PUBLIC SUMMARY DOCUMENT
Product: Aztreonam, powder for inhalation, 75 mg, with diluent, Cayston®
Sponsor: Gilead Sciences Pty Ltd
Date of PBAC Consideration: July 2012

1. Purpose of Application

Resubmission for a Section 100 (Highly Specialised Drugs Program) Authority Required listing for the management of proven *Pseudomonas aeruginosa* (*Ps. aeruginosa*) infection in patients with cystic fibrosis.

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 November 2010 meeting, the PBAC rejected a submission seeking Section 100 (Highly Specialised Drugs Program) listing for the control of gram-negative bacteria, particularly *Ps. aeruginosa* in the respiratory tract of patients with moderate to severe cystic fibrosis (CF) on the basis of an unacceptably high and uncertain cost-effectiveness ratio.

3. Registration Status

Aztreonam was TGA registered on 4 February 2010 for the control of gram-negative bacteria, particularly *Pseudomonas aeruginosa*, in the respiratory tract of patients with cystic fibrosis.

4. Listing Requested and PBAC's View

Section 100 (Highly Specialised Drugs Program)
Public Hospital Authority Required (Streamlined)
Private Hospital Authority Required
Management of a proven *Pseudomonas aeruginosa* infection in a patient with cystic fibrosis.

Note: Not to be used in combination with Tobramycin Inhaled Solution (Tobi®)
Note: Data not available for children aged less than 6 years
Note: No applications for increased maximum quantities and/or repeats will be authorised.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Cystic fibrosis is caused by a defect in an ion transport mechanism of epithelial cells that leads to abnormal movement of sodium chloride across cell membranes. This defect results in secretion of abnormally viscous mucus which makes patients highly susceptible to gram-negative bacterial pulmonary infections, especially *Ps. aeruginosa*. Chronic pulmonary infection leads to progressive decline in lung function, the leading cause of death associated with cystic fibrosis.

Aztreonam powder for inhalation would provide an alternative treatment option to tobramycin solution for inhalation for the treatment of *Ps. aeruginosa* in patients with cystic fibrosis.

6. Comparator

The submission nominated tobramycin solution for inhalation (TSI) as the comparator.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The re-submission presented one open-label randomised trial, GS-US-205-0110, comparing aztreonam powder for inhalation (AI) with TSI in 273 patients aged ≥ 6 years with moderate to severe cystic fibrosis (CF) and with chronic *P. aeruginosa* infection. AI was compared with TSI over three 28-day on/off cycles. Patients were not to receive routine anti-pseudomonal antibiotics during the off-cycle periods. The need for concomitant antibiotics in addition to AI or TSI was determined by unblinded investigators and recorded as an efficacy event. The proposed use of cyclical AI therapy, in addition to routine use of oral ciprofloxacin or inhaled antibiotic (other than AI and TSI) during the off-treatment phases as suggested by the clinical algorithm was not investigated in this trial.

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

Trial ID / First author	Protocol title / Publication title	Publication citation
Oermann CM et al.	Change in FEV_1% predicted in response to aztreonam for inhalation solution (AZLI) *vs.* tobramycin inhalation solution (TIS) in an active comparator study: Responder analyses.	Pediatric Pulmonology 2011; 46 (Suppl 34): 289
Pressler T et al.	In vitro susceptibility of *Pseudomonas aeruginosa (PA)* does not predict clinical response to aztreonam 75mg powder and solvent for nebuliser solution (AZLI): A responder analysis in subjects with cystic fibrosis (CF).	Journal of Cystic Fibrosis 2011; 10 (Suppl 1): S27
Oermann CM et al	Aztreonam for inhalation solution (AZLI) *vs.* tobramycin inhalation solution (TIS), a 6-month comparative trial in cystic fibrosis patients with Pseudomonas Aeruginosa.	Pediatric Pulmonology 2010; 45 (Suppl 33): 327

8. Results of Trials

The results of absolute changes in % forced expiratory volume in 1 second (FEV_1), predicted from baseline and averaged over three on-treatment cycles (at Week 4, Week 12 and Week 20) for Trial GS-US-205-0110 are presented in the following table:

Absolute changes from baseline in FEV_1 % predicted averaged over three on-treatment cycles

	AI (n=136)	TSI (n=132)
Primary analysis (mixed-effect repeated measures model)		
Adjusted mean[a] (SE)	2.05% (0.7%)	-0.66% (0.7%)
Treatment difference[b]	2.70%	
p-value	0.0023	

AI = aztreonam for inhalation; FEV_1 = forced expiratory volume in 1 second; SE = standard error; TSI = tobramycin solution for inhalation

[a] Adjusted means from mixed-effect repeated measures model, including terms for Visit 2 (baseline) FEV_1 % predicted, previous inhaled tobramycin use, treatment, visit, and treatment/visit interaction for all subjects.

