PUBLIC SUMMARY DOCUMENT
Product: Tobramycin, solution for inhalation, single dose units, 300 mg in 5 mL, 56, TOBI®
Sponsor: Novartis Pharmaceuticals Australia Pty Ltd
Date of PBAC Consideration: March 2011

1. Purpose of Application

The submission sought a Section 100 (Highly Specialised Drug) PBS listing for tobramycin solution for inhalation, 300 mg in 5 mL, for the treatment of a *Pseudomonas aeruginosa* respiratory infection in a patient with Cystic Fibrosis (CF).

Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

2. Background

At the March 2000 and September 2002 meetings, the PBAC rejected submissions from the previous sponsor for a Section 100 listing for tobramycin ampoules for nebulisation, 300 mg in 5 mL (TOBI®), on the basis of unacceptable cost-effectiveness and doubts over the magnitude and duration of benefit.

3. Registration Status

Tobramycin 300 mg 5 mL solution for inhalation was TGA registered on 15 February 2000 for the management of cystic fibrosis patients with *Pseudomonas aeruginosa* infections.

4. Listing Requested and PBAC's View

Section 100 (Highly Specialised Drugs Program)
Public hospital Authority Required (STREAMLINED)
Private hospital Authority Required
PBS – subsidised treatment by a respiratory physician at a cystic fibrosis clinic/centre. If patient attendance at such a centre is not possible because of geographical isolation, management (including prescribing) may be by a specialist physician or paediatrician in consultation with a cystic fibrosis clinic/centre.

Patients must satisfy all of the following criteria:

(a) has a confirmed diagnosis of cystic fibrosis; and
(b) positive culture for pulmonary *Pseudomonas aeruginosa* from a sputum, oropharyngeal or bronchoalveolar lavage/bronchoscopy sample, within the last six months

Note
Before treatment with tobramycin solution for inhalation is commenced, the patient should have his or her lung function measured by experienced personnel at an established cystic fibrosis clinic/centre or lung function testing facility. Lung function should be monitored periodically while the patient is on tobramycin solution for inhalation.

With long term treatment, periodic testing that the *Pseudomonas aeruginosa* infection remains susceptible to tobramycin should be performed.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Cystic fibrosis (CF) is a genetic disorder affecting cells in the exocrine glands. This results in abnormal ion transport and hydration at epithelial cell surfaces. In the lung, mucous clearance is compromised, and this allows bacterial infections to persist in static mucous. Over time, the resultant sub-optimal inflammatory response to the infection contributes to lung damage and progressive impairment of lung function. Patients with cystic fibrosis therefore have a greater risk of chronic lung infections and intermittently receive courses of antibiotics by injection or nebulisation to manage these infections. If chronically colonised with the organism *Pseudomonas aeruginosa* they may require multiple courses of intravenous aminoglycoside antibiotics for the management of pulmonary exacerbations. The number of patients with CF in Australia in 2008 as recorded by the Australian Cystic Fibrosis Data Registry (ACFDR) was 2,843.

The submission proposed the place in therapy of tobramycin solution for inhalation in cystic fibrosis would be to replace the "off label" use of preservative free parenteral formulations of tobramycin via nebuliser, when inhaled tobramycin is required.

6. Comparator

The submission nominated placebo or standard care without the use of inhaled tobramycin as the comparator, which the PBAC agreed was an acceptable comparator in the management of chronic *Ps. aeruginosa* infection.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The submission presented the following studies in support of the comparative effectiveness of tobramycin solution for inhalation (TSI) to placebo for management of *Pseudomonas aeruginosa* infection in patients with cystic fibrosis:

1. Management of chronic *P. aeruginosa* infection
   The submission presented the pooled results (Ramsey 1999; Quittner 2002) from two blinded randomised trials (Trial 002 and Trial 003) comparing TSI with placebo (both in addition to standard care), one open-label, supplementary randomised trial comparing TSI with standard care (Murphy 2004), and one supplementary non-comparative study (Study 004, Moss 2001, Moss 2002), which was the 96 week extension trial of 002/003.

For PBAC's view, see Recommendation and Reasons.

