

## **PUBLIC SUMMARY DOCUMENT**

**Product:** Tobramycin, inhalation: powder for, capsules 28 mg, Tobi<sup>®</sup> Podhaler<sup>®</sup>

**Sponsor:** Novartis Pharmaceuticals Australia Pty Ltd

**Date of PBAC Consideration:** November 2013

### **1. Purpose of Application**

The major re-submission requested an Authority Required (STREAMLINED) listing for the treatment of *Pseudomonas aeruginosa* infection in a patient aged 6 years or older with cystic fibrosis.

### **2. Background**

This was the second submission considered by the PBAC for tobramycin inhalation powder (TIP) for the treatment of *Pseudomonas aeruginosa* infection in patients with cystic fibrosis (CF).

At its March 2013 meeting, the PBAC rejected the submission on grounds that the claims of non-inferiority and comparative benefit to the comparator, tobramycin solution for inhalation (TSI) was not adequately established, in terms of a clinically relevant patient outcome(s) other than patient satisfaction. TIP's comparative harms compared to TSI were potentially less favourable, resulting in the cost-utility approach to the economic analysis being considered inappropriate. The Public Summary Document (PSD) is available on the [PBS website](#).

### **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**

#### **Initial treatment**

#### **Authority required (STREAMLINED)**

Treatment of a patient with cystic fibrosis who satisfies all of the following criteria:

1. Is 6 years of age or older;
2. Has a proven *Pseudomonas aeruginosa* infection;
3. Has been assessed for bronchial hyperresponsiveness as per the TGA-approved PI, with a negative test result; and
4. Is participating in a 4 week trial of tobramycin inhalation powder and will be assessed for ability to tolerate the dry powder formulation in order to qualify for continued PBS-subsidised therapy. The trial commencement date must be documented in the patient's medical records.

## **Continuing treatment**

### **Authority required (STREAMLINED)**

Treatment of a patient with cystic fibrosis who satisfies all of the following criteria:

1. Is 6 years of age or older;
2. Has a proven *Pseudomonas aeruginosa* infection;
3. Has been assessed for bronchial hyperresponsiveness as per the TGA-approved PI, with a negative test result; and
4. Has participated in a 4 week trial of tobramycin inhalation powder and has demonstrated ability to tolerate the dry powder formulation, as agreed by the patient, the patient's family (in the case of paediatric patients) and the treating physician(s). The trial commencement and assessment dates and outcome must be documented in the patient's medical records.

Note:

Special pricing arrangements apply.

No applications for increased maximum quantities and/or repeats will be authorised.

The key difference between the March 2013 and the November 2013 submissions was a proposal to separate 'initial treatment' and 'continuing treatment' PBS items in the requested restriction.

The re-submission stated that the initial/continuing treatment was intended to address PBAC concerns that was related to discontinuations due to adverse events (AEs) seen in the pivotal trial, and the need to target therapy to patients who tolerate the dry powder formulation.

The PBAC considered the criteria in the restriction of a 4 week trial of TIP was appropriate to address the issue of the higher rate of discontinuations with TIP compared to TSI observed in the trial data, and targeted continued use of TIP in patients who tolerate TIP. The PBAC considered that the 4 week trial of TIP should be cost-neutral to Government, with the cost being borne by the sponsor. This should form part of a Risk Sharing Arrangement.

The PBAC considered it appropriate that the restriction should allow for patients who have trialled and not tolerated TIP once, to try TIP at a later time, as patient may wish to re-trial TIP as they get older (such as when entering adolescence) or there are changes in the burden of disease for a patient and a re-trial is appropriate.

In relation to inclusion of an age limit in the restriction, the PBAC reconsidered its deliberations in March 2013, and concluded that it was appropriate to include an age limit of 6 years and over in the restriction for TIP.