[b] Adjusted treatment difference = AI – TSI. 95% confidence interval of the adjusted treatment difference in adjusted means was not provided in the Clinical Study Report.

The PBAC noted that there was a statistically significant difference in average absolute changes in FEV_1 % predicted at Week 4 (course 1), Week 12 (course 2) and Week 20 (course 3) between the two treatment groups. However, the observed treatment effect was considerably smaller than the minimal clinically important difference (MCID), previously accepted by the PBAC, of an absolute change in FEV_1 % predicted of 10%. Therefore, the PBAC considered the clinical importance of the difference is unclear.

Data on absolute changes in FEV_1 % predicted at each study visit were extracted from the Clinical Study Report (CSR) to demonstrate the variations in this outcome across on-treatment and off-treatment cycles. The data are presented in the following table:

Absolute changes from baseline in FEV_1 % predicted by study visit

	Adjusted mean[a] (SE)		Treatment difference[b]	p-value
	AI (n=136)	TSI (n=132)		
Week 2 / Visit 3 (during course 1)	3.67% (0.7%)	0.44% (0.7%)	3.24%	0.000
Week 4 / Visit 4 (course 1)	3.12% (0.7%)	-0.22% (0.7%)	3.35%	0.000
Week 8 / Visit 5 (off-course 1)	-0.46% (0.7%)	-0.39% (0.8%)	-0.07%	0.939
Week 12 / Visit 6 (course 2)	1.88% (0.8%)	-0.73% (0.9%)	2.61%	0.020
Week 16 / Visit 7 (off-course 2)	-0.99% (0.9%)	-0.06% (0.9%)	-0.94%	0.420
Week 20 / Visit 8 (course 3)	1.14% (0.8%)	-1.01% (0.8%)	2.15%	0.030
Week 24 / Visit 9 (off-course 3)	-2.43% (0.7%)	-1.52% (0.7%)	-0.92%	0.304
Average across study	0.85% (0.6%)	-0.50% (0.6%)	1.34%	0.066

AI = aztreonam for inhalation; FEV_1 = forced expiratory volume in 1 second; SE = standard error; TSI = tobramycin solution for inhalation

[a] Adjusted means from mixed-effect repeated measures model, including terms for Visit 2 (baseline) FEV_1 % predicted, previous inhaled tobramycin use, treatment, visit, and treatment/visit interaction for all subjects;

[b] Adjusted treatment difference = AI – TSI. 95% confidence intervals of the adjusted treatment difference in adjusted means were not given in the Clinical Study Report.

The PBAC noted that the magnitude of the treatment effect of AI relative to TSI, in terms of improving lung function, appeared to attenuate with each successive treatment cycle. Decreased FEV_1 values were reported during off-treatment phases in both arms. The absolute changes in FEV_1 % predicted, when averaged out with the trough (off-treatment cycle) values were not considered to be statistically significantly different between the two treatment groups.

Hospitalisation for respiratory events was a tertiary endpoint of the trial and was the health outcome used in the economic evaluation. Hospital admissions were at the discretion of investigators and patients who were not blinded to treatment allocation. Although a blinded committee was formed to adjudicate the subset of hospitalisations that were respiratory related, the decision to hospitalise was unblinded. In addition, the applicability of the hospitalisation results from the trial may be limited because hospital admission is dependent on the health system and its capacity to provide community or outpatient care and the trial was conducted in the United States and in the European Union.

The results of the hospitalisation for respiratory events from days 0 to 168 are shown in the table below:

Hospitalisations, Days 0 to 168

	AI (n=136)	TSI (n=132)	Rate difference [95% CI]	P-value
Number of patients hospitalised at least once	38 (27.9%)	43 (32.6%)	-0.046 [-0.156, 0.064]	0.427[a]
Number of hospitalisations	52 (38.2%[b])	65 (49.2%[b])	-0.110[c]	0.137[d]
Number of respiratory hospitalisations	40 (29.4%[b])	58 (43.9%[b])	-0.145[c]	0.044[d]

AI = aztreonam for inhalation; CI = confidence interval; TSI = tobramycin solution for inhalation

[a] p-value was for comparison of the proportion of subjects hospitalised at least once and was based on Fisher's exact test.

