NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Multiple Technology Appraisal (MTA)

Colistimethate sodium powder (Colobreathe®) and tobramycin powder for inhalation (TOBI Podhaler®) for the treatment of pseudomonas lung infection in cystic fibrosis

Novartis Pharmaceuticals

12 May 2011

Executive summary

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Background

Cystic fibrosis (CF) is the most common life-threatening autosomal recessive monogenetic disorder in the Caucasian population impacting the lives of over 8,500 people in the United Kingdom[1]. Life expectancy for CF patients has nearly doubled over the last few decades; nutritional and screening practice advancements coupled with therapy development has resulted in continuous survival improvements (with 38.8 years as the 2008 median predicted survival)[1,2]. CF is characterised over time with progressive impairment of lung function ultimately leading to respiratory complications; respiratory disease is a major cause of morbidity and accounts for approximately 90% of mortality in CF[3]. The most common bacteria causing chronic infection in CF patients is *Pseudomonas aeruginosa* (Pa) which accelerates the lung function decline[4]. Several products have historically been available in the UK for treatment of Pa in CF patients, however issues with compliance and nebuliser contamination persist which require advancements in delivery mechanisms.

Novartis has improved the delivery of tobramycin, an established effective treatment of chronic Pa infections by developing tobramycin inhalation powder (TOBI Podhaler®). With a portable device, significant reductions in administrative time and elimination of nebuliser assembly and disinfection, patients reported higher patient satisfaction which in turn may improve compliance. The development of new inhaled delivery systems for anti-infectives has led to NICE assessing therapies for chronic Pa infections in CF patients for the first time. Systematic reviews of the literature have found an absence of evidence in the public domain for one of the main interventions under evaluation by NICE (Colobreathe®) and limited evidence for the listed comparators. This has created significant issues which are difficult to address within a modeling framework. In light of the substantial information constraints and the planned Payment by Results tariff in April 2012 which means the establishment of national tariffs (including drug cost), Novartis believes an appraisal, as defined in the finalised scope, may not be appropriate.

However, to inform the ongoing appraisal of Colobreathe and TOBI Podhaler, Novartis has submitted a comprehensive assessment of the available clinical evidence. It was not possible to include Colobreathe within any of the analyses. Whilst Colobreathe data was presented at a symposium at ECFC 2010 which reportedly failed to show non-inferiority to tobramycin inhalation solution 300 mg/5ml (TOBI®) in its primary analysis, no data is available in the public domain to allow for its assessment within this appraisal. A cost-utility analysis (CUA) was explored but is not presented due to the data limitations and findings from the network meta-analysis (NMA) which reported no statistically significant difference between the comparators (which is driven by the substantial trial variability).

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The Technology: TOBI Podhaler ®

Pharmaceutical formulation	Inhalation powder, hard capsule. Each hard capsule contains 28 mg Tobramycin
Indication	Suppressive therapy of chronic pulmonary infection due to *Pa* in adults and children aged 6 years and older with CF
Acquisition cost (excluding VAT)	£1,790.00
Method of administration	Oral inhalation with a dry-powder inhaler T-326.
Doses	The dose of TOBI Podhaler is the same for all patients within the approved age range, regardless of age or weight. The recommended dose is 112 mg tobramycin (4 × 28 mg capsules) twice a day.
Dosing frequency	Administered twice daily for 28 days. The two doses (4 capsules each) should be

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[1] Cystic Fibrosis Trust (CF Trust) (2009a). Annual Data Report 2008. Accessed 1 May 2011. Available from:
<http://www.cftrust.org.uk/aboutcf/publications/cfregistryreports/UK_CF_Registry-Annual_Data_Report_2008.pdf>
[2] Dodge JA et al (2007). Cystic fibrosis mortality and survival in the UK: 1947-2003. *European Respiratory Journal*; 29: 522-6.
[3] Ramsey BW et al. (1999). Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. New England Journal of Medicine;340(1):23-30.
[4] Flume PA, O'Sullivan BP, Robinson KA, Goss CH, Mogayzel PJ, Willey-Courand DB, et al. Cystic fibrosis pulmonary guidelines. Chronic medication for maintenance of lung health. *American* Journal of Respiratory and Critical Care Medicine 2007;176(10): 957–69.

