

Tobramycin inhalation for cystic fibrosis: 24 month predicted versus actual analysis

Drug utilisation sub-committee (DUSC)

October 2014

Abstract

Purpose

To examine the utilisation of tobramycin solution for inhalation (TSI) in the 24 months since PBS listing on 1 October 2011. TSI is listed for the management of a proven *Pseudomonas aeruginosa* infection in cystic fibrosis patients. The DUSC regularly examines utilisation of PBS items when there is at least 24 months of prescription data available and where the DUSC or the PBAC has requested analysis of utilisation.

Date of listing on PBS

1 October 2011.

Data Source / methodology

The Department of Human Services (Medicare) Supplied Prescriptions Database was used for the analyses. The analyses are based on the date of prescription supply unless otherwise stated.

Key Findings

- 1,213 and 1,332 patients received TSI in the first and second year of PBS listing. The total number of patients treated with tobramycin in the second year of listing was close to what was predicted.
- The number of TSI packs supplied and Government expenditure was lower than expected. This appears to be due to patients aged 10 years and over receiving fewer prescriptions per year than expected.

Purpose of analysis

This report examines the utilisation of tobramycin solution for inhalation (TSI) in the 24 months since PBS listing on 1 October 2011. TSI is a nebulised antibiotic listed for the management of a proven *Pseudomonas aeruginosa* infection in cystic fibrosis (CF) patients.

Background

Pharmacology¹

Tobramycin is an aminoglycoside antibiotic that disrupts protein synthesis in bacterial cells, eventually leading to cell death. Tobramycin has activity against *Pseudomonas aeruginosa* (*P. aeruginosa*) and other gram negative bacteria.

Therapeutic Goods Administration (TGA) approved indications¹

TSI is indicated for the management of cystic fibrosis patients with *P. aeruginosa* infections.

Dosage and administration¹

A single ampoule containing 300 mg of TSI is administered by nebuliser twice daily, 12 hours apart, in alternating cycles of 28 days. After a cycle of 28 days of treatment, patients should stop therapy for 28 days. Treatment is continued as long as the patient is gaining clinical benefit from the treatment.

The current Product Information (PI) and Consumer Medicine Information (CMI) are available from [the TGA \(Product Information\)](#) and [the TGA \(Consumer Medicines Information\)](#).

Clinical situation

CF is a genetic condition that causes thickened, dehydrated secretions in the lungs, making patients vulnerable to chronic infection and lung damage. CF affects other organs in the body however the majority of deaths are due to pulmonary causes.² Chronic *P. aeruginosa* infection is associated with deterioration in lung function and worse prognosis. CF patients appear to develop non-muroid *P. aeruginosa* infection in the first three years of life.³ Over

¹ Tobi (tobramycin) Australian approved product information. Sydney: Novartis Pharmaceuticals Australia Pty Ltd. Approved 27 February 2012 and amended 5 November 2013. Available from <<https://www.ebs.tga.gov.au>>. Accessed 3 July 2014.

² Cystic Fibrosis Australia. Cystic Fibrosis in Australia 2012. 15th Annual Report from the Australian Cystic Fibrosis Data Registry. Cystic Fibrosis Australia; 2013. Available from <<http://www.cysticfibrosis.org.au/data-registry>>. Accessed 4 July 2014.

³ Li Z, Kosorok MR, Farrell PM, Laxova A, West SE, Green CG, Collins J, Rock MJ, Splaingard ML. Longitudinal development of muroid *Pseudomonas aeruginosa* infection and lung disease progression in children with cystic fibrosis. JAMA 2005; 293(5): 581-8.

time, it is thought non-mucoid infection transforms to mucoid *P. aeruginosa*. Mucoid *P. aeruginosa* produces an exopolysaccharide/alginate substance making it resistant to immune clearance and current antibiotics. Mucoid *P. aeruginosa* cannot be cleared by current treatments and is referred to as chronic *P. aeruginosa* infection.

