *P. aeruginosa*. In the early stages of disease, treatment aims to prevent initial infection with *P. aeruginosa* or to eradicate new and intermittent infections. If bacterial infection is not successfully prevented or treated, a chronic infection can develop, whereby bacterial microenvironments, known as biofilms, form. Biofilms are difficult for immune cells and antibiotics to penetrate. Treatment of chronic infections involves regular use of nebulised antibiotics, such as tobramycin [Bramitob® (Chiesi) or TOBI® (Novartis Pharmaceuticals)] and colistimethate sodium [Promixin® (Profile Pharma) or Colistin® (Forest Laboratories)], to prevent flare-ups (known as exacerbations) and to stabilise lung function and enhance quality of life. Treatment is time-consuming for patients, with administration of nebulised antibiotics taking up to 1 hour per day during good health, and longer during periods of ill health. Exacerbations lead to progressive respiratory failure, have a substantial negative impact on a patient's quality of life, and are usually treated using intravenous (i.v.) antibiotics.

## Objectives

The overall aim of this assessment is to evaluate the clinical effectiveness and cost-effectiveness of colistimethate sodium dry powder for inhalation (DPI) (Colobreathe®, Forest Laboratories) and tobramycin DPI [TOBI® (plus Podhaler®), Novartis Pharmaceuticals] for the treatment of *P. aeruginosa* lung infection in CF.

## Methods

A systematic literature review was conducted of the clinical effectiveness and cost-effectiveness of colistimethate sodium DPI and tobramycin DPI within their licensed or anticipated licensed indications for the treatment of chronic *P. aeruginosa* lung infection in CF. Electronic bibliographic databases were searched in February and March 2011 [MEDLINE, MEDLINE In-Process and Other Non-Indexed citations, EMBASE, The Cochrane Library databases, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, Conference Proceedings Citation Index (CPCI) and Bioscience Information Service (BIOSIS) Previews]. Ongoing and unpublished studies were searched for in relevant databases. The bibliographies of relevant systematic reviews and the manufacturers' submissions were also hand-searched. Randomised controlled trials (RCTs) were selected for inclusion in the review if they included at least one of the interventions of interest, selected only people aged ≥ 6 years with CF and chronic *P. aeruginosa* pulmonary infection, compared the intervention with the other intervention or with nebulised tobramycin or nebulised colistimethate sodium, and reported at least one of the following outcomes: rate and extent of microbial response (e.g. sputum density of *P. aeruginosa*); lung function; respiratory symptoms;

frequency and severity of acute exacerbations; health-related quality of life (HRQoL); and adverse events (AEs) of treatment (including rate of resistance to antibiotic treatment). Data were extracted using a standardised form. Critical appraisal was performed using the Centre for Reviews and Dissemination (CRD) criteria, the Consolidated Standards of Reporting Trials (CONSORT) statement for non-inferiority trials and criteria taken from the European Medicines Agency (EMA) research guidelines for CF. Study selection, data extraction and critical appraisal were performed by one reviewer and checked by a second reviewer. The broader evidence network for a mixed-treatment comparison was also examined but was not included in the review. A meta-analysis was planned subject to the availability of suitable data.

Existing economic evidence available from the literature and evidence submitted to the National Institute for Health and Care Excellence (NICE) by the manufacturers of colistimethate sodium DPI was critically appraised. Additional systematic reviews were undertaken to examine the credibility of potential relationships between intermediate end points and final outcomes. In addition, a de novo health economic model was developed to assess the cost-effectiveness of colistimethate sodium DPI compared with nebulised tobramycin. The Assessment Group model takes the form of a state transition model to estimate transitions between three forced expiratory volume in first second percentage predicted (FEV<sub>1</sub>%) (forced expiratory volume in first second) strata [(1) FEV<sub>1</sub> 70–99%; (2) FEV<sub>1</sub> 40–69%; and (3) FEV<sub>1</sub> < 40%]. Twenty-four-week transition probabilities were estimated, based on FEV<sub>1</sub> changes in those observed within the COL/DPI/02/06 trial. Different levels of HRQoL are assumed for each health state. Treatment duration, which is assumed to be directly related to survival duration, is assumed to be exactly equivalent between the competing treatment options. Costs include those associated with drug acquisition, nebuliser consumables and the management of exacerbations. The model was evaluated probabilistically over a short-term horizon (24-week duration) and a lifetime horizon using standard decision rules. The analysis was repeated over six prices for colistimethate sodium DPI. Insufficient data were available to produce a full economic evaluation of tobramycin DPI compared with any comparator during the assessment. Instead, a crude threshold analysis was undertaken to estimate the necessary quality-adjusted life-year (QALY) gain that tobramycin DPI would need to produce in order to be cost-effective, given its incremental lifetime cost. A further analysis was undertaken later using patient-level data from the Establish A new Gold standard Efficacy and safety with tobramycin in cystic fibrosis (EAGER) trial.

