PUBLIC SUMMARY DOCUMENT

Product: Tobramycin, powder for inhalation, capsules 28 mg, Tobi® Podhaler®

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

Date of PBAC Consideration: March 2013

1. Purpose of Application

The submission sought an Authority required (STREAMLINED) listing for the management of a proven *Pseudomonas aeruginosa* infection in a patient aged 6 years or older with cystic fibrosis.

2. Background

The PBAC had not previously considered a submission for a dry powder inhaler presentation of tobramycin.

In March 2011, the PBAC considered a Section 100 (Highly Specialised Drug) PBS listing for tobramycin solution for inhalation, 300 mg in 5 mL, for the treatment of *P. aeruginosa* respiratory infection in a patient with cystic fibrosis. The PBAC recommended the listing of tobramycin solution for inhalation (TSI) as a Section 85 item on the PBS, on the basis of acceptable cost effectiveness compared with placebo.

Details of this consideration are in the relevant Public Summary Document available at: http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-tobramycin-march11

3. Registration Status

Tobramycin powder for inhalation was TGA registered on 6 March 2012 for the management of cystic fibrosis patients with P. aeruginosa infections. Safety and efficacy have not been demonstrated in patients under the age of 6 years, patients with FEV1 less than or equal to 25 % or greater than or equal to 80 % predicted at screening, or patients colonized with *Burkholderia cepacia.*

4. Listing Requested and PBAC's View

Authority required (STREAMLINED)

Management of a proven *Pseudomonas aeruginosa* infection in a patient aged 6 years or older with cystic fibrosis.

Alternative Listing 1:

Management of a proven and chronic *Pseudomonas aeruginosa* infection in a patient aged 6 years or older with cystic fibrosis.

Alternative Listing 2:

Management of a proven and chronic Pseudomonas aeruginosa infection in a patient aged 6 years or older with cystic fibrosis, every alternate 28 days.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Tobramycin inhaled powder (TIP) was proposed as an additional treatment option for patients with cystic fibrosis requiring long-term management of chronic pseudomonal infection.

For PBAC's view, see Recommendation and Reasons.

6. Comparator

The submission nominated tobramycin solution for inhalation (TSI) as the comparator. The PBAC considered the nominated comparator to be appropriate.

7. Clinical Trials

The submission presented one head-to-head randomised trial comparing TIP 224 mg/day with TSI 600 mg/day over three 28-day on/off cycles with 6 months in total (Trial 2302) in 517 patients with cystic fibrosis.

The submission also presented two randomised placebo controlled trials of one cycle duration (Trial 2301 and Trial 2303) as supportive data to the pivotal trial. In study 2301 patients in the placebo arm are switched to TIP for another two cycles.

The primary outcome measure in trial 2302 was comparative safety of the two formulations. The primary outcome measure in trial 2301 was relative change in FEV1 % predicted from baseline to the end of cycle 1, while the primary outcome in trial 2303 was relative change in FEV1 % predicted from baseline to day 29. Clinical efficacy was assessed as a secondary outcome in trial 2302, reported as the relative change in FEV1 % predicted from baseline.

The PBAC noted that trial 2302 was an open-label trial and therefore carried a high risk of bias due to unblinding. The PBAC also noted that the analysed population in trial 2302 was identified as an intention-to-treat (ITT) population, but that the analyses were based on patients with observed data with no imputations performed for missing data.

Details of the trials and associated reports presented in the submission are in the table below.

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Direct randomised trial		
Trial 2302 Konstan, et al	Safety, efficacy and convenience of tobramycin inhalation powder in cystic fibrosis patients: The EAGER trial	*J of Cystic Fibrosis,* 2011; 10 (1):54-61.
Konstan, et al	Safety and efficacy of tobramycin inhalation powder (TIP) in treating CF patients infected with Pseudomonas aeruginosa (Pa)	*J of Cystic Fibrosis,* 2010;9 Suppl 1, pp.S22, Abstract no:82.
Geller	Treatment convenience and satisfaction of tobramycin inhalation powder (TIP) versus TOBI in cystic fibrosis patients [abstract]	*J of Cystic Fibrosis,* 2010;9 (Suppl 1): S22. Abstract 83
Geller	Tobramycin inhalation powder vs. tobramycin inhalation solution for cystic fibrosis: Response by age group in the eager trial	*Pediatric Pulmonology,* 2011; S337, Abstract 347
Regnault et al	Association of treatment satisfaction and compliance of cystic fibrosis (CF) patients using inhaled tobramycin treatment in the EAGER study [Abstract 323]	*J of Cystic Fibrosis,* 2011;10 (Suppl 1):S82 Abstract 323
Supplementary randomised trials		
Trial 2301 Konstan, et al	Tobramycin inhalation powder for P. aeruginosa infection in cystic fibrosis: The EVOLVE trial	*Pediatr Pulmonol*, 2011; 46(3):230-238
Konstan, et al	Tobramycin Inhalation powder Is Effective and safe in the treatment of chronic pulmonary Pseudomonas aeruginosa (Pa) infection in patients with cystic fibrosis	*Am J Respir Crit Care Med,* 2009;179: Abstract 1186
Konstan, et al	Effective treatment of chronic Pseudomonas aeruginosa (Pa) infection with tobramycin inhalation powder in CF patients [Abstract 105]	*J of Cystic Fibrosis,* 2009;8(Suppl 2):S27, Abstract
Trial 2303 Galeva et al	A randomised, double-blind, placebo-controlled study of tobramycin inhalation powder in patients with cystic fibrosis: the EDIT trial	*Pediatr Pulmonol*, 2011; S344, Abstract 366
Galeva et al	A challenging double-blind, placebo-controlled study of tobramycin inhalation powder in cystic fibrosis: Results of the EDIT trial	*J of Cystic Fibrosis,* 2012; Abstract WS5.6; S12
Quittner	Trends in health-related quality of life (HRQoL) in cystic fibrosis with tobramycin inhalation powder: The EDIT trial	*J of Cystic Fibrosis,* 2012; S73, Abstract 67