2. Eradication of early *P. aeruginosa* infection
   The submission presented one direct randomised trial comparing TSI and placebo, in the absence of other anti-pseudomonal antibiotics (Gibson 2003), and one supplementary trial comparing two durations of TSI therapy (28 days vs 56 days) (Ratjen 2010).

The submission did not present any trials in support of the use of TSI for treatment of acute exacerbations of lung disease.

The table below details the published trials presented in the submission:

Trial ID	Protocol title/ Publication title	Publication citation

Management of chronic infection		
Randomised controlled trials		
Ramsey BW et al	Intermittent administration of inhaled tobramycin in patients with cystic fibrosis.	New England Journal of Medicine 1999; 340:23-30.
Quittner A et al	Effects of tobramycin solution for inhalation on global ratings of quality of life in patients with cystic fibrosis and *Pseudomonas aeruginosa* infection.	Pediatric Pulmonology 2002; 33:269-276
Murphy T et al	Treatment with tobramycin solution for inhalation reduces hospitalisations in young CF subjects with mildling disease.	Pediatric Pulmonology 2004; 38:314-20.
Supplementary non-comparative studies		
Moss R et al	Administration of aerosolized antibiotics in cystic fibrosis patients.	Chest 2001; 120 (Suppl 3):107S-113S.
Moss RB. et al	Long-term benefits of inhaled tobramycin in adolescent patients with cystic fibrosis.	Chest 2002; 121:55-63.
Eradication of early infection		
Randomised trials		
Gibson RL et al	Significant microbiological effect of inhaled tobramycin in young children with cystic fibrosis.	American Journal of Respiratory and Critical Care Medicine 2003; 167:841-49.
Ratjen F et al	Treatment of early *Pseudomonas aeruginosa* infection in patients with cystic fibrosis: the ELITE trial.	Thorax 2010; 65:286-91.

8. Results of Trials

1. Management of chronic *P. aeruginosa* infection

TSI was administered twice daily in alternating periods of 28 days on treatment followed by 28 days off treatment.

The submission reported the results from Ramsey 1999, which analysed the pooled data from Trials 002 and 003. Whilst Chuchalin 2007 was not included in the submission due to differences in the formulations of tobramycin (300 mg/4 mL in Chuchalin 2007 vs 300 mg/5 mL in the submission), the PBAC considered the similar design to trials 002 and 003 and it being more recent than those trials meant that Chuchalin 2007 was informative and relevant.

The main primary outcome in Trial 002 and Trial 003 and Chuchalin 2007 was mean change in forced expiratory volume in 1 second (FEV_1) % of predicted from baseline to the end of the third 'on-treatment' phase (Week 20).

In the management of chronic *Ps. aeruginosa* infection, Ramsey 1999 only reported the change in FEV_1 % predicted, which was the main primary outcome, as a relative measure. This was not considered appropriate by the PBAC. The only data on the absolute change in FEV_1 % predicted was for the pooled populations of the two trials, which were sourced during the evaluation from the Commentary on the March 2000 PBAC submission. The PBAC noted that, although there was a statistically significant difference between the treatment groups in both the pooled Trials 002/003 and Chuchalin 2007, the mean treatment effect was approximately 6% and the PBAC questioned the clinical important of this difference.

In Trials 002 and 003 there was a significant decrease in the density of *Ps. aeruginosa* in sputum samples from patients randomised to TSI during the active cycle. The effects of TSI were not sustained during the 'off-treatment' phase. The magnitude of the reduction in the density of *Ps. aeruginosa* during the 'on-treatment' phase appeared to decrease with each successive cycle.

Secondary outcomes in Trials 002 and 003 included the number of patients hospitalised and the time to first hospitalisation.

The submission presented the results of an open-label extension study (Study 004), which enrolled subjects from Trials 002 and 003. Patients randomised to placebo in Trials 002 and 003 were switched to TSI at the beginning of the extension study. There were no comparative data for the effectiveness of TSI beyond 24 weeks of treatment.

As cystic fibrosis is a progressive disease, FEV1 will decrease with the natural progression of the disease. Therefore, in the absence of a control arm, it is not possible to estimate the extent of any treatment effect, nor is it possible to determine if this effect is sustained over time.

For PBAC's comments on these results, see Recommendation and Reasons.