The aim of initial treatment of *P. aeruginosa* infection may be to eradicate the infection using inhaled tobramycin with other antibiotics such as oral ciprofloxacin or ticarcillin with clavulanic acid.⁴ The Royal Children’s Hospital Melbourne recommends an eradication protocol of a three month course of nebulised tobramycin. The prevalence of *P. aeruginosa* infection increases with age.² Where the infection becomes chronic (three consecutive positive cultures at least a month apart), TSI can be used to control the infection.

PBS listing details (as at 1 August 2014)

TSI was listed on the PBS on 1 October 2011 for the management of a proven *Pseudomonas aeruginosa* infection in a patient with cystic fibrosis. Details of the listing are presented in Table 1.

Table 1: PBS listing of TSI

Item	Name, form & strength, pack size	Max. quant.	Repeat s	DPMQ*	Brand name and manufacturer
5442K	TOBRAMYCIN tobramycin 300 mg/5 mL inhalation: solution, 56 x 5 mL ampoules	1 pack (56 ampoules)	2	\$2137.70	Tobi® Novartis Pharmaceuticals Australia Pty Limited

Source: August 2014 PBS Schedule

*Special Pricing Arrangements apply

Current PBS listing details are available from the [PBS website](#).

Relevant aspects of the PBAC consideration

At its March 2011 meeting, the PBAC recommended the listing of TSI on the PBS with an Authority Required (STREAMLINED) listing for the management of proven *P. aeruginosa* infection in a patient with cystic fibrosis on the basis of acceptable cost effectiveness compared with placebo. 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. Given there is a possibility for tobramycin to be used continuously, rather than 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.

⁴ The Royal Children’s Hospital Melbourne. Ranganathan S, editor. Melbourne Handbook for the Management of Children with Cystic Fibrosis. Melbourne; 2006. Available from <http://www.rch.org.au/uploadedFiles/Main/Content/RESPMED/handbook.pdf>. Accessed 3 July 2014.

For further details refer to the [Public Summary Document](#) from the March 2011 PBAC meeting.

The PBAC recommended the listing of tobramycin powder for inhalation at the November 2013 meeting. The listing was effective from 1 April 2014 and is therefore not included in the current analysis.

For further details refer to the [Public Summary Document](#) from the November 2013 PBAC meeting.

Approach taken to estimate utilisation

The submission used an epidemiological approach to estimate the eligible patient population. The submission used the 2008 Australian Cystic Fibrosis Data Registry data to estimate prevalence and forecast future prevalence based on the historical trends from the registry data. The submission assumed the distribution of age would remain constant. The age-specific prevalence of *P. aeruginosa*-positive cultures for each age-group was also obtained from the registry report and this was used to estimate the prevalence of infection by age group.

The submission assumed that patients aged less than 10 years of age have initial *P. aeruginosa* infection and are treated with an eradication protocol; 50 % of patients aged 10-14 have initial infection and 50 % have chronic infection; and patients 15 years and over are assumed to have chronic infection. It was estimated patients require one pack for treatment of early infection (one month treatment) and six packs per year for chronic infection. Full compliance was assumed for early *P. aeruginosa* and 70 % for chronic infection. The epidemiological method was updated following the recommendation. This estimated a slightly larger number of patients treated. These estimates are presented in Table 2.

Table 2: Tobramycin estimates

	Year 1	Year 2	Year 3	Year 4	Year 5
<i>Eradication of early infection</i>					
Eligible patients	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
Treated patients	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
Number of packs of TSI	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
<i>Management of chronic infection</i>					
Eligible patients	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
Treated patients	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
Number of packs of TSI	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
Total utilisation					
Number patients	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
Number of packs of TSI	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
Net cost to PBS (effective)	\$ REDACTED	\$ REDACTED	\$ REDACTED	\$ REDACTED	\$ REDACTED
Net cost to PBS (published)	\$ REDACTED	\$ REDACTED	\$ REDACTED	\$ REDACTED	\$ REDACTED

Source: Tobramycin final estimates model

The utilisation of tobramycin vials for IV injection was expected to decrease as a result of PBS listing.

