PUBLIC SUMMARY DOCUMENT
Product: Aztreonam, powder for inhalation, 75 mg (as lysine), with diluent, Cayston®
Sponsor: Gilead Sciences Pty Ltd
Date of PBAC Consideration: November 2010

1. Purpose of Application

The submission sought a Section 100 (Highly Specialised Drugs Program) listing for the control of gram-negative bacteria, particularly *Pseudomonas aeruginosa* (*P. aeruginosa*) in the respiratory tract of patients with moderate to severe cystic fibrosis (CF) who meet certain criteria.

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

This drug had not previously been considered by the PBAC.

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. The recommended dosage in the approved Product Information for both adults and paediatric patients 6 years of age and older is one single-use vial (75 mg) administered 3 times a day for a 28-day course (followed by 28 days off aztreonam therapy).

Aztreonam was granted orphan drug status by the TGA on 16 July 2009.

4. Listing Requested and PBAC's View

Section 100 – (Highly Specialised Drugs Program)

Aztreonam for inhalation (Cayston) is listed for the control of gram negative bacteria, particularly *Pseudomonas aeruginosa*, in the respiratory tract of patients with moderate to severe cystic fibrosis who meet the following criteria:

1. Documentation of cystic fibrosis diagnosis as evidenced by one or more clinical features consistent with the cystic fibrosis phenotype and one or more of the following criteria:
   - sweat chloride ≥ 60 mEq/L by quantitative pilocarpine iontophoresis test; or
   - two well characterised mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene; or
   - abnormal nasal potential difference.
2. *P. aeruginosa* present in expectorated sputum or throat swab culture.
3. FEV_1 (forced expiratory volume in the first second) greater than or equal to 25% and less than or equal to 75% predicted.

The PBAC did not comment on the requested restriction

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 *P. aeruginosa*. Chronic pulmonary

infection leads to progressive decline in lung function, the leading cause of death associated with cystic fibrosis.

The submission claimed aztreonam powder for inhalation would provide an additional treatment option to the current inhaled, intravenous or oral antibiotic regimens for the treatment of *P. aeruginosa* in patients with cystic fibrosis.

For PBAC's view, see Recommendation and Reasons.

6. Comparator

The submission nominated standard of care as the comparator.

The submission stated that a physician survey indicated that aztreonam inhalation (AI) would not replace any particular management strategy and that it would be used in addition to current antibiotic treatment strategies for patients with CF and *P. aeruginosa* infections. This includes nebulised intravenous (IV) tobramycin (not TGA approved or PBS-subsidised), oral ciprofloxacin, and oral azithromycin. The submission stated that as AI was used in the trials as an add-on therapy to patients pre-treated with tobramycin, a comparison between AI and placebo treated patients represented a comparison between AI and standard of care.

Evidence from the sponsor-commissioned physician survey in Australia indicated that about 68% of CF patients with *P. aeruginosa* infection were on maintenance therapy with antibiotics and that inhaled administration of tobramycin IV formulation is a mainstay of maintenance treatment, used on demand, on a 28-day cycle (28 days on tobramycin / 28 days with another antibiotic or with no therapy), or on continuous therapy. Nebulised IV formulation of tobramycin is the therapy most likely to be replaced with AI, if AI was PBS-listed. However, it is likely that AI would only partially substitute tobramycin if AI was reimbursed on the PBS. Evidence from the survey demonstrated that inhaled IV tobramycin would still be the first choice in control of *P. aeruginosa* in CF patients for most of the physicians surveyed (54.5%), and that about one-quarter (27.3%) of the doctors would use nebulised IV tobramycin during the 28-day AI-off-cycle for the maintenance treatment of *P. aeruginosa* in CF patients.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The submission presented two double-blind, placebo-controlled randomised studies (CP-A1-005 and CP-A1-007) and one open-label follow up study (CP-A1-006) in support of the comparative effectiveness of AI relative to placebo for control of *P. aeruginosa* in the respiratory tract of patients with CF.