	inhaled as close as possible to 12 hours apart and not less than 6 hours apart.
Average length of a course of	Taken in alternating cycles of 28 days on treatment followed by 28 days off treatment
Anticipated number of repeat treatments	Continued on a cyclical basis for as long as the physician considers the patient is gaining clinical benefit and is tolerating treatment

Clinical Effectiveness

EVOLVE (TBM100C2301)[5]. This demonstrated that treatment was generally well tolerated and produced significant improvements in $FEV_1\%$ predicted versus placebo at Day 28 (difference 13.3, 95%CI: 5.31-21.28, p=0.0016). TOBI Podhaler was also found to reduce sputum Pa density, respiratory-related hospitalisation and antipseudomonal antibiotic use versus placebo.

Comparability of TOBI Podhaler to TOBI was explored within the open-label EAGER trial (TBM100C2302)[6] and reported similar safety and efficacy profiles for the two therapies; increases in $FEV_1\%$ predicted and mean reduction in sputum Pa density were comparable between the groups. Compared to TOBI, TOBI Podhaler was found to have significantly shortened administration time, and patients reported greater satisfaction with treatment:

- Administration time was reduced by 72% (mean 5.6 versus 19.7 minutes, p<0.0001);
- Patient reported treatment satisfaction was significantly higher for:
    - effectiveness (least squares mean difference (LS mean) 9.36, p<0.0001);
    - convenience (LS mean difference 24.35, p<0.0001), and
    - global satisfaction (LS mean 5.20, p=0.0018).

Systematic literature reviews conducted by Novartis on the comparator products yielded a limited and heterogeneous network of evidence with a maximum of 11 studies. Whilst colistimethate sodium inhalation solution (Colistin) is included as a comparator due to its historical use within the UK, the Colistin placebo controlled trial was conducted under a different clinical environment with very low patient numbers, milder population and limited study duration which are not comparable to TOBI Podhaler and TOBI trials. Furthermore, evidence from direct comparison suggests that TOBI is superior to Colistin although there was discrepant previous exposure to these antibiotics within this study[7].

Moreover, a publication from the CF Trust[8] recommends the use of colistimethate sodium inhalation solution for first line treatment of chronic Pa lung infection, and thus these two groups may not be appropriate comparators. The comparative analysis was additionally complicated by marked differences in other baseline patient characteristics than disease severity and year of publication such as previous exposure to the study drug, mean age of patients and inclusion of patients with first or intermittent Pa infection. The tobramycin inhalation solution 300 mg/4 ml (Bramitob) trial was different from other trials in the latter criteria.

Within the constraints of the limited evidence base for comparator products, a NMA was attempted with seven of the eleven identified studies. Four studies were excluded due to:

- One study introduced inconsistencies within the network. The Cayston-TOBI comparison reported Cayston as more efficacious than TOBI; however this is in contradiction to the rest of the network where the improvement in Cayston vs placebo is smaller than the improvement in TOBI versus placebo. As the exposure status is believed to be an effect modifier, this inconsistency is likely due to the inclusion of one naïve arm (Cayston) and one arm exposed to the study drug (TOBI) prior at baseline.

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[5] Konstan MW et al. (2010a). Tobramycin inhalation powder for *P.aeruginosa* infection in cystic fibrosis: The EVOLVE trial. *Pediatric Pulmonology*.46(3): 233-8.

[6] Konstan MW et al. (2010b). Safety, efficacy and convenience of tobramycin inhalation powder in cystic fibrosis patients: The EAGER trial. *Journal of Cystic Fibrosis*.10: 54-61

[7] Hodson ME et al. (2002). A randomized clinical trial of nebulised tobramycin or colistin in cystic fibrosis. European Respiratory Journal 2002;20:658-64.