Patient numbers and packs of TSI in each of the first five years of listing were less than 10,000 per year. The estimated net financial implication to the PBS in each of the first five years of listing was less than \$10 million.

Previous reviews by the DUSC

The DUSC examined the utilisation of TSI in its first year of listing at the June 2013 meeting.

At the June 2013 meeting, the DUSC noted that while the actual number of prescriptions and expenditure of TSI were similar to predicted values, there were a number of differences in how TSI was predicted to be used and how it was used in practice. The uptake rate of TSI was underestimated, while the number of prescriptions per person was overestimated. The DUSC considered there to be a number of possible explanations for these findings such as:

- Potential 'stock management' occurring within families, given that CF is a genetic disease and families may be sharing prescriptions;
- Patients may be on continuous therapy rather than cyclical – however DUSC did not think that this was likely to be a major reason – if there was a lot of continuous therapy, the prescriptions and expenditure would have been higher;
- Patients may be on two month rather than one month *P. aeruginosa* eradication protocols.

Methods

The Department of Human Services, Medicare Supplied Prescriptions Database was used for the analyses. The analyses are based on the date of prescription supply unless otherwise stated.

The number of patients was determined by counting the number of deidentified patient identification numbers (PINs) in the relevant period. New patients were those receiving their first PBS prescriptions for TSI since the date of listing.

Where patient age is presented, this is the patient's age at the time of their first TSI prescription.

The defined daily doses (DDDs) for tobramycin are 300 mg for TSI and 240 mg for the injectable form. The DDD for injectable tobramycin may not be appropriate if this form is nebulised, however for the purposes of this analysis the magnitude of change of injectable tobramycin was the parameter of interest.

Eradication and chronic treatment

The following analyses were undertaken to identify treatment patterns of patients using chronic TSI versus those using TSI for eradication protocols:

- Number of prescriptions per 12 months by age cohort

- Time to next dispensing by age cohort

The DUSC suggested the Secretariat assess the average age of patients who receive 1, 2, 3, 4 etc. prescriptions per 12 month period. This analysis has not been undertaken for this report due to small patient numbers and the potential for extremes of age to skew average values. Alternatively, the number of prescriptions per 12 months and time to next prescription analyses has been presented by age cohorts to help discern between use for eradication and chronic treatment. The prescriptions per 12 months and time to next dispensing analyses were undertaken for patients who started TSI between October 2011 (listing) and March 2013 inclusive. These analyses show data for the first 12 months from the start of an individual patient's treatment. All data analyses were undertaken using SAS.

Results

Analysis of drug utilisation

Overall utilisation

Table 3 presents the number of patients treated with TSI in the first two years of listing.

Table 3: Tobramycin patient numbers

	Year 1	Year 2
Total patients	1,213	1,333
Predicted	REDACTED	REDACTED
Difference	REDACTED %	REDACTED %
New patients	1,213	531

Source: Department of Human Services Supplied Prescriptions Database, extracted July 2014

The total number of patients treated with tobramycin in the second year of listing was close to what was predicted.

Figure 1 presents the age distribution of patients when they first received TSI on the PBS. The age distribution of CF patients from the Australian Cystic Fibrosis Data Registry in 2012 is also presented.²