## **5. Clinical Place for the Proposed Therapy**

The therapeutic class of tobramycin is antimicrobial – aminoglycoside, active against a wide range of gram-negative organisms, including *P. aeruginosa*. Tobramycin is bactericidal in activity and acts primarily by disrupting protein synthesis, leading to altered cell membrane permeability, progressive disruption of the cell envelope, and eventual cell death. When inhaled, tobramycin remains concentrated primarily in the airways.

TIP was proposed as an additional treatment option for patients with cystic fibrosis requiring long-term management of chronic pseudomonas infection.

The PBAC acknowledged that the manner of administration of TIP would be of benefit to various patient groups with a high burden of treatment.

## **6. Comparator**

The re-submission nominated TSI as the comparator on the basis that TSI is a pharmacological analogue and that TSI is currently the only antibiotic on the PBS for patients with cystic fibrosis and *P. aeruginosa* infection, which is formulated for inhalation. Therefore, TSI would likely be the main treatment replaced if TIP was listed on the PBS.

As in March 2013, the PBAC accepted TSI as the appropriate comparator.

## **7. Clinical Trials**

The re-submission presented the same trials as in the March 2013 submission. The characteristics and results of these studies have been summarised in the March 2013 PSD.

The re-submission presented results for two extension phases of Trial 2303 and an additional post-hoc analyses of Trial 2302 to address the concerns arising from the March 2013 submission, in particular the higher discontinuation rates and higher antibiotic use in TIP compared to TSI.

The PBAC recalled from its March 2013 consideration 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 population analysed in Trial 2302 was identified as an intention-to-treat (ITT) population, but that the analyses were based on observed data with no imputations performed for missing data.

## **8. Results of Trials**

With regard to comparative effectiveness, the PBAC had previously noted that the outcome of increase in FEV<sub>1</sub> % predicted from baseline to pre-dose day 28 of cycle 3 favoured TIP numerically, but analysis confirmed non-inferiority to TSI, with the lower confidence interval within the 6% margin.

The PBAC noted the results of the post-hoc analysis conducted to address the issue of higher rate of discontinuation with TIP compared to TSI. The results of this post-hoc analysis showed that TIP discontinuers had a higher rate of coughing and antibiotic use; had a similar rate of hospitalisations, and higher convenience scores on the Treatment Satisfaction Questionnaire for Medication (TSQM) compared to TSI discontinuers.

The PBAC noted that a formal claim of improved adherence or compliance had not been made, but that the sponsor presented real world data, as well as data from a stated preference survey that estimated that patients were less likely to miss taking their twice daily medications when using TIP (median: once per week) compared to TSI (median: 3 times per week).

The comparative harms reported in the key trials were summarised in the March 2013 PSD.

The PBAC recalled their previous concern about the higher use of additional anti-pseudomonal antibiotics in the TIP arm of Trial 2302. The post-hoc analysis performed in the re-submission to address this issue showed that the difference in anti-pseudomonal antibiotic use was driven by an increase in oral, rather than IV antibiotic use. The analysis of patients that completed the trial (i.e. did not discontinue) showed higher oral antibiotic use remained in the TIP arm (53.8%) compared to the TSI arm (43.3%); odds ratio (OR) 0.66 [95% CI: 0.44, 0.98].

The PBAC noted that the trial was non-blinded and clinicians may have been more sensitive to cough and more likely to prescribe oral antibiotics in the TIP arm which may have contributed to the higher oral antibiotic use in the TIP arm. There was no difference in ‘any new antibiotic use and any hospitalisations’ reported as 21.4% (TIP) vs. 21.1% (TSI), OR 0.98 [95%CI: 0.64, 1.50] (ITT analysis), suggesting there was no difference in major infection events.

The PBAC noted that while the adverse events that occurred were not serious, adverse events remained higher, compared to TSI, in the group who completed TIP therapy (the closest match to the population identified in the proposed restriction).

## **9. Clinical Claim**

The re-submission claimed that TIP is non-inferior to TSI in terms of comparative clinical efficacy, and TIP is superior to TSI with respect to the patient-relevant outcomes of lower treatment burden and satisfaction with treatment; and TIP is non-inferior to TSI in terms of comparative safety.