[b] = the number of (respiratory) hospitalisations / the number of patients.

[c] Rate difference = AI – TSI. The 95% CIs of the treatment difference (*ie* rate difference) from the negative binomial regression model, with the logarithm of person years of follow-up included as an offset variable, were not provided by the Clinical Study Report.

[d] p-value was for comparison of the number of events for each subject and was based on the negative binomial regression method, with the logarithm of person years of follow-up included as an offset variable.

The PBAC noted that respiratory hospitalisation was the only statistically significant hospitalisation outcome (a tertiary outcome) in the unblinded trial which was conducted in a health system that may differ from Australia. The PBAC considered that the results from Trial GS-US-205-0110 showed that the rates of hospitalisations were not significantly different between the two treatment groups.

The PBAC further noted that the treatment effect of aztreonam relative to tobramycin in terms of improving respiratory symptoms (as measured by scores on the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Symptoms Scale (RSS)) decreased with each successive on-treatment cycle and was not sustained during the off-treatment phases. The difference in average improvements in CFQ-R RSS scores over three on-treatment cycles (4.13) did not achieve the clinically important margin of 5 points previously accepted by the PBAC. The average changes across all study visits (including off-cycle visits) were neither statistically significant nor clinically meaningful between the two treatment arms.

The overall adverse events are summarised in the table below:

	Number (%)		p-value[a]	RD [95% CI][b]	RR [95% CI][c]
	AI (n=136)	TSI (n=132)			
Subjects reporting ≥ 1 adverse event	130 (95.6%)	128 (97.0%)	0.750	-1.4% [-5.9%, 3.1%]	1.0 [0.9, 1.0]
Subjects reporting ≥ 1 drug-related adverse event	**31 (22.8%)**	**17 (12.9%)**	**0.039**	**9.9% [0.8%, 19.0%]**	**1.8 [1.0, 3.0]**
Subjects reporting ≥ 1 serious adverse event	42 (30.9%)	44 (33.3%)	0.696	-2.5% [-13.6%, 8.7%]	0.9 [0.7, 1.3]
Subjects reporting ≥ 1 severe adverse event	22 (16.2%)	11 (8.3%)	0.063	7.8% [0.1%, 15.6%]	1.9 [1.0, 3.8]
Subjects with study drug	**9**	**1**	**0.019**	**5.9%**	**8.7**

withdrawn as a result of an adverse event	**(6.6%)**	**(0.8%)**		**[1.4%, 10.3%]**	**[1.1, 68.0]**
Subjects who died	0 (0.0%)	0 (0.0%)	1.000	0.0% [0.0%, 0.0%]	Not calculable

AI = aztreonam for inhalation; CI = confidence interval; RD = risk difference; RR = relative risk; TSI = tobramycin solution for inhalation

[a] p-values based on Fisher's exact test

[b] RD = AI – TSI. RDs and 95% CIs were calculated during the evaluation

[c] RR = AI / TSI. RRs and 95% CIs were calculated during the evaluation

The PBAC noted that statistically significantly higher proportions of patients receiving aztreonam treatment experienced drug-related adverse events and adverse event-associated treatment discontinuation than patients in the tobramycin solution for inhalation group. More aztreonam-treated patients reported severe or life-threatening adverse events than subjects in the tobramycin solution for inhalation group (16.2% vs 8.3%).

The PBAC considered the argument that selection bias was the primary cause of the differences between aztreonam and tobramycin drug-related adverse events was reasonable, as the study included a majority of patients who were highly experienced with tobramycin and therefore able to tolerate it. On balance, aztreonam may have a similar safety profile to tobramycin solution for inhalation.

9. Clinical Claim

The submission described AI as superior in terms of comparative effectiveness and equivalent in terms of comparative safety when compared with TSI.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The re-submission presented a trial-based cost-effectiveness analysis, based on the claim of superior effectiveness and equivalent safety for AI relative to TSI.

