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**VERMONT**  
**Department of Vermont Health Access**

***Therapeutic Class Review***  
***Inhaled Cystic Fibrosis Agents***

**Overview/Summary**

There are two agents in the Inhaled Cystic Fibrosis Agents therapeutic class review and they are aztreonam lysine for inhalation (AZLI) and tobramycin solution for inhalation (TSI). These agents are Food and Drug Administration (FDA) approved for the management of patients with cystic fibrosis (CF) complicated by *Pseudomonas aeruginosa*.<sup>1-3</sup> AZLI is a synthetic monobactam antibiotic that was FDA approved in February 2010, and TSI is an aminoglycoside antibiotic that was FDA approved in December 1997. Neither of these inhalational products is available generically.

CF is a genetic disorder characterized by thickened secretions, acute and chronic endobronchial infections and inflammation which result in pulmonary obstruction and destruction.<sup>4,5</sup> Lung disease accounts for about 85% of the mortality in CF patients.<sup>5</sup> Airway secretions in CF patients may become colonized with *P aeruginosa*, *Haemophilus influenzae*, *Staphylococcus aureus* and *Burkholderia cepacia*.<sup>4</sup> *P aeruginosa* is the most common airway pathogen in CF patients, and chronic colonization is associated with a more rapid decline in pulmonary function.<sup>5,6</sup>

AZLI is administered via nebulizer at a dose of 75 mg three times daily for 28 days, followed by 28 days off therapy.<sup>1,2</sup> TSI is administered via nebulizer at a dose of 300 mg twice daily for 28 days, followed by 28 days off therapy, and then resume the cycle.<sup>3</sup> Several studies have demonstrated the ability of AZLI and TSI to significantly improve lung function and decrease the density of *P aeruginosa* in the sputum of CF patients.<sup>8-11</sup> AZLI also increased the time before additional antipseudomonal antibiotics were required.<sup>9</sup> TSI also significantly decreased hospitalization rates and reduced the need for antipseudomonal antibiotics.<sup>10</sup> Prospective studies have reported continued benefit with TSI for up to two years.<sup>11</sup> *P aeruginosa* susceptibility decreased slightly, but the average number of hospitalizations and antibiotic courses did not increase over time.<sup>11</sup> The most recent guidelines from the CF Foundation recommends chronic use of inhaled tobramycin for asymptomatic and symptomatic CF patients ≥6 years of age who persistently present with *P aeruginosa* in airway cultures to improve lung function and/or reduce exacerbations.<sup>5</sup> These guidelines were published prior to the FDA approval of AZLI. At this time, there are no published clinical studies evaluating the long-term efficacy and safety of AZLI (beyond a 28-day course of therapy) or comparing the efficacy and safety of AZLI to TSI.

During clinical trials, AZLI and TSI were generally well tolerated with cough reported as the most common adverse event. The manufacturer warns that TSI should be prescribed cautiously in patients with known or suspected auditory, neuromuscular, renal or vestibular dysfunction.<sup>3</sup> During postmarketing experience, hearing loss was reported in patients receiving TSI. Efficacy and safety have not been established for the use of AZLI in patients <7 years of age and TSI in patients <6 years of age.<sup>1,3</sup> AZLI and TSI are classified as pregnancy categories B and D, respectively.

**Medications**

**Table 1. Medications Included Within Class Review**

<b>Generic Name (Trade Name)</b>	<b>Medication Class</b>	<b>Generic Availability</b>
Aztreonam lysine for inhalation (Cayston <sup>®</sup> )	Inhaled cystic fibrosis agent	-
Tobramycin solutin for inhalation (TOBI <sup>®</sup> )	Inhaled cystic fibrosis agent	-

## Indications

**Table 2. Food and Drug Administration Approved Indications<sup>1,3</sup>**

Generic Name	Management of Cystic Fibrosis Patients with <i>Pseudomonas aeruginosa</i>
Aztreonam lysine for inhalation	✓ *
Tobramycin solution for inhalation	✓

\*Indicated to improve respiratory symptoms in cystic fibrosis patients with *P aeruginosa*.