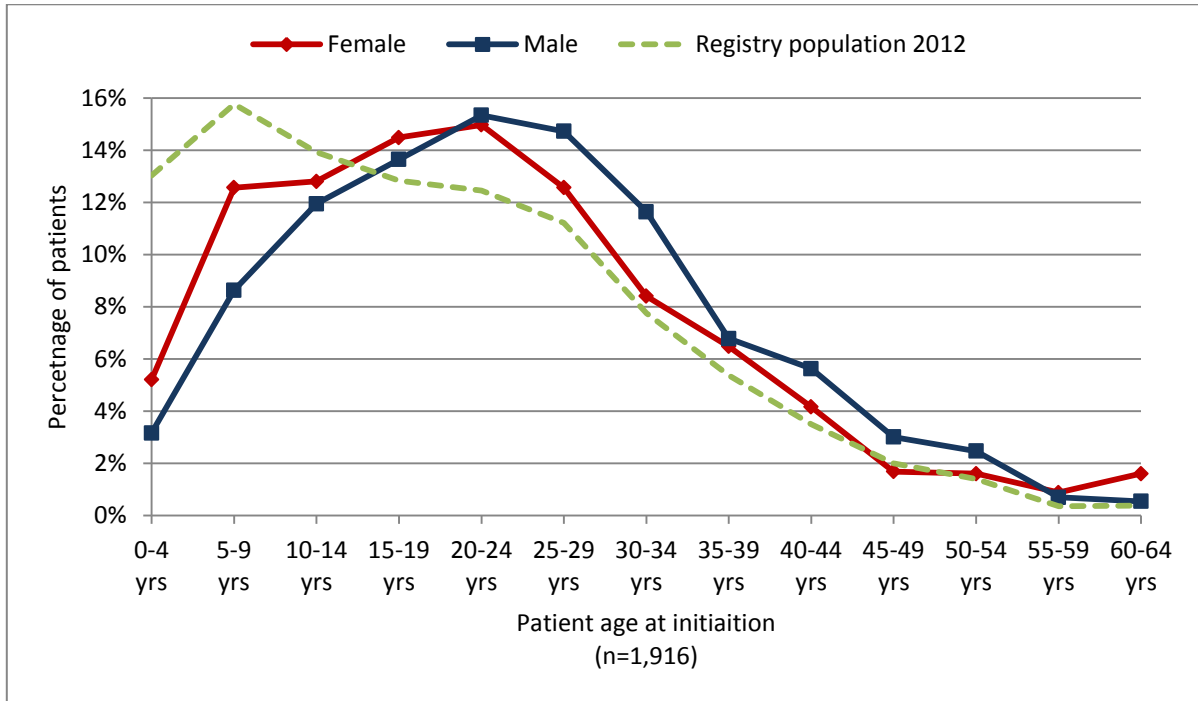


Figure 1: Age distribution of TSI patients

Source: Department of Human Services Supplied Prescriptions Database, extracted July 2014. Australia Cystic Fibrosis Registry Report 2012 (Registry population only)

The utilisation of TSI is broadly consistent with the prevalence of CF, noting *P. aeruginosa* infection is acquired progressively in childhood.

Figure 2 presents the number of prescriptions and quantity supplied.

