Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence

11th January 2011

1. Title of the project:

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

2. Name of TAR team and 'lead'

TAR team

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3. Plain English Summary

Cystic fibrosis (CF) is an inherited condition characterised by the abnormal transport of salts in the exocrine tissues of the body. 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. Amongst other problems, people with CF have difficulties breathing and digesting food.

CF affects over 8,500 children and young adults in the UK.[1] In 2009, CF was recorded as the cause of death in 100 cases in England and Wales.[1] Disease incidence is around 1 in 2,500 live births and approximately 1 in 25 people in the UK of white European descent are carriers of the CF gene.[2] It is much less common in Afro-Caribbean and Asian people. Whilst CF limits life expectancy, more people with the condition are living longer. More than half of CF sufferers in the UK are older than 16 years of age, and around 10% are older than 36.[1]

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.[3] The most common bacterial infection is *Pseudomonas aeruginosa*. In 2008, the age-specific prevalence of chronic *Pseudomonas aeruginosa* in UK children aged three and under with CF was 3% rising to 25% for 12 to 15 year olds.[1] Around 60% of adults over 20 with CF had a chronic *Pseudomonas aeruginosa* infection.[1]

In the early stages of disease, treatment aims to prevent initial infection with *Pseudomonas aeruginosa*, or eradicate new and intermittent infections.[4] 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. Once an infection is established, death over an 8 year period is 2 to 3 times more likely.[5] Treatment of chronic infections involves regular use of nebulised antibiotics such as tobramycin and colistimethate sodium to prevent flare-ups (known as exacerbations) and to improve lung function and quality of life. Treatment is time consuming for patients, with administration of nebulised antibiotics taking up to an hour per day during good health and longer during periods of ill health.[3] Exacerbations have a substantial negative impact upon a patient's quality of life[6] and are usually treated using intravenous antibiotics.[4]

The overall aim of this assessment is to evaluate the clinical and cost-effectiveness of colistimethate sodium powder and tobramycin powder for inhalation for the treatment of *Pseudomonas aeruginosa* lung infection in cystic fibrosis. These interventions will be compared against each other and against conventional treatments (nebulised antibiotics).

4. Decision problem

4.1 Purpose of the decision to be made

This assessment will address the question "what is the clinical and cost-effectiveness of colistimethate sodium and tobramycin powder for inhalation for the treatment of *Pseudomonas aeruginosa* lung infection in cystic fibrosis as compared against current treatments?"

4.2 Clear definition of the intervention (e.g. licensed indications, dosages being considered)

Two interventions will be included in the assessment:

(1) Colistimethate sodium (Colobreathe, Forest Laboratories UK) for inhalation as dry powder, used in conjunction with the Turbospin device.

(2) Tobramycin (Tobi Podhaler, Novartis) for inhalation as dry powder, used in conjunction with the TOBIPodhaler device.

Neither colistimethate sodium nor Tobramycin in their dry powder form have yet been granted marketing authorisation by the European Medicines Agency (EMEA). The dosages for colistimethate sodium and tobramycin powder assessed within this review will be determined according to the available clinical trial data.

4.3 Place of the intervention in the treatment pathway(s)

The interventions included in this assessment are specifically for the treatment of chronic *Pseudomonas aeruginosa* pulmonary infection to control chronic infections rather than to eradicate new infections or treat exacerbations. Currently, nebulised anti-pseudomonal antibiotics such as tobramycin and colistimethate sodium are usually used.

4.4 Relevant comparators

The interventions will be compared against each other. Other relevant comparators include antibiotics used for nebulised inhalation, including colistimethate sodium for nebulised inhalation and Tobramycin for nebulised inhalation. Whilst these are the most commonly used antibiotics in the UK, where evidence is available other nebulised antibiotics with antipseudomonal activity may also be considered as comparators.

4.5 Population and relevant sub-groups

The population for the assessment will include people aged 6 years and over with cystic fibrosis and chronic *Pseudomonas aeruginosa* pulmonary infection. Where possible, subgroups may be considered such as number of prior eradication therapies.

4.6 Key factors to be addressed

The objectives of the assessment are:

(1) To assess the clinical effectiveness of colistimethate sodium and tobramycin powder for inhalation for the treatment of *Pseudomonas aeruginosa* lung infection in terms of lung function, microbial response, respiratory symptoms and the frequency/severity of acute exacerbations.