8. Results of Trials

Trial 2302 was a safety study and all efficacy outcomes investigated were secondary outcomes. The most relevant outcome for the PBAC's consideration of the efficacy of TIP was change in FEV_1 % predicted from baseline. This was reported only as a relative measure in trial 2302. The PBAC recalled it has previously considered that the presentation of change in FEV_1 as a relative measure only is not appropriate (March 2011, tobramycin submission Public Summary Document).

The submission presented a non-inferiority analysis, using a one-sided 85% confidence interval. The table below summarises the results.

FEV_1 % predicted relative change from baseline to Day 28 of Cycle 3 in trial 2302

Trial 2302	TIP N=308	TSI N=209	Difference (SE)	85% one-sided CI of the diff
n analysed (%)	227 (73.7%)	171 (81.8%)		
LS Mean	5.8	4.7	1.1 (1.75)	-0.67, 2.96

SE = standard error; n=number of patients with values at baseline and Day 28 of cycle 3.

There was an increase in FEV_1 % predicted from baseline to pre-dose day 28 of cycle 3 in both TIP and TSI treatment groups. The increase favoured TIP numerically, but analysis confirmed non-inferiority to TSI, with the lower CI within the pre-defined non-inferiority margin of 6%.

Discontinuations were greater in the TIP arm of trial 2302 (26.9% versus 18.2%), and there was a significantly greater use of anti-pseudomonal antibiotics in the TIP arm (Relative risk RR: 1.19; (95% CI 1.03, 1.38))

Microbiology and pharmacokinetic outcomes indicated that TIP administration appears to result in comparable lung exposure to TSI. Drug administration time (from first to last inhalation; not including setup and cleaning) was significantly shorter with TIP compared to TSI: 5.6 vs 19.7 minutes, giving a saving of 14.1 minutes per session, twice a day.

Assessment of treatment satisfaction demonstrated statistically significant advantages for TIP compared to TSI for the effectiveness, convenience and global satisfaction domains of the Treatment Satisfaction Questionnaire for Medication (TSQM). There was no difference between the groups for the side effects outcome.

In terms of comparative harms, cough that was probably related to the dry powder formulation of the study drug, occurred in significantly more TIP-treated patients (25.3%) compared to TSI patients (4.3%). Dysphonia also occurred significantly more with TIP. Overall adverse events suspected to be related to treatment, were experienced by 51.0% of TIP-treated patients and 20.1% of TSI-treated patients.

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The submission claimed TIP was non-inferior to TSI in terms of clinical efficacy and clinical safety, and superior to TSI with respect to the patient-relevant outcome of self-reported satisfaction with treatment.

In relation to clinical safety, it was noted that cough and dysphonia were regarded as local tolerability issues, and did not compromise the overall finding of non-inferiority.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost-utility analysis on the basis of superior effectiveness, which was based on improved patient satisfaction with treatment compared to tobramycin solution for inhalation (TSI).

The economic model was of 5 years duration, with 6 months treatment cycles, focussing on treatment administration and including pulmonary exacerbations. There was an assumption of no difference between the treatments for these variables.

The results of the model were driven by the utilities derived from a time-trade-off study. The risk, cost, duration and disutility associated with exacerbations, and the risk of death were the same for both treatment groups. The costs included in the model were the cost of therapy, and out-of-pocket expenses for patients associated with the administration of TSI.

The incremental cost per quality adjusted life year (QALY) was between $15,000 and $45,000.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated PBS usage and financial implications for TIP using a combined epidemiology and market share approach.

The estimated net cost per year to the PBS was less than $10 million in Year 5.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC rejected the submission based on uncertainty in the comparative benefit of TIP over TSI, and on the basis that TIP's comparative tolerability compared to TSI was potentially less favourable, resulting in the cost-utility approach to the economic analysis being considered inappropriate.