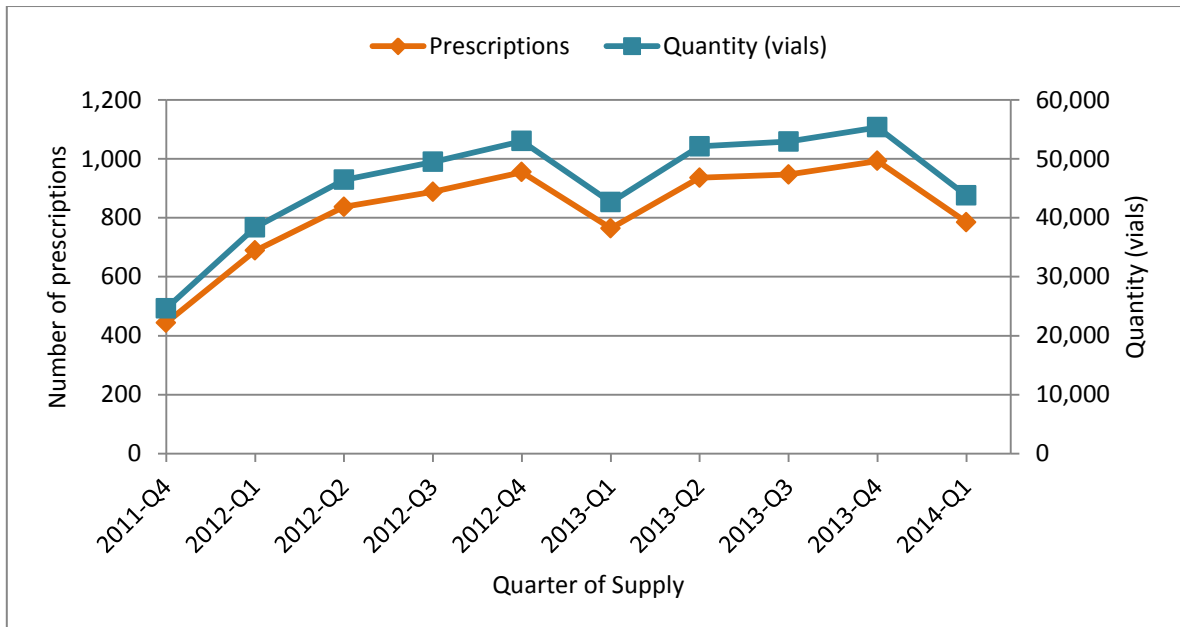


Figure 2: Prescriptions and Vials Supplied

Source: Department of Human Services Supplied Prescriptions Database, extracted July 2014.

The number of prescriptions and vials of TSI supplied appear to have peaked at the end of 2012 and remained steady. The relative increase and subsequent decrease in use at the end and then start of the calendar year is due to the impact of the safety net.

Patterns of use

Figure 3 presents the number of prescriptions per patient in their first 12 months by age cohort. All patients included in this analysis had at least 12 months follow-up since their first prescription.

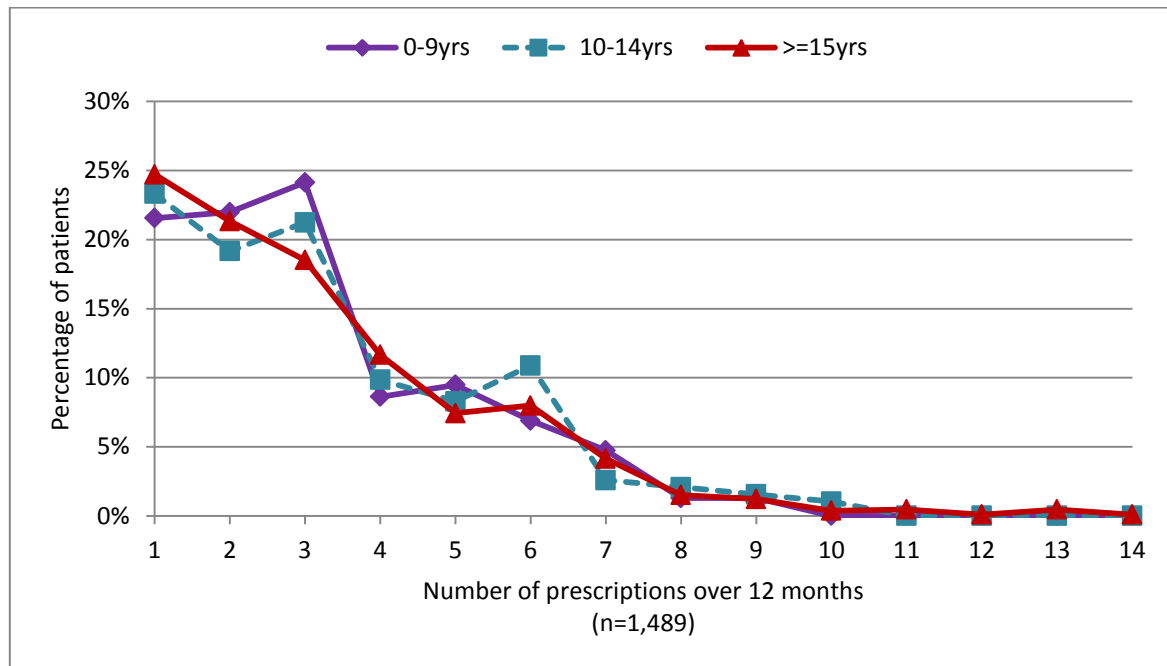


Figure 3: Prescriptions per patient over 12 months

Source: Department of Human Services Supplied Prescriptions Database, extracted July 2014.