(2) To assess the adverse event profile associated with colistimethate sodium and tobramycin powder

(3) To estimate the incremental cost-effectiveness of colistimethate sodium and tobramycin powder as compared against current treatments for the treatment of *Pseudomonas aeruginosa* lung infection.

4.7 Issues that are outside the scope of the appraisal

The use of treatments for other symptoms or complications of CF will be excluded from this assessment.

5. Report methods for synthesis of evidence of clinical effectiveness

5.1 Search strategy

A comprehensive search will be undertaken to systematically identify clinical effectiveness literature concerning colistimethate sodium powder for inhalation and tobramycin powder for inhalation in people aged 6 years and over with cystic fibrosis and chronic *Pseudomonas aeruginosa* pulmonary infections.

The search strategy will comprise the following main elements:

- Searching of electronic databases
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers

Search strategies will be used to identify relevant trials (as specified under the inclusion criteria, below) and systematic reviews/meta-analyses (for identification of additional trials). The following databases will be searched: MEDLINE; MEDLINE in-Process and Other Non-Indexed Citations; EMBASE; Cochrane Library including the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials; CINAHL; Web of Science Citation Index with Conference Proceedings and BIOSIS Previews. Searches for ongoing and recently completed research projects will be undertaken within the National Research Register and the metaRegister of Controlled Trials. Searches for unpublished research or research reported in the grey literature will also be undertaken within the Research Register and the metaRegister of Controlled Trials, in addition to contact with experts.

Searches will not be restricted by language, date or publication type. The MEDLINE search strategy is presented in Appendix 1. This will be adapted for other databases. Industry submissions and relevant systematic reviews will also be hand-searched in order to identify any further clinical trials. A comprehensive database of relevant published and unpublished articles will be constructed using Reference Manager® software.

5.2 Inclusion criteria

The inclusion criteria for the assessment are as follows:

Interventions

- Colistimethate sodium powder for inhalation (used in conjunction with the Turbospin device)
- Tobramycin powder for inhalation (used in conjunction with the TOBIPodhaler device)

Population

- People aged 6 years and over with cystic fibrosis and chronic *Pseudomonas aeruginosa* pulmonary infection

Comparators

- Interventions compared with each other
- Antibiotics for nebulised inhalation including
    - Colistimethate sodium for nebulised inhalation
    - Tobramycin for nebulised inhalation

Outcomes

- 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 (HRQoL)
- Adverse events of treatment (including rate of resistance to antibiotic treatment)

Study design

- Randomised controlled trials (RCTs) will be included for the clinical effectiveness review. If no RCTs are identified for an intervention, non-randomised studies will be considered for inclusion. Non-randomised studies may also be included as a source of evidence from which to derive information relating to the adverse event profiles associated with the interventions.

5.3 Exclusion criteria

The following studies will be excluded: studies based on animal models; preclinical and biological studies; editorials, opinion pieces; and reports published as meeting abstracts only where insufficient details are reported to allow inclusion. Studies which are only published in

languages other than English are also likely to be excluded. Studies retrieved for full paper screening which are excluded will be listed in an appendix to the report with reasons justifying their exclusion.

Based on the above inclusion/exclusion criteria, study selection will be made by one reviewer with involvement of a second reviewer where necessary. Titles and abstracts will be examined for inclusion. Full manuscripts of potentially relevant articles will be retrieved and assessed for inclusion.

5.4 Data extraction strategy

Data will be extracted by one reviewer using a standardised data extraction form and checked by a second reviewer. Discrepancies will be resolved by discussion. Data will be extracted with no blinding to authors or journal. Where multiple publications of the same study are identified, data will be extracted and reported as a single study.

5.5 Quality assessment strategy

The quality of the individual studies will be assessed by one reviewer. The quality of the clinical effectiveness studies will be assessed according to criteria based on NHS CRD Report.[7]

5.6 Methods of analysis/synthesis

Pre-specified outcomes will be tabulated and discussed within a descriptive synthesis. Where populations, interventions and outcome measures are comparable and statistical synthesis is considered appropriate, meta-analysis will be conducted using fixed and random effect models, using Cochrane Collaboration Review Manager® Software (version 5.0).[8] If sufficient trials are available, sensitivity analysis will be undertaken to examine whether the removal of poor quality trials influences the results of the meta-analysis. Network meta-analysis may be undertaken if considered appropriate given the available evidence.