The PBAC accepted the non-inferiority claim with regard to clinical efficacy.

The PBAC considered the claim of superiority with respect to patient satisfaction remained inadequately supported by the trial data, although better persistence and adherence for continuing patients may be expected in clinical practice if the continuation rule in the proposed restriction proves adequate to target treatment to patients who can best tolerate TIP treatment.

The PBAC noted that the issue of increased use of oral antibiotics in the comparisons within both the ITT population and those who complete 3 courses remained unresolved and of some concern. The Committee recalled that they had previously considered that the submission’s explanation that the greater rate of cough may be attributable to the dry powder formulation of TIP to be reasonable. Overall, the Committee considered that the claim of non-inferior safety in continuing patients was likely to be reasonable.

## **10. Economic Analysis**

The re-submission presented three economic analyses to support the requested price premium of TIP over TSI based on the re-submission’s claim of superiority of TIP over TSI with respect to the patient-relevant outcomes of lower treatment burden.

The primary analysis presented was derived from a discrete choice experiment (DCE) which was used to estimate consumer surplus (CS) for TIP. Two supplementary analyses were provided: a cost-utility analysis comparing TIP to TSI and cost offset analysis to estimate savings from reduced time and equipment costs with TIP.

The PBAC did not accept the supplementary cost minimisation analysis with TSI, with cost-offset for reduced nebulising equipment costs, due to uncertainty of the actual annual cost of a nebuliser attributed to TSI use. The PBAC noted that some patients are still likely to need a nebuliser for other treatments, such as dornase-alpha and hypertonic saline, so cost savings using TIP may be over-estimated and may not be realised. The PBAC considered that the supplementary cost-utility analysis was not informative for decision making for this re-submission.

The DCE presented scenarios to choose between two unnamed products of TSI, TIP or no treatment, including attributes which were common to both TSI and TIP (time of administration, chance of cough, chance of dysphonia and out of pocket costs and alternate specific attributes (which are fixed for TIP and TSI and relate to the different administration of the products). The DCE was used to estimate the latent utility function for the treatments, and used a latent class approach to modelling to take account of heterogeneity in preferences across individuals. The resulting estimated coefficients were calibrated to real world utilisation based on survey responses, which related to frequency of use of products, in order to estimate willingness to pay for each product. The willingness to pay estimates were estimated using a decision support system in which the out of pocket cost attribute and other information, was used to estimate a weighted average of the CS for the difference between the set of TIP attributes and the set of TSI attributes across the different latent class models. The PBAC noted the sponsor's comment that the estimate CS value would be constrained by the attributes in the survey, but also the Economic Sub-Committee (ESC) advice that the value must be interpreted in the context of whether the survey attributes overall matched the real world attributes of the two drugs.

During the evaluation, errors in the DCE were identified by the ESC and sponsor. The re-calculated estimated median CS derived from the DCE was lower than that initially presented in the re-submission. The PBAC noted that the re-calculated median CS provided could be interpreted as a measure of the additional benefit of TIP attributes as described in survey over the TSI attributes as described in the survey and as estimated over simulation from the DCE survey.

The PBAC considered that overall the DCE was conducted using appropriate methods, although it noted a number of limitations of the methods as listed below. As such, it provided an approach to estimate an upper bound on benefits to patients and carers. However, the PBAC remained concerned that the re-estimated value was uncertain and on balance likely to over-estimate the CS. The PBAC noted that:

- Antibiotic use was not adequately captured in the DCE, favouring TIP. The PBAC did not accept the assumption that higher cough was a surrogate maker of higher oral antibiotic use.
- The representativeness of the sample (n=83) to the CF registry (N= 2,234) and selection bias of the respondents was not clear, and likely to favour TIP.
- The value of CS was driven in part by the ability of the respondent to pay, and would most likely be related to their household income.
- The CS estimate was to some extent influenced by the upper bound of the 'cost' attribute.
- A large proportion of respondents were found in the latent class analysis to have not considered the cost attribute. The sponsor argued in its Pre-PBAC response

that ‘some patients not varying choice by cost means that they would be prepared to pay the maximum price to attain their preferred treatment’. Another interpretation was that respondents would not be prepared to pay extra for the treatment, or that the respondents did not treat the cost attribute as meaningful.