Preliminary results from an ongoing phase III trial (GS-US-205-0110), which investigated AI relative to tobramycin solution for inhalation (TSI) in control of *P. aeruginosa* infection in patients with CF, were provided by the sponsor as supplementary evidence.

The studies published at the time of the submission are as follows:

Trial ID / First author	Protocol title / Publication title	Publication citation
Aztreonam vs placebo		
McCoy et al	Inhaled aztreonam lysine for chronic airway *Pseudomonas aeruginosa* in cystic fibrosis.	American Journal of Respiratory and Critical Care Medicine 2008; 178(9): 921-928
McCoy et al	Aztreonam lysine for inhalation (AI) for CF patients with *P. aeruginosa* (PA) infection [abstract].	Journal of Cystic Fibrosis, 2007, 6 (Suppl 1): S10
Supplementary evidence		
Aztreonam vs tobramycin		
GS-US-205-0110		
Assael et al	Aztreonam for inhalation solution (AZLI) head to head trial, a comparative trial vs tobramycin nebuliser solution (TNS) in cystic fibrosis (CF) patients with *Pseudomonas aeruginosa* (PA): results of first treatment cycle	33rd European Cystic Fibrosis Society Conference, Poster 16-19 June 2010

8. Results of Trials

The submission claimed that in comparison to twice a day (bid) dosing, three times a day (tid) dosing might achieve additional time above the minimum inhibitory concentration (MIC) of AI required to suppress *P. aeruginosa* and would therefore provide better control of *P. aeruginosa* infection. Therefore, AI 75 mg tid was chosen as the AI treatment regimen.

Although trial CP-AI-005 included bid dosing arms (for both AI and placebo) the submission did not present results for bid dosing, given that bid dosing does not have regulatory approval. Relevant data for bid dosing were extracted from the original study report during the evaluation.

Time to the need for inhaled or IV anti-pseudomonal antibiotics:

The primary effectiveness endpoint in trial CP-AI-005 was time to the need for inhaled or IV antibiotics, due to at least one of the following four symptoms used as predictors of pulmonary exacerbation: increased cough, increased sputum/chest congestion, decreased levels of exercise tolerance and decreased appetite.

The median time to the need for antibiotics in response to pre-defined symptoms was statistically significantly longer in the AI tid group than in the placebo tid group (87 days vs. 54 days; HR=0.43; [95%CI: 0.24–0.77; p=0.0043]). The treatment effect of AI tid could have been overestimated due to the fact that patients in this group had relatively better lung function (higher FEV_1 % predicted) and respiratory symptoms (higher CFQ-R respiratory domain scores) than placebo tid patients at Day 0.

A comparison of this outcome across all four treatment arms in CP-AI-005 (AI tid, AI bid, placebo tid and placebo bid, where bid data were extracted during the evaluation) suggested a stronger regimen effect than drug treatment effect. There was a numerical, but not

statistically significant, difference in favour of both AI bid and placebo bid over AI tid. The time to the need for anti-pseudomonal antibiotics in placebo tid patients was statistically significantly shorter than patients in the other three groups. Furthermore, the regimen effect, as demonstrated in this trial, could be slightly conservative, as there were higher proportions of "sicker" patients withdrawing from AI/placebo treatment in the two tid groups than in the two bid groups.

The PBAC noted there were no statistically significant differences between aztreonam bid and tid dose regimens.

Change in Cystic Fibrosis Questionnaire, Revised (CFQ-R) respiratory domain scores:

The submission presented the results of changes in CFQ-R respiratory domain scores which were the primary endpoint in CP-AI-007 and a secondary outcome in CP-AI-005.

A trend towards a clinically meaningful improvement (i.e. a change of 5 points) in respiratory symptoms favouring AI tid therapy over pooled placebo was suggested in trial CP-AI-005, however no statistically significant difference was found between the two treatment groups.