The safety and effectiveness of aztreonam lysine for inhalation and tobramycin solution for inhalation have not been established in patients colonized with *Burkholderia cepacia*.<sup>1,3</sup> To reduce the development of drug-resistant bacteria and maintain the effectiveness of these antibiotics, aztreonam lysine for inhalation and tobramycin solution for inhalation should only be prescribed for cystic fibrosis patients with a known *Pseudomonas aeruginosa* infection.<sup>1</sup>

## Pharmacokinetics

**Table 3. Pharmacokinetics<sup>1,3,7</sup>**

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Aztreonam lysine for inhalation	Low (% not reported)	10	None	2
Tobramycin solution for inhalation	1 to 17	60 to 85	None	2

## Clinical Trials

Key pivotal trials evaluating the efficacy and safety of the inhaled cystic fibrosis (CF) agents for the management of *Pseudomonas aeruginosa* infections in CF patients are outlined in Table 4. There are two published short-term studies that evaluate aztreonam lysine for inhalation (AZLI) and several short- and long-term studies that evaluate tobramycin solution for inhalation (TSI).<sup>8-18</sup> At this time, there are no published clinical trials evaluating the long-term efficacy and safety of AZLI beyond a 28-day course of therapy. In addition, there are no published clinical trials comparing the efficacy and safety of AZLI to TSI in the management of CF patients with *P aeruginosa* infections.

In a randomized, double-blind study, the efficacy and safety of AZLI 75 mg three times daily for 28 days was evaluated in CF patients with *P aeruginosa* airway infections (N=164).<sup>8</sup> In a second study, patients initially received TSI 300 mg twice daily for 28 days and were subsequently randomized to AZLI 75 mg twice daily, AZLI 75 mg three times daily, or placebo for an additional 28 days (N=211).<sup>9</sup> In both studies, when compared to placebo, participants in the AZLI arms experienced significant improvement in respiratory symptoms (as measured by the Cystic Fibrosis Questionnaire-Revised) and forced expiratory volume in one second (FEV<sub>1</sub>).<sup>8,9</sup> The sputum density of *P aeruginosa* decreased as a result of AZLI therapy and treatment with AZLI significantly delayed the time before additional antipseudomonal antibiotics were needed when compared to placebo. Patients in these two studies were allowed to continue in an open-label study evaluating the efficacy and safety of repeated courses of AZLI in cycles of 28 days on drug followed by 28 days off drug (up to nine 28-day courses); however, the results of this follow-on study have not been published.<sup>2</sup>

In a pivotal study by Ramsey et al, the safety and efficacy of intermittent TSI was evaluated in 520 CF patients with *P aeruginosa* airway infections.<sup>10</sup> Over the 24 week study, TSI 300 mg twice daily administered in cycles of 28 days on therapy and 28 days off therapy significantly improved FEV<sub>1</sub> by 10%, decreased the density of *P aeruginosa* in sputum, decreased the risk of hospitalization by 26% and decreased the need for intravenous antipseudomonal antibiotics by 36% when compared to placebo. During an open-labeled extension of this study, all patients received cyclic TSI for an additional 72 weeks.<sup>11</sup> Continued treatment with TSI was associated with continued improvement in FEV<sub>1</sub> and with an increase in body mass index. Pulmonary function also improved in patients initially randomized to receive placebo who subsequently received TSI; however, improvements in FEV<sub>1</sub> did not catch up with those

attained by patients initially randomized to receive TSI. *P aeruginosa* susceptibility to tobramycin decreased slightly over time, but the average number of hospitalizations and intravenous antibiotic courses did not increase over time. During the 96 week study period, no cases of nephrotoxicity or ototoxicity were reported; however, 2 patients experienced tinnitus. In the Early Inhaled Tobramycin for Eradication (ELITE) trial, the short- and long-term efficacy and safety of TSI in the treatment of early onset *P aeruginosa* infections in CF patients was evaluated.<sup>15</sup> After 28 days of TSI 300 mg twice daily, 93% of patients were free of *P aeruginosa* infection one month after the end of treatment, and the median time to recurrence of *P aeruginosa* was 26 months. Similar results were observed for patients receiving TSI for 56 continuous days.