- The method of calibration may have favoured TIP.
- The sponsor argued that the median CS presented in the re-submission was likely to be an under-estimate.

The PBAC therefore considered that at best, the DCE approach provided an upper-bound estimate of the consumer surplus associated with TIP being included on the PBS. However, the PBAC did not agree that the median consumer surplus provided an appropriate basis for determining the price premium for a product. In this context, the PBAC noted that a price premium equivalent to the median consumer surplus would result in a deadweight loss to society. This is because the government will pay this premium for all consumers, not just those who value the product at greater than the price premium (hence the marginal benefit is less than the marginal opportunity cost). Further, if the price premium is set at the median consumer surplus, this, in effect, transfers all the welfare gains from listing to the sponsor. While any price premium in the context of the PBS implies some level of deadweight loss, the PBAC agreed with the ESC that the price premium should reflect an appropriate distribution of the welfare benefits from listing between patients and the sponsor without resulting in a net welfare loss to society (paid by the government). The PBAC agreed with the ESC that if a price premium is accepted, the value of the welfare benefits and welfare loss should be shared by all stakeholders.

## **11. Estimated PBS Usage and Financial Implications**

The usage and financial estimates for TIP was derived from a combined epidemiology and market share approach. In the re-submission, the likely number of patients treated in Year 5 was estimated to be less than 5,000 per year

Based on the re-submission’s revised patient numbers and price, the total net cost to the PBS was projected to be less than \$10 million in Year 5. The estimated cumulative cost to the PBS over the first 5 years of listing was in the range of \$10-30 million.

Consistent with its comparator, the submission proposed, subject to discussions with the Department of Health, a Special Pricing Arrangement (SPA) for TIP for inclusion on the PBS.

The PBAC noted the full financial impact of listing TIP could not be calculated until the price for TIP was determined. The PBAC noted that the cost would likely be lower than estimated in the re-submission and considered that listing of TIP would have a minor cost to the PBS.

## **12. Recommendation and Reasons**

The PBAC recommended listing tobramycin powder for inhalation as an Authority Required (STREAMLINED) benefit for the treatment of *Pseudomonas aeruginosa* infection in a patient aged 6 years or older with cystic fibrosis. The Committee considered that the price should be based on the cost minimisation with TSI with a price premium based on likely improved adherence by CF patients burdened by a time-consuming and complex treatment regime, and a minor cost to the PBS.

The PBAC recommended that the restriction match the restriction of TSI, with the modification that the 'Patient must be aged 6 years or older' and that the patient trials TIP initially. The PBAC considered that the sponsor should bear the cost of providing TIP to the patient for the 4 week trial period before the patient can access continuing PBS-subsidised TIP.

The PBAC accepted that TIP is non-inferior in terms of clinical efficacy to TSI. The PBAC disagreed with the claim that TIP was non-inferior to TSI in terms of clinical safety, but considered that cough and dysphonia are not major adverse events. The PBAC noted that a major clinical concern identified in the March 2013 submission was the higher rate of discontinuation in Trial 2302. The PBAC considered this issue had been addressed by the addition of the trial period to the restriction's criteria. Overall, the PBAC considered that TIP was clinically no worse than TSI and was likely to provide an adherence benefit in CF patients who were able to tolerate TIP.

The PBAC noted that the price premium was sought on the basis of patient preferences as measured by consumer surplus, estimated from a DCE. The PBAC noted that supportive evidence was provided with a cost utility analysis and a cost offset analysis, but this evidence was not directly considered for decision making purposes.