## Results

### Clinical effectiveness results

Three trials were included in the review of clinical effectiveness. Both colistimethate sodium DPI and tobramycin DPI were reported to be non-inferior to nebulised tobramycin in pivotal Phase III trials for the outcome FEV<sub>1</sub>%. A small trial comparing colistimethate sodium DPI with nebulised colistimethate sodium in a younger, healthier cohort of patients showed no significant change in lung function in either arm but was primarily a safety trial.

The quality of the included studies was generally poor to moderate. None of the trials scored well on all risk of bias items, with blinding and non-adherence to the EMA research guidelines being key problems [Committee for Medicinal Products for Human Use (CHMP). *Guideline on the clinical development of medicinal products for the treatment of cystic fibrosis*. 2009. URL: [www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/12/WC500017055.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/12/WC500017055.pdf). (accessed June 2011)]. This could lead to selection bias and reporting bias for subjective outcomes, such as AEs, inaccuracies and imprecision in the results, and may limit the generalisability of the study. Follow-up was nearly adequate to detect effects in respiratory efficacy but not long enough to detect slowing of the rate of decline in respiratory function, according to EMA research guidelines.

As FEV<sub>1</sub>% is a surrogate outcome, the EMA recommends that it should be considered alongside microbiological outcomes and harder clinically relevant outcomes, such as frequency of exacerbations and antibiotic use. Both tobramycin DPI and colistimethate sodium DPI appeared to result in more people

experiencing at least one exacerbation (as indicated by the surrogate outcome 'lung disorders' in the EAGER trial than nebulised tobramycin, but less time on antibiotics. Sputum density was available only from the EAGER trial and supported the direction of effect seen in FEV<sub>1</sub>%. Resistance of around 20% was reported for tobramycin arms across both key trials; this was  $\leq 1.1\%$  for colistimethate sodium DPI in the COL/DPI/02/06 trial. AEs were mostly similar between arms within trials, except for cough, which was higher in both DPI arms. More patients in the DPI arms withdrew owing to AEs in both trials. The statistical and clinical significance of the changes seen in sputum density, exacerbations, resistance and AE data is not known. There was no direct preference-based assessment of HRQoL within any of the trials included in the review.

It was not possible to draw any firm conclusions as to the relative efficacy of any intervention compared with any other intervention (except where there was direct evidence comparing with nebulised tobramycin) owing to missing data, uncertain comparability of patient characteristics and incompatible populations used when analysing the data.

### Cost-effectiveness results

The results of the health economic analysis suggest that colistimethate sodium DPI is expected to produce fewer QALYs than nebulised tobramycin, both in the short term and over a lifetime horizon. If the price of colistimethate sodium DPI is set at one of the prices which is higher than that of nebulised tobramycin, it is expected to be more expensive and hence dominated by nebulised tobramycin. If the price of colistimethate sodium DPI is set at £9.11, the incremental cost-effectiveness of nebulised tobramycin compared with colistimethate sodium DPI is expected to be in the range of £126,000–277,000 per QALY gained. If the price of colistimethate sodium DPI is set at £10.60, the incremental cost-effectiveness of nebulised tobramycin compared with colistimethate sodium DPI is expected to be in the range of £24,000–50,000 per QALY gained. The range of sensitivity analyses suggest that in those cases in which colistimethate sodium DPI offers a positive QALY gain, prices above parity with nebulised tobramycin result in a very high cost per QALY ratio.

Given the incremental discounted lifetime cost of tobramycin DPI compared with nebulised tobramycin, the Assessment Group model suggests that it is not possible for tobramycin DPI to have an incremental cost-effectiveness ratio (ICER) that is better than £30,000 per QALY gained.

## Discussion

A key strength of this assessment is that the systematic review has been conducted to a high standard, including comprehensive search strategies with study selection, data extraction and quality assessment checked by a second reviewer. The assessment is limited by the small number of trials available, and methodological weaknesses and incompatibilities within the trials, which limit the between-trial comparability. There are variations in the definition and measurement of the key outcomes, owing to non-compliance with EMA research guidelines. None of the trials included a preference-based HRQoL instrument.