**Table 4. Clinical Trials**

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Retsch-Bogart et al<sup>8</sup></p> <p>AZLI 75 mg TID</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, MN, PC, RCT</p> <p>Patients ≥6 years old (mean age 30 years) with CF and moderate to severe lung disease (FEV<sub>1</sub> ≥25% and ≤75% of predicted value), arterial oxygen saturation ≥90% on room air, and <i>P aeruginosa</i> airway infection</p>	<p>N=164</p> <p>42 days (28 days of treatment and 14 days of additional monitoring)</p>	<p>Primary: Change in clinical symptoms (as measured by the CFQ-R-Respiratory Symptom Scale with an MCID score of 5 reflecting improvement or worsening of respiratory symptoms)</p> <p>Secondary: Changes in pulmonary function, hospitalizations, non-respiratory CFQ-R scores, sputum <i>P aeruginosa</i> density, MIC of aztreonam for <i>P aeruginosa</i>, number of isolates and proportion of patients with an aztreonam MIC &gt;8 µg/mL for <i>P aeruginosa</i>, prevalence of other pathogens, adverse events, changes in clinical laboratory values, vital signs, airway reactivity</p>	<p>Primary: Mean CFQ-R-Respiratory scores increased for AZLI-treated patients and decreased for placebo-treated patients. At day 28, the treatment difference was 9.7 points (<math>P&lt;0.001</math>). Two weeks after treatment ended, scores in all groups declined. However, in the AZLI treatment arm, the scores remained above baseline, while the scores for placebo-treated patients continued to decrease; at day 42, the treatment difference was 6.3 points (<math>P=0.015</math>).</p> <p>CFQ-R-Respiratory scores increased in AZLI-treated patients, regardless of whether the disease was moderate or severe. Overall, CFQ-R-Respiratory scores improved for more AZLI-treated patients than placebo-treated patients (day 28; ≥5 point increase: AZLI, 56%; placebo, 37%). When compared to placebo, fewer scores worsened with AZLI treatment (day 28; ≥5 point decrease: AZLI, 25%; placebo, 45%; <math>P=0.006</math> for overall comparison).</p> <p>Secondary: The mean FEV<sub>1</sub> increased for AZLI-treated patients and decreased for placebo-treated patients. At day 28, a 10.3% difference was observed (<math>P&lt;0.001</math>). Two weeks after treatment ended, both treatment arms had a decline in mean FEV<sub>1</sub>. While the FEV<sub>1</sub> in the AZLI group remained above baseline after treatment ended, FEV<sub>1</sub> in the placebo group continued to decline and fell below baseline at the end of the study. At day 42, the FEV<sub>1</sub> treatment difference was 5.7% (<math>P=0.002</math>).</p> <p>The mean FEV<sub>1</sub> improved in AZLI-treated patients with different severities of lung disease, as well as among patients of different ages. The mean relative change in FEV<sub>1</sub> increased for AZLI-treated patients and decreased for placebo-treated patients; the difference at day 28 was 10.2% (<math>P&lt;0.001</math>). The mean FEV<sub>1</sub> decreased in both treatment arms by day 42, at which time the treatment difference was 5.7% (<math>P=0.003</math>).</p> <p>The adjusted mean sputum <i>P aeruginosa</i> density decreased for AZLI-treated patients and stayed near baseline for placebo-treated patients. At day 28, the treatment difference in <i>P aeruginosa</i> sputum density was <math>-1.4533 \log_{10}</math> CFU/g (<math>P&lt;0.001</math>). In both treatment arms, at day 42, the <i>P aeruginosa</i></p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>density values were near baseline (<math>P=0.822</math>).</p> <p>Fewer patients in the AZLI group were hospitalized compared to the placebo group (5 vs 14%, respectively; <math>P=0.064</math>). There were significantly fewer hospitalization days in the AZLI group compared to the placebo group (0.5 vs 1.5, respectively; <math>P=0.049</math>).