2. Eradication of early *P. aeruginosa* infection

In Gibson 2003, TSI was administered twice daily for 28 days. The primary outcome was the mean change in *P. aeruginosa* density in bronchoalveolar lavage (BAL) fluid from baseline to end of treatment. This trial was terminated early after an interim efficacy analysis which was not stipulated in the trial protocol.

***P. aeruginosa* eradication therapy results (Gibson 2003)**

	TSI N=8	Placebo N=13	Risk difference (95% CI)
Change in density Pa (baseline to Day 28), log_{10}CFU/mL Mean (SD) Adjusted for stopping rule	-5.25 (2.34)	0.30 (2.15)	5.55 (3.46, 7.64) 5.36 (3.52, 7.54)
Patients free of Pa at day 28 by BAL sampling, n/N (%)	8/8 (100%)	1/13 (7.4%)	92% (70%, 114%)
Patients free of Pa at day 56 by OP sampling, n/N (%)	6/8 (75.0%)	3/13 (23.1%)	52% (14%, 90%)

BAL=bronchoalveolar lavage; CFU=colony forming units; CI=confidence interval; Pa=*P. aeruginosa*; OP=oropharyngeal

While there was a clinically important reduction in *P. aeruginosa* density, and a significant difference in the number of patients free of infection at both end of treatment and 28 days after discontinuation of treatment, the PBAC noted that this trial did not establish if "eradication" was maintained over a clinically important time-frame, nor how this translated into patient-relevant final outcomes, such as hospitalisation and survival. The data at 56 days was considered more relevant than at 28 days, but overall remain uncertain based on the quality of the data.

The PBAC noted that in Trials 002 and 003, the only adverse events (AEs) reported by considerably more TSI patients than placebo patients were voice alteration (13% vs 7%,

respectively) and tinnitus (3% vs 0%, respectively). All episodes of tinnitus resolved with discontinuation of TSI and were not associated with loss of hearing.

9. Clinical Claim

1. Management of chronic *P. aeruginosa* infection

The submission described TSI as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety over placebo, which was considered reasonable.

2. Eradication of early *P. aeruginosa* infection

The submission described TSI as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety over placebo. The claim that TSI is superior to placebo in terms of the comparative effectiveness for short-term eradication of early *P. aeruginosa* infection was considered reasonable, although it was only supported by one small randomised trial that was terminated early as a result of an unplanned interim analysis. The PBAC noted that there were insufficient data to make any conclusions regarding the comparative safety of TSI in this indication.

10. Economic Analysis

Management of chronic infection:

A trial-based economic evaluation was presented based on the rate of hospitalisations in the pooled populations of Trials 002 and 003. An incremental cost per extra hospitalisation avoided over 24 weeks was calculated to be less than $15,000.

Eradication of early infection

The resources considered in the economic evaluation were costs of tobramycin, outpatient services and pathology services. The outcome used in the evaluation was the proportion of patients with a *P. aeruginosa*-negative BAL culture at the end of treatment (28 days).
An incremental cost per patient free of *P.aeruginosa* at the end of treatment was calculated to be less than $15,000.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated to be less than 5,000 in Year 5.
The financial cost per year to the PBS was estimated to be less than $10 million in Year 5.

12. Recommendation and Reasons

The PBAC recommended the listing of tobramycin solution for inhalation (TSI) on the PBS with an Authority Required (STREAMLINED) listing for the management of proven *Pseudomonas aeruginosa* infection in a patient with cystic fibrosis on the basis of acceptable cost effectiveness compared with placebo. The PBAC acknowledged that there is a high clinical need to allow PBS access to this treatment which is currently the standard of care, that the price provided acceptable cost-effectiveness, and although the data are poor, a clinical benefit is demonstrated and likely to be underestimated.

The PBAC agreed that placebo or standard care without the use of inhaled tobramycin was an acceptable comparator in the management of chronic *Ps. aeruginosa* infection, although it noted that use (in the trial) without the addition of IV and oral antibiotics in the eradication of early *Ps. aeruginosa* infection was not consistent with current clinical guidelines. Although

the clinical treatment paradigm for inhaled antibiotics was uncertain, the PBAC acknowledged that this had now become standard practice. Even taking into account areas of uncertainty around continuous versus intermittent therapy and duration of benefit, the PBAC recognised that this was an area of clinical need.