The majority of patients under 10 years receive one to three supplies over 12 months. This appears consistent with one to three month eradication protocols. A similar pattern is also evident for patients aged 10-14 years. There is no clear pattern of treatment for patients aged 15 years and older and only 8.1 % of patients received seven or more prescriptions over 12 months. The average number of prescriptions per year was similar across the three age cohorts with an average of 3.2 prescriptions per year for patients aged 0-9 years and 15 and over, and 3.3 prescriptions per year for patients 10-14 years.

Figure 4 presents the time to next prescription data by age cohort.

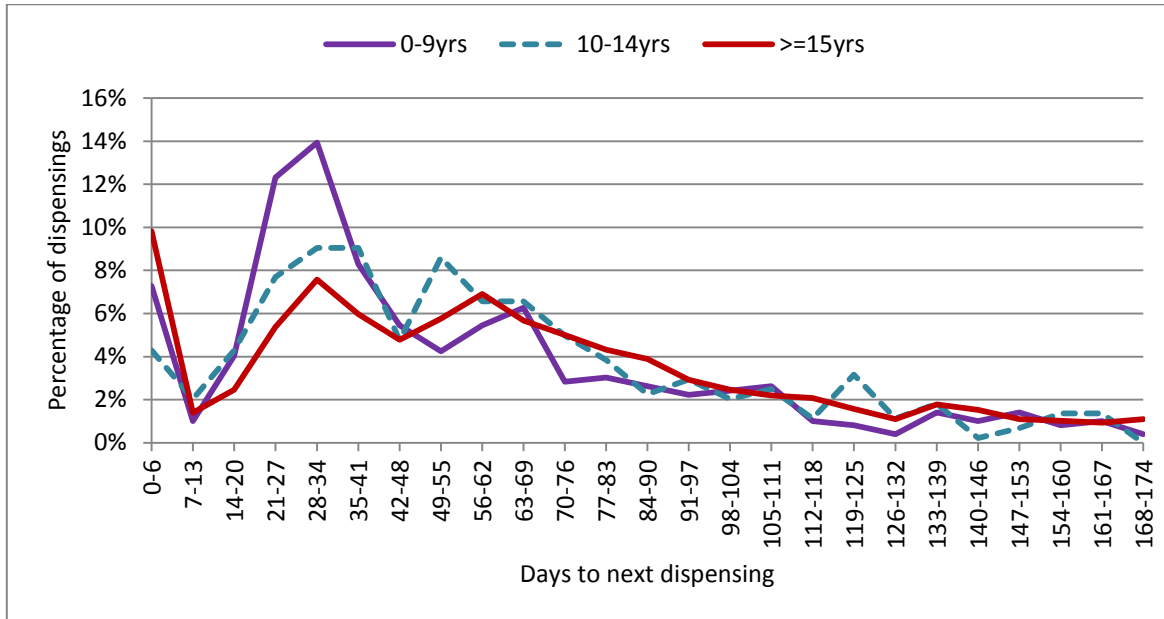


Figure 4: Time to next dispensing by age cohort

Source: Department of Human Services Supplied Prescriptions Database, extracted July 2014.

There is a large proportion of same day supply for TSI, accounting for 6.8 % of all repeat prescriptions. For prescriptions dispensed up to 31 December 2013, less than 1 % of supplies were for higher maximum quantities. The majority of these were Regulation 24 prescriptions where the repeats were dispensed on the same day.

There is a large peak for patients aged 0-9 years around one month, likely to be indicative of eradication regimens. There are peaks at around one and two months for both patients aged 10-14 years and patients 15 and over.

Changes in the use of injectable tobramycin

Figure 5 presents the number of prescriptions and DDDs of injectable tobramycin supplied on the PBS.