</p> <p>The responses of AZLI-treated patients were significantly larger than those of the placebo patients in the following nonrespiratory CFQ-R categories: eating (<math>P&lt;0.001</math>), emotional functioning (<math>P=0.005</math>), health perceptions (<math>P&lt;0.001</math>), physical functioning (<math>P=0.001</math>), role limitation/school performance (<math>P=0.014</math>), and vitality (<math>P=0.005</math>). The following CFQ-R categories did not yield significant differences between the AZLI and placebo groups: body image (<math>P=0.327</math>), digestion (<math>P=0.889</math>), social functioning (<math>P=0.248</math>), treatment burden (<math>P=0.177</math>), and weight (<math>P=0.376</math>).</p> <p>There was a significant difference in the percentage of patients reporting productive cough in the AZLI and placebo groups (12.5 vs 25.0%, respectively; <math>P=0.047</math>). There were no other significant differences in treatment-emergent adverse events. Three patients in the AZLI group experienced airway reactivity compared to five patients in the placebo group (<math>P</math> value not reported). There were no clinically significant changes in vital signs or mean clinical laboratory values, although AZLI patients tended to have fewer shifts above the reference range for hematology variables.</p> <p>Aztreonam MIC<sub>50</sub> and MIC<sub>90</sub> values for all <i>P aeruginosa</i> isolates from placebo-treated patients either remained unchanged or decreased. In AZLI-treated patients, there was a transient fourfold increase in MIC<sub>90</sub>. The number of <i>P aeruginosa</i> isolates with an aztreonam MIC &gt;8 µg/mL and the proportion of patients with such isolates did not increase during AZLI treatment. AZLI treatment did not result in increases in <i>Stenotrophomonas maltophilia</i>, <i>Staphylococcus aureus</i>, or <i>Achromobacter xylosoxidans</i>. There were no isolates of <i>Burkholderia cepacia</i> complex.</p>
McCoy et al <sup>9</sup> TSI 300 mg BID for 28	DB, PC, MC, RCT Patients ≥6 years old	N=211 112 days	Primary: Time to need additional inhaled or	Primary: The median time before additional inhaled or IV antipseudomonal antibiotics were required to treat symptoms indicative of pulmonary exacerbation was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>days (all participants) followed by AZLI or placebo for 28 days</p> <p>AZLI 75 mg BID</p> <p>vs</p> <p>AZLI 75 mg TID</p> <p>vs</p> <p>placebo</p>	<p>(mean age 26 years) with CF, <math>\geq 3</math> TSI courses within the previous year, FEV<sub>1</sub> <math>\geq 25\%</math> and <math>\leq 75\%</math> of predicted value, arterial oxygen saturation <math>\geq 90\%</math> on room air, current <i>P aeruginosa</i> airway infection</p>	<p>(including 28 days of OL TSI, 28 days of AZLI or placebo, and 56 days of additional monitoring)</p>	<p>IV antipseudomonal antibiotics to treat symptoms indicative of pulmonary exacerbation</p> <p>Secondary: Changes in CFQ-R score, pulmonary function (FEV<sub>1</sub>), sputum <i>P aeruginosa</i> density, time to hospitalization, weight, MIC of aztreonam for <i>P aeruginosa</i>, adverse events, changes in clinical lab values, vital signs, airway reactivity</p>	<p>significantly longer in the AZLI-pooled group (92 vs 71 days; <math>P=0.007</math>). When comparing the AZLI-BID and AZLI-TID groups with placebo, the median time until need for antibiotics was longer in the AZLI-BID group (<math>&gt;92</math> days; <math>P=0.002</math>) and AZLI-TID group (87 days; <math>P=0.182</math>) than in the placebo group (71 days). AZLI therapy resulted in a 45% risk reduction for needing additional inhaled or IV antibiotics.