Data from the study report extracted during the evaluation indicated a statistically significant and clinically important improvement in respiratory symptoms in AI bid patients relative to pooled placebo patients. A greater increase in the CFQ-R respiratory domain score was observed in the AI bid group than in the AI tid group (5.10 vs 3.65), which paradoxically suggested a trend of better treatment effect of lower AI dose regimen with respect to symptom control.

In trial CP-AP-007, AI tid therapy resulted in a clinically relevant and statistically significant difference relative to placebo tid in the improvement of CFQ-R respiratory domain scores from baseline.

Change in forced expiratory volume in 1 second (FEV_1) % predicted:

In CP-AI-005 and CP-AI-007, a treatment effect was observed favouring AI tid therapy over placebo in terms of an increase in FEV_1 % predicted from baseline, which indicated an improvement in lung function. The difference in the changes between AI tid and placebo was not clinically important (defined as a change of 10% in FEV_1 % predicted) in either of the trials.

Relevant data on FEV_1 % predicted extracted from the CP-AI-005 study report during the evaluation indicated that AI bid resulted in a slighter greater improvement in lung function than AI tid (2.00 vs 1.71), with no statistical significance or clinical relevance.

Trial results for CP-AI-007 for absolute change in FEV_1 % predicted (treatment difference of 5.22) were used in the economic model.

Supplementary data:
Preliminary results of the comparative effectiveness of AI relative to tobramycin solution for inhalation (TSI) reported in the ongoing trial GS-US-205-0110 were presented in the submission. (Tobramycin TSI is not currently PBS listed [as at 1 February 2011]).

In GS-US-205-0110, 28 days of AI treatment demonstrated superior treatment effect over TSI in terms of improving lung function and respiratory symptoms. A course of 28-day TSI treatment resulted in a substantially smaller absolute change in FEV_1 % predicted in GS-US-205-0110 than in other RCTs assessing TSI in control of *P. aeruginosa* infection in patients with CF. No detailed information was available for a full assessment of this trial; and, therefore, no firm conclusions on the relative effectiveness of AI versus TSI could be drawn.

For the safety analysis, the submission detailed the adverse events (AEs) that occurred in the key trials CP-1-A1-005, CP-1-A1-007, and CP-1-A1-006, and in the supporting ongoing phase III trial GS-US-205-0110.

No patients died during trial CP-AI-005 or trial CP-AI-007. A comparison of AEs was performed between AI tid and pooled placebo in CP-AI-005 and between AI tid and placebo tid in CP-AI-007. In both trials, most patients in the AI tid group and in the placebo group had at least one AE. Drug-related AEs were reported by one-fifth to one-third of patients who received at least one dose of AI/placebo. No statistically significant differences in the incidence rates of serious/severe AEs were observed between the AI tid arm and the placebo arm. The most common treatment-emergent AE was cough in both trials, with no difference in the incidence between two interventions. Placebo was associated with higher rates of productive cough and arthralgia in trial CP-AI-007 and decreased appetite in CP-AI-005. Meanwhile, patients treated with AI tid in CP-AI-005 were more likely to develop pyrexia. In trial CP-AI-007, a higher rate of AE-related patient withdrawal was observed in the placebo tid group than in the AI tid group.

Data extracted from the study report during the evaluation showed similar or lower rates of AEs, drug-related AEs, severe AEs and patient withdrawal due to AEs in AI bid patients than in those treated with AI tid. Severe AEs occurred more frequently in AI bid group. No consistent regimen effect on the occurrence of various common treatment-emergent AEs was observed.