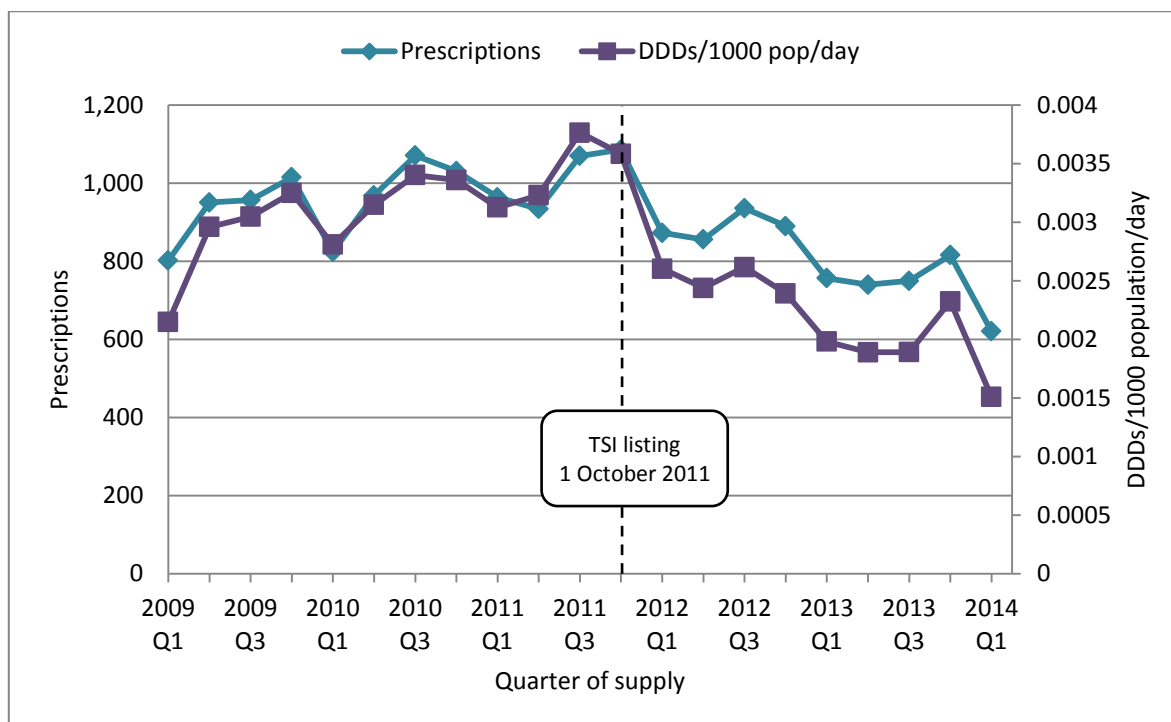


Figure 5: Total PBS supply of injectable tobramycin

Source: DUSC Database, extracted July 2014

Note: The DDD for the tobramycin injection is 240 mg. This is lower than the DDD for TSI (300 mg)

Figure 5 shows the total amount of tobramycin supplied on the PBS, in terms of prescriptions and DDDs have decreased since the listing of TSI.

The application of the World Health Organisation DDD for injectable tobramycin (240 mg) may not be ideal for the proportion of injectable tobramycin that is inhaled. However it is considered reasonable for the purposes of comparing use before and after PBS listing of TSI.

Analysis of actual versus predicted utilisation

Table 4 presents an overview of predicted versus actual utilisation for TSI. The results presented are based on date of supply. As a result, there may be small differences between publicly available DHS Medicare date of processing data. The Department of Health uses date of processing data for the management of risk-share arrangements.

Table 4: Predicted versus actual utilisation

	Year 1	Year 2
Patients	Patients	Patients
Predicted	REDACTED	REDACTED
Actual	1,213	1,333
Difference	REDACTED %	REDACTED %
Packs	Packs	Packs
Predicted	REDACTED	REDACTED

	Year 1	Year 2
Actual	2,838	3,585
Difference	REDACTED %	REDACTED %
Published expenditure	Published expenditure	Published expenditure
Predicted	\$ REDACTED	\$ REDACTED
Actual	\$6,152,405	\$7,762,363
Difference	REDACTED %	REDACTED %
Effective expenditure	Effective expenditure	Effective expenditure
Predicted	\$ REDACTED	\$ REDACTED
Actual	\$ REDACTED	\$ REDACTED
Difference	REDACTED %	REDACTED %

Source: TSI Final Estimates (predicted), DHS Supplied Prescriptions Database (actual), extracted July 2014.

