NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Multiple Technology Appraisal

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

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of colistimethate sodium powder and tobramycin powder for inhalation within their licensed indications for the treatment of *pseudomonas* lung infection in cystic fibrosis.

Background

Cystic fibrosis is an inherited condition characterised by abnormal transport of chloride and sodium across the epithelium in all exocrine tissues, leading to thick viscous secretions in the lungs, pancreas, liver, intestine, and reproductive tract, and an increase in the salt content in sweat gland secretions.

Cystic fibrosis affects over 8,500 children and young adults in the UK and has an incidence of 1 in 2500 live births. About 1 in 25 people in the UK of white European descent are carriers of the cystic fibrosis gene. It is much less common in Afro-Caribbean and Asian people. Although cystic fibrosis is a progressive condition that limits life expectancy, it has an improving prognosis. More than half of people with cystic fibrosis in the UK are older than 16 years of age. In 2009, 100 deaths from cystic fibrosis were recorded in England and Wales.

The lungs of individuals with cystic fibrosis can become infected by bacteria such as *Pseudomonas*, and the species *Pseudomonas aeruginosa* is the most frequent cause of lung infection in early childhood. These bacteria thrive in the altered mucus of people with cystic fibrosis, which collects in the small airways of the lungs. If bacterial infection is not controlled, chronic infection can develop, where bacterial microenvironments known as biofilms are formed that are difficult for immune cells and antibiotics to penetrate. The bacterial infection is rarely eradicated once chronic infection has developed. Prior to establishment of chronic infection, recurrent, intermittent infection of the airways with *Pseudomonas aeruginosa* is seen.

While cystic fibrosis is a multi system disease, the primary cause of death in people with cystic fibrosis is respiratory failure resulting from chronic pulmonary infection. In 2002, it was estimated that approximately 60% of people with cystic fibrosis had a chronic respiratory infection caused by *Pseudomonas aeruginosa.*

The length and quality of life for people with cystic fibrosis is thought to be strongly influenced by the success or failure to eradicate *Pseudomonas aeruginosa* in early childhood and by subsequent antibiotic treatment of respiratory infective exacerbations. In 2003, the age-specific prevalence of *Pseudomonas aeruginosa* in pre-school aged children with cystic fibrosis was 9% rising to 32% for 10 to 15 year olds.

Management of *Pseudomonas aeruginosa* lung infection in cystic fibrosis involves treatment with antibiotics to suppress bacterial growth. The aims of treatment are three fold: eradication of intermittent acute *Pseudomonas aeruginosa* infections; suppression of *Pseudomonas aeruginosa* infection (with long-term therapy) in patients who have become chronically infected and; treatment of acute exacerbations in patients chronically infected with *Pseudomonas aeruginosa*. Current treatment options include the use of inhaled antibiotics (such as nebulised colistimethate sodium or tobramycin) effective against *Pseudomonas aeruginosa*. Inhaled antibiotic therapy may also be combined with oral antibiotics (such as ciprofloxacin) to eradicate first or intermittent *Pseudomonas aeruginosa* colonisation. Intermittent administration of intravenous anti-pseudomonal antibiotics may also be given for chronic infection.

The technologies

Colistimethate sodium powder for inhalation (Colobreathe, Forest Laboratories UK) is a formulation of colistimethate sodium supplied as hard capsules. It belongs to the polymixins class of antibacterials and works by disrupting the structure of the bacterial cell membrane, leading to bacterial death. It is active against Gram-negative organisms including *Pseudomonas aeruginosa, Acinetobacter baumannii, and Klebsiella pneumoniae.* Colistimethate sodium powder for inhalation is administered using the 'Turbospin' device (PH&T) which is a breath-activated, reusable dry powder inhaler.

Colistimethate sodium powder for inhalation does not currently have UK marketing authorisation for the treatment of *Pseudomonas aeruginosa* lung infection in cystic fibrosis. It has been studied in a clinical trial in people aged over 6 years old with *Pseudomonas aeruginosa* lung infection (including colonisation) in cystic fibrosis compared with nebulised tobramycin.

Tobramycin inhalation powder (Tobi Podhaler, Novartis) is a dry powder formulation of tobramycin. It acts primarily by disrupting protein synthesis leading to altered cell membrane permeability, progressive disruption of the cell envelope and eventual cell death. Tobramycin inhibits protein synthesis of numerous Gram-negative bacteria and it is active against *Pseudomonas aeruginosa*. Tobramycin dry powder is administered using the Tobi Podhaler device.

Tobramycin inhalation powder does not currently have UK marketing authorisation for the treatment of *Pseudomonas aeruginosa* lung infection in

cystic fibrosis. The Committee for Medicinal Products for Human Use (CHMP) has issued a positive opinion for tobramycin inhalation powder as a suppressive therapy for chronic infection due to *Pseudomonas aeruginosa* in people aged 6 years and older with cystic fibrosis.

Intervention(s)	• Colistimethate sodium powder for inhalation (used in conjunction with the Turbospin device) • Tobramycin powder for inhalation (used in conjunction with the TOBIPodhaler device)
Population(s)	People aged 6 years and over with cystic fibrosis and chronic *Pseudomonas aeruginosa* pulmonary infection
Comparators	• Colistimethate sodium and tobramycin dry powder will be compared with each other Antibiotics for nebulised inhalation, including: • Colistimethate sodium for nebulised inhalation • Tobramycin for nebulised inhalation
Outcomes	The outcome measures to be considered include: • Rate and extent of microbial response (for example sputum density of *Pseudomonas aeruginosa*) • lung function • respiratory symptoms • frequency and severity of acute exacerbations • health related quality of life • adverse events of treatment (including rate of resistance to antibiotic treatment)
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies compared. Costs will be considered from an NHS and Personal Social Services perspective.

Other considerations	Guidance will only be issued in accordance with the marketing authorisation. If evidence allows the appraisal will seek to identify subgroups for whom the technology is particularly clinically and cost effective (such as by number of prior eradication therapies). Consideration will be given to people who may have difficulties using inhaler devices. This appraisal will consider both individual technologies and devices.
Related NICE recommendations	Technology Appraisal in Preparation, 'Mannitol dry powder for inhalation for the treatment of cystic fibrosis. Publication date tbc.