</p> <p>The investigators examined the effects of age (<math>&lt;18</math> years old and <math>\geq 18</math> years old). In both subgroups, the proportion of participants needing inhaled or IV antibiotics was smaller in the AZLI-treated groups (<math>&lt;18</math> years old: AZLI-pooled, 26%; placebo, 42%; <math>\geq 18</math> years old: AZLI-pooled, 34%; placebo, 52%; <math>P</math> value not reported). In patients <math>\geq 18</math> years old, the time to need additional antibiotics was significantly longer for AZLI-treated patients when compared with placebo-treated patients (<math>P=0.021</math>). The time to need additional antibiotics was not significantly longer in patients <math>&lt;18</math> years old; however, the group sizes were small.</p> <p>Secondary: In the AZLI-pooled group, the CFQ-R-Respiratory score increased 5.01 points compared with placebo (<math>P=0.020</math>). Both AZLI-BID and AZLI-TID regimens led to significant improvements in the CFQ-R-Respiratory scores, and the responses to AZLI-BID and AZLI-TID were similar.</p> <p>During the follow-up period after the treatment course, adjusted mean CFQ-R-Respiratory scores decreased (day 84; AZLI, 0.71 points; placebo, <math>-0.78</math> points; change from day 0; <math>P</math> value not reported).</p> <p>During the treatment period with AZLI or placebo (days 0 to 28), the CFQ-R-Respiratory scores improved for more AZLI patients (52 vs 37%) and worsened for fewer AZLI patients (28 vs 38%) compared to placebo. The overall categorical comparison was significant (<math>P=0.029</math>).</p> <p>Compared with placebo, the adjusted mean FEV<sub>1</sub> improved 6.3% in the AZLI-pooled group (day 28; <math>P=0.001</math>). Responses for the AZLI-BID and AZLI-TID regimens were similar. Significantly greater improvement in FEV<sub>1</sub> was observed in the AZLI group compared with the placebo group at day 28 (4.1</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>vs -2.5%; <math>P &lt; 0.001</math>). It should be noted that at the end of the TSI run-in period, by chance, the AZLI-TID group had a notable improvement in FEV<sub>1</sub>. In both of the AZLI groups and the placebo group, the FEV<sub>1</sub> decreased during the follow-up period.</p> <p>The adjusted mean <i>P aeruginosa</i> sputum density decreased 0.66 log<sub>10</sub> CFU/g in the AZLI-pooled group when compared to placebo at day 28 (<math>P = 0.006</math>); the decrease was significant for both the AZLI-BID and AZLI-TID groups. During follow-up, the <i>P aeruginosa</i> density increased for the AZLI and placebo groups.</p> <p>During the TSI run-in period, the mean CFQ-R-Respiratory scores decreased -1.47, mean FEV<sub>1</sub> increased 0.9%, and mean <i>P aeruginosa</i> density decreased 0.28 log<sub>10</sub> CFU/g sputum.</p> <p>There was no significant difference in either time to hospitalization or median days/number of patients hospitalized.</p> <p>Compared with placebo, weight increased 0.77% at day 28 for AZLI-pooled patients (<math>P = 0.051</math>).</p> <p>There were no statistically significant differences regarding the incidence of treatment-emergent adverse events. Airway reactivity after treatment occurred in four AZLI-treated patients (3.0%) and two placebo-treated patients (2.6%). Also, the mean changes in vital signs, hematology, and serum chemistry were comparable for all treatment groups.</p> <p>The MIC<sub>50</sub> and MIC<sub>90</sub> values remained unchanged between Days 0 and 56, except for a transient fourfold increase in the AZLI-TID group on day 14. As AZLI treatment progressed, the proportion of patients with <i>P aeruginosa</i> isolates and aztreonam MIC values &gt;8 µg/mL increased; however, this increase was transient in the AZLI-TID group (day 0, 28, 42: AZLI-BID=27%, 44%, 39%; AZLI-TID=33%, 43%, 28%; placebo: 38%, 37%, 30%, respectively; <math>P</math> values not reported). The proportion of patients who had <i>P aeruginosa</i> with tobramycin MIC values ≥8 µg/mL did not increase throughout the course of the study. There were no increases observed for the prevalence</p>