The outcome of the economic evaluation was cost per respiratory hospitalisation avoided. Results from Trial GS-US-205-0110 indicated that the rates of hospitalisations were not significantly different between the two treatment groups. Respiratory hospitalisation was the only statistically significant hospitalisation outcome (a tertiary outcome) in the unblinded trial (Trial GS-US-205-0110) and was conducted in a health system that may differ from Australia. The health care costs considered in the cost-effectiveness analysis included:

1) costs of AI and TSI;
2) costs of nebuliser device;
3) clinician costs associated with non-hospitalised treatment of respiratory events; and
4) costs of concomitant use of anti-pseudomonal antibiotics for non-hospitalised treatment of respiratory events.

The health outcome used in the economic evaluation was the difference in the rate of hospitalisations for respiratory events over the 24-week trial period.

The economic evaluation for management of chronic infection produced an incremental cost per respiratory hospitalisation avoided over 24 weeks of less than $15,000.

The PBAC noted that the submission's calculated cost-effectiveness ratio compared favourably to the estimated costs of cystic fibrosis hospitalisations (AR-DRG E60A and E60B) in the current Australian setting of between $15,000 and $45,000, however the PBAC considered there to be various confounding factors.

As a result of these concerns, the PBAC considered aztreonam's cost-effectiveness to be unacceptably high and uncertain at the reduced price offered.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients treated per year was estimated in the submission to be less than 10,000 in Year 5, at an estimated net cost per year to the PBS of $10 – $30 million in Year 5.

The estimates were considered uncertain and may vary if uptake rates are not as predicted (30% in Year 1, increasing by 5% p.a.).

12. Recommendation and Reasons

The PBAC recommended listing aztreonam on the PBS as an Authority Required (Streamlined) listing for the management of a proven *Pseudomonas aeruginosa* infection in patients with cystic fibrosis on a cost-minimisation basis compared to tobramycin solution for inhalation. The PBAC recommended the price of aztreonam be equivalent to tobramycin solution for inhalation on a 28 day treatment cost basis, as the data provided in the submission were insufficient to allow determination of equi-effective doses.

The submission's nominated comparator of tobramycin solution for inhalation was considered appropriate by the PBAC.

The PBAC did not consider a Section 100 (Highly Specialised Drugs Program) listing to be appropriate. Instead, the PBAC recommended an Authority Required (Streamlined) listing, consistent with the comparator's PBS listing. The PBAC noted that in clinical practice patients commonly cycle between cystic fibrosis treatments. Given the 28 day on-off dosage regimen for aztreonam and the lack of evidence to support using tobramycin during the 'off' periods, the PBAC did not consider cycling between aztreonam and tobramycin solution for inhalation was appropriate, and therefore the restrictions for both products should reflect this limitation. The words "in combination" in the proposed NOTE were considered to be potentially problematic because if interpreted literally, prescribers could still give tobramycin during the aztreonam 'off' periods. The PBAC suggested that the restriction should preclude the use of other PBS-subsidised antibiotic treatment within the same 6 month period, but that patients intolerant of tobramycin should still be able to access aztreonam.

The PBAC noted that the basis of the resubmission was a new clinical trial: an open-label, randomised trial, GS-US-205-0110, comparing aztreonam with tobramycin solution for inhalation in 273 patients aged 6 years or older with moderate to severe cystic fibrosis (CF) and with chronic *P. aeruginosa* infection. The submission reported a statistically significant treatment difference favouring aztreonam, based on absolute changes of 2.7% from baseline in predicted FEV_1 %, averaged over three on-treatment cycles. The PBAC recalled that it had

previously considered an absolute change of 10% in predicted FEV_1% to be the minimal clinically important difference, and therefore the clinical importance of a 2.7% difference was not clear.

The PBAC noted that respiratory hospitalisation was the only statistically significant hospitalisation outcome (a tertiary outcome) in the unblinded trial which was conducted in a health system that may differ from Australia. The PBAC considered that the results from Trial GS-US-205-0110 showed that the rates of hospitalisations were not significantly different between the two treatment groups.

The PBAC further noted that the treatment effect of aztreonam relative to tobramycin in terms of improving respiratory symptoms (as measured by scores on the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Symptoms Scale (RSS)) decreased with each successive on-treatment cycle and was not sustained during the off-treatment phases. The difference in average improvements in CFQ-R RSS scores over three on-treatment cycles (4.13) did not achieve the clinically important margin of 5 points previously accepted by the PBAC. The average changes across all study visits (including off-cycle visits) were neither statistically significant nor clinically meaningful between the two treatment arms.

Overall, the PBAC considered that the data presented did not support a claim of superior effectiveness and that a claim of non-inferiority would have been more appropriate.