The PBAC noted that the consumer surplus was re-estimated during the evaluation process to be lower than that initially presented in the re-submission. The PBAC considered that the methodology presented in the re-submission was an appropriate way to derive willingness to pay for a treatment choice. The PBAC noted the value of TIP to patients, but the committee strongly disagreed that the Government should pay the calculated consumer surplus in its entirety.

The PBAC noted the consumer comments for this submission from patients, carers, patient support groups and health care providers, which particularly highlighted the heavy burden of treatment and the clinical need for TIP, and the strong preference in adolescents to use TIP. The presentation at the sponsor's hearing reiterated that CF patients make daily decisions on which of their many treatments are performed or delayed. The hearing submitted that TIP is a product that improves adherence by decreasing the burden of treatment and offering a transportable and easy-to-use device.

In the context of the high treatment burden for CF and the minor cost to Government, the PBAC accepted that a price premium should be applied to the price of TIP over the price of TSI, where the consumer surplus presented in the submission is shared between the sponsor, the consumer and the Government.

The PBAC recommended that a Risk Sharing Arrangement (RSA) be implemented for the listing of TIP for CF patients.

The PBAC considered that tobramycin powder for inhalation is not suitable for prescribing by nurse practitioners.

In accordance with subsection 101(3BA) of the *National Health Act* 1953, the PBAC advised that it is of the opinion that, on the basis of the material available to it at its November 2013

meeting, tobramycin powder for inhalation should not be considered substitutable on an individual patient basis with any other therapies currently listed on the PBS.

**Outcome:**

Recommended

Name, Restriction, Manner of administration and form	Max Qty	No. of Rpts	Proprietary Name and Manufacturer
TOBRAMYCIN tobramycin 28 mg inhalation: powder for, 224 capsules	1	0	Tobi Podhaler NV
<b>Condition:</b>	Proven <i>Pseudomonas aeruginosa</i> infection		
<b>Treatment phase:</b>	Initial treatment		
<b>Restriction:</b>	Authority required (STREAMLINED)		
<b>Clinical criteria:</b>	Patient must have cystic fibrosis.  AND  Patient must have been assessed for bronchial hyperresponsiveness as per the TGA-approved Product Information, with a negative test result.  AND  Patient must be participating in a four week trial of tobramycin inhalation powder and will be assessed for ability to tolerate the dry powder formulation in order to qualify for continued PBS-subsidised therapy. The trial commencement date must be documented in the patient's medical records.		
<b>Population criteria:</b>	Patient must be aged 6 years or older		
<b>Administrative Advice</b>	No increase in the maximum quantity or number of units may be authorised.  No increase in the maximum number of repeats may be authorised.  <u>Note</u> Special Pricing Arrangements apply.		

Name, Restriction, Manner of administration and form	Max Qty	No. of Rpts	Proprietary Name and Manufacturer
TOBRAMYCIN tobramycin 28 mg inhalation, 224 capsules	1	2	Tobi Podhaler NV
<b>Condition:</b>	Proven <i>Pseudomonas aeruginosa</i> infection		
<b>Treatment phase:</b>	Continuing treatment		
<b>Restriction:</b>	Authority required (STREAMLINED)		

<b>Clinical criteria:</b>	<p>Patient must have cystic fibrosis.</p> <p>AND</p> <p>Patient must have previously been issued with an authority prescription for tobramycin inhalation capsules</p> <p>AND</p> <p>Patient must have demonstrated ability to tolerate the dry powder formulation following the initial 4-week treatment period, as agreed by the patient, the patient's family (in the case of paediatric patients) and the treating physician(s).</p>
<b>Population criteria:</b>	Patient must be aged 6 years or older.
<b>Administrative Advice</b>	<p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p><u>Note</u> Special Pricing Arrangements apply.</p>

### 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 is very pleased that tobramycin powder, with hand-held inhaler, will be available on the PBS for people with cystic fibrosis. We believe that the cost utility analysis and cost offset analysis presented in the submission were patient relevant; and we do not concur with the PBAC's position of not directly considering these for decision making.