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<p>Ramsey et al<sup>10</sup></p> <p>TSI 300 mg BID for 3 cycles (each cycle consisting of 28 days during which the medication was administered and 28 days during which it was not administered)</p> <p>vs</p> <p>placebo</p>	<p>MC, DB, PC, RCT</p> <p>Patients ≥6 years old (mean age 21 years) with CF, a respiratory tract culture positive for <i>P aeruginosa</i>, FEV<sub>1</sub> ≥25% and ≤75% of predicted value</p>	<p>N=520</p> <p>24 weeks</p>	<p>Primary: Change in FEV<sub>1</sub>, density of <i>P aeruginosa</i> in sputum at 20 weeks</p> <p>Secondary: Hospitalization, treatment with IV antipseudomonal antibiotics</p>	<p>of <i>Staphylococcus aureus</i>, <i>Stenotrophomonas maltophilia</i>, or <i>Achromobacter xylosoxidans</i> (days 0-28). <i>Burkholderia cepacia</i> complex was not isolated.</p> <p>Primary: At the end of 20 weeks, patients treated with TSI had an average 10% increase in FEV<sub>1</sub>, as compared to a 2% decline for the patients receiving placebo (<i>P</i>&lt;0.001).</p> <p>At the end of 20 weeks, patients treated with TSI had an average reduction of 0.8 log<sub>10</sub> <i>P aeruginosa</i> CFU/g of sputum, as compared with the value at zero weeks, whereas the density in the placebo group had increased by 0.3 log<sub>10</sub> CFU/g (<i>P</i>&lt;0.001).</p> <p>Secondary: Patients receiving tobramycin were 26% less likely to be hospitalized and 36% less likely to require IV antipseudomonal antibiotics (<i>P</i> value not reported).</p>
<p>Moss et al<sup>11</sup></p> <p>TSI 300 mg BID for 28 days for 3 cycles (each cycle consisting of 28 days during which the medication was administered and 28 days during which it was not administered)</p> <p>vs</p> <p>placebo</p> <p>After 3 cycles (24 weeks), all patients continued on TSI cycles for 72 weeks.</p>	<p>MC, DB, PC, RCT for 24 weeks then OL for 72 weeks</p> <p>Adolescent CF patients (13 to 17 years old) with <i>P aeruginosa</i> and mild to moderate lung disease (FEV<sub>1</sub> ≥25% and ≤75% of predicted value)</p>	<p>N=128</p> <p>24 weeks TSI or placebo cycles then 72 weeks TSI cycles</p>	<p>Primary: Change in FEV<sub>1</sub>, <i>P aeruginosa</i> density, incidence of hospitalization and IV antibiotic use, weight gain, aminoglycoside toxicity</p> <p>Secondary: Not reported</p>	<p>Primary: Patients originally randomized to TSI and placebo treatments exhibited improvements in FEV<sub>1</sub> percent predicted of 13.5 and 9.4%, respectively (<i>P</i> value not reported). At the end of the last treatment period (92 weeks), patients originally randomized to TSI and placebo showed improvements of 14.3 and 1.8%, respectively (<i>P</i> value not reported).</p> <p>Improvement in pulmonary function was significantly correlated with reduction in <i>P aeruginosa</i> density (<i>P</i>=0.0001). <i>P aeruginosa</i> susceptibility to tobramycin decreased slightly over time, but this was not correlated with clinical response. The average number of hospitalizations and IV antibiotic courses did not increase over time (<i>P</i> value not reported).</p> <p>TSI treatment was associated with increased weight gain and body mass index (<i>P</i>=0.0002).</p> <p>During the 96-week study period, mean serum creatinine levels remained within normal limits and exhibited no clinically relevant changes. Serial audiograms revealed no evidence of aminoglycoside-induced hearing loss; however, two patients experienced tinnitus.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
<p>Quittner et al<sup>12</sup></p> <p>TSI 300 mg BID for 3 cycles (each cycle consisting of 28 days during which the medication was administered and 28 days during which it was not administered)</p> <p>vs</p> <p>placebo</p>	<p>Retrospective analysis of RCT data</p> <p>Patients ≥6 years old (mean age 21 years) with CF, a respiratory tract culture positive for <i>P aeruginosa</i>, FEV<sub>1</sub> ≥25% and ≤75% of predicted value</p>	<p>N=520</p> <p>24 weeks</p>	<p>Primary: Improvement in quality of life</p> <p>Secondary: Not reported</p>	<p>Primary: Patients treated with TSI were more likely to report improvement in quality of life than those receiving placebo (<math>P&lt;0.005</math>).</p> <p>Secondary: Not reported</p>