In the second year of listing, the total number of patients who received TSI was close to the number predicted. However, the total number of packs supplied and expenditure were below what was predicted.

Discussion

The results of the 24 month predicted versus actual analysis show the total number of patients treated with TSI was similar to that predicted. However, the number of packs supplied is lower. This is also shown in the number of prescriptions per patient analysis, showing few patients received five or more prescriptions over 12 months in the patient cohort aged 15 years or older. This DUSC considered the analysis demonstrated that younger patients may be on eradication protocols of one to three months in duration. The patterns of treatment used by patients aged 15 years and older is not clear. It was expected these patients predominantly had chronic *P. aeruginosa* infection and would be expected to use approximately six prescriptions per year.

There is difficulty in ascertaining patterns of TSI usage by using PBS data. The PBS data does not capture other factors that affect apparent utilisation patterns. These include:

- variability of treatment regimens, including cyclical versus continuous TSI, and possible cycling with non-PBS medicines such as aztreonam and colistin;
- public hospital supply of larger quantities of tobramycin for patient convenience;
- temporary cessation in inhaled therapy to receive IV antibiotics for exacerbations;
- patients maintaining a stock of medicines to be used when symptoms appear or worsen;
- prescription sharing in families where more than one family member has CF;
- age of onset of chronic *P. aeruginosa* infection; and
- success rate of eradication therapy and re-treatment where eradication has not been successful.

The DUSC considered that the time to next dispensing analysis was consistent with older children having longer eradication protocols, and that the concern raised by the PBAC

regarding the possibility of continuous use rather than cyclical 28 days on/28 days off use, does not appear to be occurring in the PBS population.

The utilisation patterns of TSI may have been influenced by clinical trials and/or compassionate use of tobramycin inhalation powder. A number of Australian sites participated in the tobramycin inhalation powder trials.⁵ Tobramycin powder for inhalation (TIP, Tobi Podhaler®) was listed on the PBS on 1 April 2014.

The number of tobramycin injection prescriptions and DDDs supplied on the PBS appears to have decreased since TSI listing. There has been further decline in use of injectable tobramycin in the second year since TSI has been available. The Sponsor response from the 12 month predicted versus actual analysis noted that physicians would aim to switch the majority of their patients inhaling the I.V. form of tobramycin over to TSI at their next clinic visit (after PBS listing of TSI). The declining use of injectable tobramycin may be due to decline in for use infections other than *P. aeruginosa* in CF patients.

DUSC actions

- The DUSC considered it appropriate to analyse the utilisation of tobramycin products for cystic fibrosis when two years of utilisation data are available for Tobi Podhaler®. Tobi Podhaler® was listed on the PBS on 1 April 2014.
- The DUSC referred the report to PBAC for information.

Context for analysis

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

⁵ Clinicaltrials.gov. Accessed 30 July 2014. Trials NCT00388505, NCT01519661 and NCT01775137 had Australian sites.

Sponsor's comment

Novartis Pharmaceuticals Australia Pty Limited: Novartis is pleased that patients with cystic fibrosis have been able to access PBS-subsidised TSI since October 2011. The number of patients treated in the first two years of PBS listing has been close to what was estimated through utilising data from the Australian Cystic Fibrosis Data Registry.

Disclaimer

The information provided in this report does not constitute medical advice and is not intended to take the place of professional medical advice or care. It is not intended to define what constitutes reasonable, appropriate or best care for any individual for any given health issue. The information should not be used as a substitute for the judgement and skill of a medical practitioner.

The Department of Health (DoH) has made all reasonable efforts to ensure that information provided in this report is accurate. The information provided in this report was up-to-date when it was considered by the Drug Utilisation Sub-committee of the Pharmaceutical Benefits Advisory Committee. The context for that information may have changed since publication.

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