The PBAC noted that the two key randomised trials presented in the submission (Trials 002 and 003) were more than 10 years old and had previously been considered by PBAC in 2000 and 2002. Another randomised trial (Chuchalin 2007) was identified during the evaluation but not included by the sponsor due to differences in the formulations of tobramycin (300 mg/4 mL in Chuchalin 2007 vs 300 mg/5 mL in the submission). While PBAC accepted this, it was nonetheless informative and relevant to consideration as it was of similar design to Trials 002 and 003 and featured more recent data.

In the management of chronic *Ps. aeruginosa* infection, Trials 002 and 003 only reported the change in FEV_1 % predicted, which was the main primary outcome, as a relative measure. This was not considered appropriate by the PBAC. The only data on the absolute change in FEV_1 % predicted was for the pooled populations of the two trials. The PBAC noted that, although there was a statistically significant difference between the treatment groups in both the pooled Trials 002/003 and Chuchalin 2007, the mean treatment effect was approximately 6% and the PBAC questioned the clinical important of this difference.

At the Hearing the clinician emphasised that the primary focus was to decrease the loss of lung function and that better long-term outcomes resulted from earlier commencement on therapy. It was also noted that a clinically meaningful change in FEV_1 % predicted depended on patients baseline lung function and that patients with good lung function have more to lose. Thus, in the older tobramycin trials where patients had poor lung function at baseline (approximately 50% FEV_1 % predicted), it was difficult to show large absolute changes in FEV_1 % predicted.

The PBAC noted that in Trials 002 and 003 there was a significant decrease in the density of *Ps. aeruginosa* in sputum samples from patients randomised to TSI during the active cycle but that the effects of TSI were not sustained during the 'off-treatment' phase. The magnitude of the reduction in the density of *Ps. aeruginosa* during the 'on-treatment' phase appeared to decrease with each successive cycle. In the Chuchalin 2007 study, the PBAC noted that the statistically significant difference in hospitalisations between treatment arms supported the findings reported in Trial 002. The difference in hospitalisation rate was used as the basis of the economic evaluation.

In the eradication of early *Ps. aeruginosa* infection, the primary outcome in the key trial (Gibson 2003) was the mean change in *Ps. aeruginosa* density in bronchoalveolar lavage fluid from baseline to end of treatment. The PBAC noted that the submission did not establish how this translated into patient-relevant final outcomes, such as hospitalisation and survival however considered that eradication is a reasonable clinical outcome. The data at 56 days was considered more relevant than at 28 days, but overall remain uncertain based on the quality of the data.

For the management of chronic *Ps. aeruginosa* infection, a trial-based economic evaluation was presented based on the rate of hospitalisations in the pooled populations of Trials 002 and 003. The PBAC noted that the current hospitalisation rates of cystic fibrosis patients in

Australia were likely to be lower than the trial-based estimates based on a US trial conducted fourteen years ago. Based on a Section 85 listing, the incremental cost per extra hospitalisation avoided was less than $15,000.

Given there is a possibility for tobramycin to be used continuously, rather then one month on/one month off, a risk share arrangement with expenditure thresholds based upon 6.5 prescriptions per patient per year may be necessary to ensure PBS use reflects the treatment paradigm considered for establishing cost effectiveness.

The PBAC noted the consumer comments received for this item. The Committee also noted the advice from the Highly Specialised Drugs Working Party, that the submission did not meet all the criteria for a highly specialised drug.

The PBAC recommended that tobramycin solution for inhalation is not suitable for inclusion in the list of PBS medicines for prescribing by nurse practitioners or midwives.

Recommendation:
TOBRAMYCIN, solution for inhalation, single dose units, 300 mg in 5 mL, 56

Restriction:	Authority Required (STREAMLINED) Management of a proven *Pseudomonas aeruginosa* infection in a patient with cystic fibrosis. NOTE: Special Pricing Arrangements apply. No applications for increased maximum quantities and/or repeats will be authorised.
Max qty:	56
Repeats:	2

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Novartis welcomes the PBAC's decision to recommend the listing of tobramycin solution for inhalation on the PBS for patients with cystic fibrosis who have a high clinical need for this treatment.