With regard to the requested listing, the PBAC noted the sponsor's reasons for limiting treatment to patients aged 6 years or older but expressed a preference for the proposed restriction not to specify an age limit as the management of cystic fibrosis tends to be specialised, therefore the likelihood that tobramycin inhaled powder (TIP) is prescribed age-inappropriately would be low.

The PBAC did not express a particular preference for one of the three listing proposals at this meeting.

The PBAC noted a video presentation provided by the sponsor, demonstrating the administration of TIP. The PBAC acknowledged that the manner of administration of TIP would be of benefit to various patient groups and was sympathetic towards those patients who would benefit from an increased level of convenience resulting from the manner of drug administration.

With regard to the evidence presented in the submission, the PBAC noted that Trial 2302 was an open-label trial and therefore carried a high risk of bias due to lack of blinding. The PBAC also noted that the analysed population in Trial 2302 was identified as an intention-to-treat (ITT) population, but that the analyses were based on patients with observed data with no imputations undertaken for missing data.

The PBAC did not consider that "improved treatment satisfaction" was an appropriate measure of comparative effectiveness and would have preferred data examining clinical improvements. Furthermore, the higher rate of discontinuation with TIP (26.9%) compared to TSI (18.2%), along with a higher rate of major protocol violations due to failure to adhere to medication, do not appear to be consistent with a claim of improved treatment satisfaction.

The PBAC recalled that it previously did not consider mean relative change in FEV1% predicted from baseline to be appropriate, and reaffirmed this view. The PBAC considered that FEV1% reported in absolute terms would have been more informative. The PBAC further noted that no justification was provided for the non-inferiority margin used (a one-sided 85% confidence interval).

The PBAC considered the submission's explanation that the greater cough rate in TIP treated patients is attributable to the dry powder formulation of TIP as reasonable. The PBAC noted that while the adverse events that occurred were not serious, there was an impact on trial discontinuation, with 14.0% of TIP patients and 8.1% of TSI patients discontinuing the trial as a consequence.

In the context of minimising the development of antimicrobial resistance as well as the claim of non-inferior clinical efficacy, the PBAC was concerned about the increased use of additional anti-pseudomonal antibiotics in the TIP arm of Trial 2302, with 'any use of anti-pseudomonal antibiotics' reported as 65.6% (TIP) vs. 55% (TSI), relative risk 1.19 [95%CI: 1.03, 1.38]. The explanation for this increased antibiotic use was not clear.

The higher rate of discontinuations with TIP compared to TSI concerned the PBAC and seemed at odds with the idea that TIP's method of administration would result in greater patient satisfaction and, in turn, greater patient adherence/compliance. Additionally, the PBAC considered that the derivation of costs of decreased nebulising equipment use should be made clearer.

The PBAC did not accept the submission's claim that TIP was non-inferior to TSI in terms of clinical efficacy and safety, and superior to TSI with respect to patient relevant outcomes. The PBAC considered that the clinical efficacy data establishing non-inferiority was of limited quality, the comparative effectiveness measure of improved treatment satisfaction was not considered an appropriate measure, and, the incidence of adverse events and number of treatment discontinuations with TIP appeared worse compared to TSI.

The PBAC also considered that the price premium for TIP over TSI was not well justified but acknowledged the inherent difficulty in valuing the benefits of increased convenience derived from new forms of drug administration.

The PBAC considered that the evidence presented in the submission did not provide a reasonable basis for a cost-utility approach to the economic analysis as patient treatment satisfaction was not considered to be an appropriate basis for a cost-effectiveness claim.

The PBAC noted that the economic model presented in the submission did not take into account the potential differences in discontinuation between TIP and TSI treatment and the implications for treatment options post discontinuation. Given that discontinuations were higher in the TIP arm of Trial 2302, differences in discontinuations were likely to bias the result in favour of TIP. The PBAC noted that this aspect of the economic model was addressed in the pre-PBAC response, but that the incremental cost/QALY remained higher than that presented in the submission despite the lower price proposed in the pre-PBAC response.

The PBAC considered that the methodology of deriving utility values from a time-trade-off study focusing primarily on the mode of administration of tobramycin for TIP and TSI was inappropriate. The PBAC further considered that isolating and valuing one component of the management of cystic fibrosis out of context of the whole impact of the condition is likely to overestimate the value of that component, as the relative benefit in the whole picture of disease is not captured.

The PBAC considered that the estimated number of patients treated, and the net cost to the PBS would require further clarification.

As a potential way forward, the PBAC considered that a cost-minimisation claim against TSI with a cost-offset for reduced nebulising equipment costs, may be an option for the sponsor to consider. Alternatively, a cost-minimisation claim against TSI with a price premium based on the willingness-to-pay study explored in the March 2013 submission, is also an option for the sponsor to consider.

In making this recommendation the PBAC noted the consumer comments on this item.

The PBAC noted that the submission is eligible for an Independent Review.

Recommendation:
Rejected

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 acknowledges the views of the PBAC – the issues of concern as well as the positive statement regarding potential benefit for patients. Novartis is committed to addressing the issues of concern, so that patients with cystic fibrosis who have a high treatment burden may access this therapy.