The health economic model developed within this assessment was based on clinical opinion regarding current treatment pathways and systematic reviews of evidence relating to the plausibility of relationships between intermediate and final end points (rather than pure assumption). The model was populated using the best available evidence and was peer reviewed by several individuals with clinical and methodological expertise.

The Assessment Group model involves extrapolation of FEV<sub>1</sub>% estimates within the COL/DPI/02/06 trial. Within this analysis, the observable period is 24 weeks in duration, whereas the extrapolated period is around 43 years (when < 1% of patients are still alive). The considerable uncertainty surrounding the short-term evidence base inevitably results in uncertainty surrounding the long-term cost-effectiveness of

colistimethate sodium DPI. One particular strength of the assessment is that the model analysis considers the impact of this extrapolation on the cost-effectiveness of treatment. In addition, uncertainty surrounding the appropriate method of health state valuation is explored by applying a variety of health utility estimates within the model.

A key anticipated benefit of colistimethate sodium DPI and tobramycin DPI concern the increased convenience afforded by reduced treatment administration time compared with nebulised antibiotics. This may be expected to increase compliance with treatment. In addition, the DPIs are more portable than nebulisers, which may also make them a more convenient option. The DPIs may also result in savings in terms of the time associated with cleaning traditional nebulisers. These aspects of benefit may represent 'process utilities'. However, none of the clinical trials attempted to capture these potential effects using a preference-based instrument. Furthermore, the available evidence does not support the argument for increased compliance with DPIs. As a consequence, this potential effect is not reflected in the health-economic analysis. It should be also noted that newer nebulisers, such as the I-neb™ (Philips Respironics, Murrysville, PA, USA) and PARI eFlow® (PARI GmbH, Starnberg, Germany) devices, also allow for faster treatment delivery than conventional nebulisers. The incremental benefits of this aspect of DPI delivery therefore remain unclear.

The key uncertainties within this assessment are:

- the relative efficacy and safety profiles of colistimethate sodium DPI and tobramycin DPI
- the long-term efficacy of treatment using colistimethate sodium DPI and tobramycin DPI compared with current standard nebulised therapies
- the validity of the relationship between short-term impact on lung function and longer-term final patient outcomes (mortality and HRQoL)
- the long-term impact of DPI treatment on patient survival
- long-term treatment compliance with DPIs
- the clinical relevance of resistance to antibiotics and its impact on treatment efficacy
- the trade-off between ease/speed of drug administration using the inhaler devices and AEs (and the impact of both on patients' quality of life).

## Conclusions

Both DPI formulations have been shown to be non-inferior to nebulised tobramycin as measured by FEV<sub>1</sub>%. However, the results of these trials should be interpreted with caution owing to the means by which the results were analysed, the length of follow-up, and concerns about the ability of FEV<sub>1</sub>% to accurately represent changes in lung health. The impact of resistance to tobramycin is not known. When considered alongside other outcomes, it would appear possible that, when compared with nebulised treatment, patients on DPI formulations experience more exacerbations but less time on antibiotics, more cough AEs and may be more likely to not tolerate the treatment. As such, based on the clinical evidence, the advantages and non-inferiority of DPI treatments compared with nebulised tobramycin remain unclear when all relevant outcomes are considered. Inevitably, the cost-effectiveness of the dry powder formulations is subject to considerable uncertainty. The Assessment Group model suggests that colistimethate sodium is expected to produce fewer QALYs than nebulised tobramycin. Depending on the price adopted for colistimethate sodium DPI, this results either in a situation whereby colistimethate sodium DPI is dominated by nebulised tobramycin, or one whereby the incremental cost-effectiveness of nebulised tobramycin compared with colistimethate sodium DPI is in the range of £24,000–277,000 per QALY gained (south-west quadrant). The economic analysis also suggests that, given its price, it is highly unlikely that tobramycin DPI has an ICER of < £30,000 per QALY gained when compared with nebulised tobramycin. Future research may be useful in reducing these uncertainties. A RCT to assess the longer-term ( $\geq 12$  months) efficacy of colistimethate sodium DPI and tobramycin DPI in comparison with nebulised treatments would be beneficial. Such a study should include the direct assessment of HRQoL using a

relevant preference-based instrument. Future studies should adhere to the EMA guidelines. In addition, high-quality research concerning the relationship between FEV<sub>1</sub>% or other measures of lung function and survival/HRQoL would be useful.

## Study registration

This study is registered as PROSPERO CRD42011001350.

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