[8] Cystic Fibrosis Trust (CF Trust) (2009b). Antibiotic treatment for cystic fibrosis. CF Trust. 93.

- Two studies included mild FEV1% predicted patient populations at baseline. Patients today may be less severely ill which may impact outcomes. For all other studies, figures ranged between 49.9 and 63.6 (ie, moderate impairment) with the two excluded studies as outliers (>70 and >80).
- One study included 24.1% of patients in the Bramitob arm and 16.7% of patients in the placebo arm with a first or intermittent Pa infection. As these patients were not chronically infected with Pa, they might be considered less severe patients, and may be expected to have better outcomes. Furthermore, the intention of antibiotic treatment for first or intermittent Pa infection is eradication of the infection. This falls outside of the licensed indication for TOBI and TOBI Podhaler, and also falls outside of the scope of this appraisal.

Due to the small network of studies and the underlying differences in population, a series of scenario analyses were run using different covariates or subgroups to assess the relative treatment effects. Below are the scenario analyses which were explored as potential treatment effect modifiers:

- **Baseline mean FEV$_1$% predicted:** This is an indicator of disease severity which may play a role in treatment outcomes.
- **Study publication date:** Treatment has evolved and the expected outcomes for patients today are substantially different to 10 years ago. The oldest study publication date was 1987, followed by 1999 and 2002. All other studies were published after 2006.
- **Naïve or exposed status to the active ingredient used in the study arm:** Prior exposure to the study drug accounts for differences in treatment effect sizes observed. In studies where patients were previously using tobramycin, the effect of TOBI was to maintain or slightly improve FEV$_1$% predicted at 4 weeks. In studies where patients were naïve to tobramycin, much larger improvements in FEV$_1$% predicted were observed at 4 weeks.
- **Baseline mean age:** Age (≤ 18 years, > 18 years) is a known modifier which has indirect implications on outcomes. Figures ranged from 11 to 16 for five of the studies whereas the means ranged from 20 to 32 years old for six studies.

The NMA found TOBI Podhaler to be comparable to TOBI, Bramitob, Colistin and Cayston in improving FEV$_1$% predicted at 4 weeks. Limited data were available for the other endpoints (FEV$_1$% predicted at 20 weeks, sputum density at 4 weeks and 20 weeks, respiratory hospitalisation at 24 weeks and anti-Pa antibiotic use at 24 weeks) but generally found active treatments had comparable effects to each other and were expected to have better outcomes than placebo. Colobreathe was not included in any of the scenario analyses due to the absence of clinical evidence in the public domain.

Cost effectiveness

A CUA was explored but not presented due to the limitations in the data set; assumptions and limitations in conducting a CUA with the identified evidence base are presented in detail. With the EAGER study directly confirming the similarity of TOBI and TOBI Podhaler, and the lack of data for all other comparator treatments, the resulting model would be driven by assumptions derived from these two products which have already been directly proven to have similar safety and efficacy profiles and thus minimal differences in measurable incremental health economic benefits. In light of this as well as the magnitude of uncertainty from the marked variability in patient populations, study designs and outcomes within the clinical studies, it was concluded that a CUA would not be appropriate or feasible.

Conclusion

A limited evidence base in cystic fibrosis coupled with vast differences in trial design and outcomes led to substantial uncertainty in statistical analyses. Large credible ranges around point estimates found the active treatments to be comparable with each other which raises further questions regarding the validity of undertaking a cost-utility analysis.

The identified literature and corresponding analyses support the conclusion that CF patients aged 6 years and over with chronic Pa pulmonary infection can achieve a comparable response with TOBI Podhaler as with the other active comparators (excluding Colobreathe due to an absence of data in the public domain). TOBI Podhaler was found to significantly lessen administration time, decrease treatment burden and significantly improve patient satisfaction which may have implications on compliance and thus treatment efficacy in some patients.