Extended assessment of AEs from multiple courses of AI therapy was reported in the follow-on study CP-AI-006, which recruited patients from trials CP-AI-005 and CP-AI-007. No difference in AEs was determined by regimen (tid or bid) and the rate of AEs tapered off with multiple courses of AI therapy. Two deaths were observed in CP-AI-006 (including one after data cut-off for the 12-month analysis), but neither was considered drug-related. Like the results in trial CP-AI-005 and trial CP-AI-007, nearly all patients treated with multiple courses of AI therapy experienced at least one AE. Treatment-related AEs occurred in slightly more than one-third of all the treated participants. No statistically significant differences in the rates of AEs, drug-related AEs, serious AEs, severe AEs and AE resulting in patient withdrawal were observed between AI tid and AI bid. Cough was the most common treatment-related AE in the follow-on study.

Evidence from trial GS-US-205-0110 indicated similar or lower rates of AEs in AI patients than in TSI treated patients. Due to the absence of detailed study information, conclusions on the safety of AI relative to the active comparator TSI could not be reached.

9. Clinical Claim

The submission claimed that the data from the two randomised trials CP-AI-005 and CP-AI-007 and the follow-on study CP-AI-006 indicated that AI was superior to placebo in terms of effectiveness, and was as safe as placebo.

The claim of superior effectiveness of AI was based on a statistically significant difference for most outcomes between AI tid and placebo. However, there was considerable uncertainty with respect to the clinical relevance of some of these differences, e.g. difference in time to the need for treatment of pre-defined symptoms. Clinically meaningful difference in changes of FEV_1 % predicted was not observed between the AI tid and placebo groups. Additionally, the validity of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain as an instrument to detect clinically important changes in control of PA infection in the respiratory tract in patients with CF was inadequately justified in the submission.

The trend of better treatment effect of AI bid compared with AI tid raised an issue regarding the justification of the AI tid regimen, recommended in the approved Product Information, for controlling *P. aeruginosa* infection in patients with CF.

It was most likely that multiple courses of AI therapy would be used for control of *P. aeruginosa* infection in CF patients, if this drug was PBS-listed. No evidence was available to inform the relative effectiveness and safety of multiple courses of AI treatment versus placebo.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

A stepped economic evaluation was presented. The model was a cohort analysis over 12 years, and considered quality adjusted life-years (QALYs) gained and direct treatment (aztreonam) drug costs.

The model was driven by applying the results of trial CP-AI-007 to the cohort (in terms of improved FEV_1 % predicted values), extrapolating the results over 12 months, and then transforming this into a reduced mortality in the treatment arm. The life-years survived were transformed to quality adjusted life years, and these were further extrapolated to 12 years.

The resultant base case ICER was greater than $200,000 per QALY, which was considered high and uncertain by the PBAC.

11. Estimated PBS Usage and Financial Implications

The cost per year to the PBS was estimated in the submission to be between $10 and $30 million in year 5 assuming 6 x 4 week cycles per year and 100% compliance.

The submission's estimates were likely overestimates, as it assumed a total prevalence for CF together with an annual growth rate.

The Evaluator considered that given the continuation rates for treatment with aztreonam beyond 12 months appeared low, and the relatively low incidence of CF, the estimated cost to the PBS would be less than $10 million in year 5.

12. Recommendation and Reasons

The PBAC acknowledged that there was a high clinical need for a nebulised antibiotic to treat cystic fibrosis. However, the PBAC agreed with the Economics Sub-Committee (ESC) that placebo was not the appropriate comparator. The PBAC considered that the appropriate comparator was the therapy most likely to be replaced in clinical practice, regardless of whether or not it was PBS listed, which in this case was nebulised IV formulation of tobramycin. The PBAC noted there was widespread clinical use of nebulised IV formulation of tobramycin for this indication. However, the PBAC considered that the issue of selecting the most appropriate comparator for AI was complicated by the uncertainty in how the therapy will be used in clinical practice and agreed with the ESC that assessment of the clinical and cost effectiveness of aztreonam depended on its clinical place.