5.7 Methods for estimating qualify of life

Any HRQoL data available from studies included within the review will be extracted. In the absence of such evidence, the mathematical model may use evidence on HRQoL drawn from alternative sources. HRQoL data will be reviewed and used to generate the quality adjustment weights required for the model.

6. Report methods for synthesising evidence of cost-effectiveness

6.1 Identifying and systematically reviewing published cost-effectiveness studies

The systematic searches will include a health economics filter to identify existing economic evaluations of interventions for the treatment of aeruginosa lung infection in patients with CF. Any existing health economic analyses identified by the searches will be critically appraised using checklists published by Eddy[9] and Drummond *et al*.[10] In addition, any economic analyses presented in the sponsor submissions to NICE will also be critically appraised using these checklists. Existing cost-effectiveness analyses may also be used to identify sources of evidence to inform structural assumptions and parameter values for the Assessment Group model.

6.2 Development of a de novo economic model

A *de novo* economic evaluation will be undertaken from the perspective of the UK NHS. The model will draw together evidence concerning treatment efficacy, withdrawal, treatment-related adverse events, relevant diagnostic interventions, chronic care costs, and HRQoL. Costs will be identified through literature searches. In line with current recommendations, costs and health outcomes will be discounted at 3.5%. Key health economic outcomes are likely to include the cost per life year gained, and the cost per quality adjusted life year (QALY) gained. The cost-effectiveness of interventions will be compared incrementally against each other.

Sensitivity analysis will be undertaken to examine the key determinants of cost-effectiveness. Probabilistic sensitivity analysis (PSA) will be undertaken to generate information on the likelihood that each treatment produces the greatest amount of net benefit. The results of this PSA will be presented as cost-effectiveness acceptability curves (CEACs).

7. Handling the company submission(s)

All data submitted by the manufacturers/sponsors will be considered if received by the TAR team no later than 19th May 2011. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluation included in the company submission, provided it complies with NICE's advice on presentation, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model. If the TAR team judge that the existing economic evidence is not robust, then further work will be undertaken, either by adapting what already exists or developing a *de novo* model.

Any ‘commercial in confidence’ data taken from a company submission will be underlined and highlighted in the assessment report (followed by an indication of the relevant company name e.g. in brackets).

8. Competing interests of authors

None to declare

9. Appendices

Draft search strategy

Database: Ovid MEDLINE(R) <1950 to December Week 3 2010>

Search Strategy:

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1 Cystic Fibrosis/ (24327)
2 cystic fibrosis.tw. (25986)
3 fibrosis cystic.tw. (46)
4 1 or 2 or 3 (30660)
5 Pseudomonas aeruginosa/ (26734)
6 Pseudomonas Infections/ (14212)
7 pseudomonas aeruginosa.tw. (31342)
8 pseudomonas infection$.tw. (720)
9 "P. aeruginosa".tw. (12259)
10 Respiratory Tract Infections/ (26943)
11 respiratory tract infection$.tw. (11274)
12 infection$ respiratory tract.tw. (55)
13 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (75580)
14 4 and 13 (4565)
15 Colistin/ (1794)
16 colistin.tw. (1522)
17 colistimethate sodium.tw. (16)
18 colobreathe.tw. (0)
19 turbospin device.tw. (1)
20 pentasodium colistimethanesulfate.tw. (0)
21 1066-17-7.rn. (1794)
22 12705-41-8.rn. (30)
23 polymyxin.tw. (4383)
24 coly-mycin.tw. (9)
25 colisticin.tw. (0)
26 colimycin.tw. (210)
27 colomycin.tw. (14)
28 colymycin.tw. (12)
29 totazina.tw. (0)
30 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 (6725)
31 Tobramycin/ (3367)
32 tobramycin.tw. (4821)
33 tip.tw. (32726)
34 tobi podhaler.tw. (0)
35 32986-56-4.rn. (3367)
36 nebicin.tw. (1)
37 nebcin.tw. (7)
38 nebramycin factor 6.tw. (8)
39 brulamycin.tw. (13)
40 obracin.tw. (2)
41 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 (38274)
42 Colistin/ (1794)
43 colistin.tw. (1522)
44 colomycin.tw. (14)
45 promixin.tw. (0)