The PBAC noted that statistically significantly higher proportions of patients receiving aztreonam treatment experienced drug-related adverse events and adverse event-associated treatment discontinuation than patients in the tobramycin solution for inhalation group. More aztreonam-treated patients reported severe or life-threatening adverse events than subjects in the tobramycin solution for inhalation group (16.2% vs 8.3%).

The PBAC considered the argument that selection bias was the primary cause of the differences between aztreonam and tobramycin drug-related adverse events was reasonable, as the study included a majority of patients who were highly experienced with tobramycin and therefore able to tolerate it. On balance, aztreonam may have a similar safety profile to tobramycin solution for inhalation.

Therefore, the PBAC did not accept the submission's clinical claim that aztreonam is superior in terms of comparative effectiveness compared with tobramycin solution for inhalation. In terms of safety, the PBAC accepted the claim that aztreonam is equivalent in comparative safety compared with tobramycin solution for inhalation.

The re-submission presented a trial-based cost-effectiveness analysis, based on the claim of superior effectiveness and equivalent safety for aztreonam relative to tobramycin solution for inhalation. However, as noted above, the PBAC did not accept the claim of superior effectiveness.

The submission's calculated cost-effectiveness ratio of less than $15,000 per respiratory hospitalisation averted compared favourably to the estimated costs of cystic fibrosis

hospitalisations (AR-DRG E60A and E60B) in the current Australian setting of $15,000 - $45,000 but the PBAC considered there to be various confounding factors. These included:

- Differences in the trial population compared to the proposed PBS population. Patients in the trial were older, had more severe cystic fibrosis (i.e. lower predicted FEV_1%) and received no anti-*Pseudomonas aeruginosa* therapy (i.e. ciprofloxacin treatment during 'off' periods).
- Hospital admission costs, which are related to the length of stay. A possible explanation for the difference in the length of hospital stay between the AR-DRG data and the trial result was that cystic fibrosis patients with respiratory events may have been admitted under other AR-DRG items (e.g. respiratory infection/inflammation - E62A, E62B and E62C).
- Whether the time horizon in the economic evaluation (i.e. 24 weeks), was appropriate, given the chronic progressive nature of cystic fibrosis and the decreasing effectiveness of aztreonam relative to tobramycin with the number of cycles during that time.

As a result of these concerns, the PBAC considered aztreonam's cost-effectiveness to be unacceptably high and uncertain at the price offered. However, given that the PBAC considered there is a clinical need for aztreonam, the PBAC was prepared to recommend listing aztreonam on a cost-minimisation basis against tobramycin solution for inhalation, with the price of aztreonam being based on an equivalent monthly treatment cost to tobramycin solution for inhalation.

The PBAC considered that the submission's revised estimates, presented in the Pre-Sub-Committee response, of the financial implications to the PBS and patient numbers were uncertain because of the difficulty in estimating the uptake of aztreonam. In recognition that a current risk share agreement is in place for tobramycin solution for inhalation and there is a possibility of aztreonam being used cyclically with tobramycin (i.e. 28 days aztreonam, 28 days tobramycin), the PBAC recommended that aztreonam be included in the same risk share cap with tobramycin solution for inhalation. The PBAC accepted the sponsor's offer to supply the unique inhalation device and handsets free of charge to patients and recommended that this should be included in the risk share agreement.

In accordance with subsection 101(3BA) of the *National Health Act 1953* ('the Act'), the PBAC advised that the Committee is of the opinion that, on the basis of the material available to its July 2012 meeting, that aztreonam powder for inhalation should not be treated as interchangeable on an individual patient basis with tobramycin solution for inhalation.

Recommendation:
AZTREONAM, powder for inhalation, 75 mg, with diluent.

Restriction:	Authority Required (Streamlined) Management of a proven *Pseudomonas aeruginosa* infection in a patient with cystic fibrosis. Note: Aztreonam is not PBS-subsidised for use in combination with PBS-subsidised tobramycin solution for inhalation.

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

To be finalised (cycling prevention to be finalised)

Max qty:	84
Rpts:	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

Gilead welcomes the positive PBAC recommendation to list Cayston® (Aztreonam powder for inhalation) acknowledging the PBAC's recognition of the clinical need for a new inhaled antibiotic for cystic fibrosis patients. However, given the linkage of Cayston® and tobramycin solution for inhalation (TSI) as a result of the PBAC recommendation, Gilead will review the viability of listing this product on the PBS.