The PBAC considered that the clinical place of AI was dependent on whether the main aim of treatment was to avoid development of resistance thereby preventing/delaying *P. aeruginosa* infection and progression of cystic fibrosis, or respiratory symptom improvement, and that the relevance of the outcomes used to show a treatment benefit depended on the reason for use of the drug. Further, the relationship between time to antibiotic need and FEV_1 % predicted, claimed to be the most significant predictor of mortality, had not been demonstrated.

The PBAC noted the three phase III trials (CP-AI-005, CP-AI-007 and CP-AI-006) presented in support of the comparative effectiveness of AI relative to placebo for control of P. aeruginosa in the respiratory tract of patients with CF. The primary effectiveness endpoint in trial CP-AI-005 was time to the need for inhaled or IV antibiotic. The PBAC considered that the time to the need for antibiotics was patient relevant and appeared to be an appropriate measure of the treatment effect of AI in terms of preventing pulmonary exacerbations. However, in this case, aztreonam would most likely replace another antibiotic such as tobramycin, not placebo. The PBAC concluded that the efficacy of aztreonam beyond 28 days, in the appropriate treatment algorithm with the appropriate comparator, had not been provided. Antibiotic resistance rates might also be informative.

The PBAC considered that the superior effectiveness of AI relative to placebo was uncertain, given that, for the primary outcome in trial CP-AI-005, time to the need for anti-pseudomonal antibiotics for pre-defined symptoms, placebo twice daily (bid) was as effective as or possibly more effective than AI three times daily (tid). The PBAC noted that the numerical, although not statistically significantly, longer time to the need for antibiotics, greater improvement in the CFQ-R respiratory domain score and greater increase in FEV_1 % predicted was observed in the AI bid group compared to the AI tid group, which paradoxically suggested a trend of better treatment effect of lower AI dose regimen with respect to symptom control.

The PBAC agreed that the "regimen effect" identified by the Commentary is due largely to differences in the placebo bid and tid groups. The PBAC noted that in CP-AI-005 and CP-AI-007, a treatment effect favouring AI tid therapy over placebo in terms of an increase in FEV_1 % predicted from baseline, indicating an improvement in lung function, was observed. However, a clinically meaningful difference in changes of FEV_1 % predicted was not observed between the AI tid and pooled placebo groups.

The PBAC agreed that the quality of the randomised controlled trials CP-AI-005 and CP-AI-007 were not adequate to reliably assess the comparative effectiveness and safety of

AI relative to placebo as identified in the ESC advice.

The PBAC noted that a stepped economic evaluation was presented. The model was a cohort analysis over 12 years, and considered quality adjusted life-years gained and direct treatment (aztreonam) drug costs.

The PBAC considered that the assumptions used in the translation of the trial to the modelled outcomes, in terms of applicability, extrapolation, transformation of the surrogate outcome to reflect mortality and assignation of utility values were highly uncertain and favoured aztreonam. Also, the high and uncertain base case ICER of more than $200,000/QALY stemmed from the uncertainty regarding the clinical issues and, in particular, the structure of the model which did not appropriately capture how aztreonam would be used in clinical practice.

The PBAC agreed that the main areas of economic uncertainty were identified in the ESC advice, which included concern regarding maintenance of a treatment effect of up to 12 years, validity of the average FEV_1 % over 56 days, relevance of FEV_1 % to mortality association and the analyses of Kerem et al (1992), the appropriateness of a applying a RR of mortality of 2.0 to an improvement in FEV_1 % predicted of less than 10%, the simplicity of the model and quality of life assumptions.

The PBAC therefore rejected the submission on the basis of an unacceptably high and uncertain cost-effectiveness ratio.

Recommendation:
Reject

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 is disappointed with the PBAC decision to reject the application for PBS listing, noting with concern the recommendation that an unapproved, non-PBS listed product be used as the comparator. Gilead is committed to finding a means to provide equitable access to aztreonam for the control of gram-negative bacteria, particularly *Pseudomonas aeruginosa*, in the respiratory tract of patients with moderate to severe cystic fibrosis.