46 Tobramycin/ (3367)
47 tobramycin.tw. (4821)
48 bramitob.tw. (5)
49 tobi.tw. (72)
50 Amikacin/ (3153)
51 amikacin.tw. (5511)
52 Gentamicins/ (15049)
53 gentamicin$.tw. (16572)
54 Ceftazidime/ (2830)
55 ceftazidime.tw. (5493)
56 cephalosporin.tw. (6732)
57 Aztreonam/ (1168)
58 aztreonam.tw. (2093)
59 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 (41873)
60 30 or 41 or 59 (78310)
61 14 and 60 (712)
62 randomized controlled trial.pt. (293155)
63 controlled clinical trial.pt. (80545)
64 randomized controlled trials/ (68881)
65 random allocation/ (69064)
66 double blind method/ (106196)
67 single blind method/ (14233)
68 clinical trial.pt. (453275)
69 exp Clinical Trial/ (613380)
70 (clin$ adj25 trial$).ti,ab. (178153)
71 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (106719)
72 placebos/ (28744)
73 placebos.ti,ab. (1489)
74 random.ti,ab. (117274)
75 research design/ (60069)
76 or/62-75 (988584)
77 61 and 76 (195)
78 Meta-Analysis/ (25865)
79 meta analy$.tw. (30080)
80 metaanaly$.tw. (947)
81 meta analysis.pt. (25865)
82 (systematic adj (review$1 or overview$1)).tw. (23168)
83 exp Review Literature/ (1547482)
84 or/78-83 (1572901)
85 cochrane.ab. (14406)
86 embase.ab. (11970)
87 (psychlit or psyclit).ab. (783)
88 (psychinfo or psycinfo).ab. (3807)
89 (cinahl or cinhal).ab. (4697)
90 science citation index.ab. (1157)
91 bids.ab. (283)
92 cancerlit.ab. (464)
93 or/85-92 (22522)
94 reference list$.ab. (5475)
95 bibliograph$.ab. (8360)
96 hand-search$.ab. (2420)
97 relevant journals.ab. (416)
98 manual search$.ab. (1374)
99 or/94-98 (16185)

100 selection criteria.ab. (12857)
101 data extraction.ab. (5967)
102 100 or 101 (17824)
103 review.pt. (1545342)
104 102 and 103 (12133)
105 comment.pt. (420320)
106 letter.pt. (689121)
107 editorial.pt. (263251)
108 animal/ (4574946)
109 human/ (11295477)
110 108 not (108 and 109) (3391613)
111 or/105-107,110 (4374889)
112 84 or 93 or 99 or 104 (1578509)
113 112 not 111 (1435435)
114 61 and 113 (96)

Additional information that is needed by NCCHTA and NICE.

TAR Centre:

The ScHARR Technology Assessment Group (ScHARR-TAG) undertakes reviews of the effectiveness and cost-effectiveness of healthcare interventions for the NHS R&D Health Technology Assessment Programme on behalf of a range of policymakers in a short timescale, including the National Institute for Health and Clinical Excellence. The group has extensive expertise in information retrieval, systematic reviewing and health economic modelling.

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Timetable/milestones

Milestone	Date to be completed
Draft protocol	11th January 2011
Final protocol	1st February 2011
Progress report	20th June 2011
Draft assessment report	25th July 2011
Assessment report	22nd August 2011

Reference List

(1) UK CF Registry Annual Data Report 2008. 2009. Cystic Fibrosis Trust, Kent, UK.

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(5) Emerson J, Rosenfeld M, McNamara S, Ramsey B, Gibson RL. Pseudomonas aeruginosa and other predictors of mortality and morbidity in young children with cystic fibrosis. *Pediatr Pulmonol* 2002; 34(2):91-100.

(6) Britto MT, Kotagal UR, Hornung RW, Atherton HD, Tsevat J, Wilmott RW. Impact of recent pulmonary exacerbations on quality of life in patients with cystic fibrosis. *Chest* 2002; 121(1):64-72.

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(8) RevMan version 5. The Cochrane Review Manager. [Cochrane Collaboration, Oxford UK ; 2008.

(9) Eddy DM. Technology assessment: the role of mathematical modeling. Assessing medical technology. Washington, DC: National Academy Press; 1985.

(10) Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 1996; 313(7052):275-283.