<p>Gibson et al<sup>13</sup></p> <p>TSI 300 mg BID for 28 days</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT</p> <p>Children with CF, &gt;6 months old and &lt;6 years old, positive oropharyngeal culture for <i>P aeruginosa</i> within 2 weeks to 12 months before screening</p>	<p>N=21</p> <p>56 days (study was terminated prematurely because of evidence of a significant microbiological treatment effect)</p>	<p>Primary: Change in BAL <i>P aeruginosa</i> density from baseline to day 28</p> <p>Secondary: Frequency of lower airway <i>P aeruginosa</i> eradication, safety</p>	<p>Primary: The mean reduction in <i>P aeruginosa</i> density in the TSI group from baseline to day 28 was 5.25 log<sub>10</sub> CFU/mL, whereas the placebo group had a mean increase of 0.30 log<sub>10</sub> CFU/mL (<math>P&lt;0.0001</math>).</p> <p>Secondary: <i>P aeruginosa</i> eradication was noted in eight of eight TSI-treated patients compared to one of 14 placebo-treated patients (<math>P</math> value not reported).</p> <p>There was no difference in the incidence of adverse events between the treatment groups. No abnormalities in serum creatinine or audiometry and no episodes of significant bronchospasm were observed in association with TSI treatment (<math>P</math> values were not reported).</p>
<p>Murphy et al<sup>14</sup></p> <p>TSI 300 mg BID for 7 cycles (each cycle consisting of 28 days during which the</p>	<p>MC, OL, PG, RCT</p> <p>Patients with CF and chronic <i>P aeruginosa</i>, 6 to 10 years old with FEV<sub>1</sub></p>	<p>N=184</p> <p>56 weeks (study was terminated prematurely</p>	<p>Primary: Rate of lung function decline (FEV<sub>1</sub>), rates of hospitalization, concomitant antibiotic</p>	<p>Primary: Patients treated with TSI trended toward improvement in percent predicted FEV<sub>1</sub> over the control group at weeks 20 and 32, but the improvement was not statistically significant (<math>P</math> value not reported).</p> <p>Significantly fewer TSI-treated patients were hospitalized for worsening of</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
medication was administered and 28 days during which it was not administered)  vs  placebo	≥70% and ≤110% predicted values, or 11 to 15 years old with FEV <sub>1</sub> ≥70% and ≤90% of predicted value	secondary to poor recruitment)	use, safety  Secondary: Not reported	respiratory symptoms (11.0 vs 25.6%; <i>P</i> <0.011), and fewer TSI patients were hospitalized overall (16.5 vs 27.8%; <i>P</i> <0.065). Fewer TSI patients received antibiotics other than the study drug (78.0 vs 95.6%), and significantly fewer patients received oral antibiotics (76.9 vs 91.1%; <i>P</i> <0.009).  No other differences in safety or adverse event were observed.  Secondary: Not reported
Ratjen et al <sup>15</sup>  TSI 300 mg BID for 28 days  vs  TSI 300 mg BID for 56 days	MC, MN, OL, RCT  Patients with CF, ≥6 months old (mean age 9 years), with a first or early infection with <i>P aeruginosa</i>	N=88  Follow-up to 27 months	Primary: Median time to recurrence of <i>P aeruginosa</i>  Secondary: Proportion free of <i>P aeruginosa</i> one month after end of treatment, safety	Primary: The median time to recurrence of <i>P aeruginosa</i> (any strain) was 26.12 and 25.82 months following TSI for 28 and 56 days, respectively ( <i>P</i> =0.593 for differences between groups).  Secondary: In total 93 and 92% of the patients were free of <i>P aeruginosa</i> infection one month after the end of treatment, and 66 and 69% remained free at the final visit in the 28- and 56-day groups, respectively ( <i>P</i> values not reported).  No major short- or long-term changes in spirometric parameters were observed during the study period.  Adverse events reported within the first three months of the study that were considered possibly or probably related to treatment were cough (9% of patients in the 28-day group) and dysphonia (11 and 14% of patients in the 28- and 56-day groups, respectively) ( <i>P</i> values not reported). No significant changes in serum creatinine concentrations were observed in either group. In the 56-day TSI group, there was no difference between serum tobramycin levels at days 28 and 56 ( <i>P</i> value not reported). One mild case and one moderate to severe case of reversible hearing loss were reported in patients receiving TSI for 56 days.
Stelmach et al <sup>16</sup>  TSI 300 mg BID/cycle (each cycle consisting of 28 days during	OL, OS  Children with CF, 6 to 18 years old, with moderate to severe	N=12  4 years (2 years prior to treatment and	Primary: Changes in pulmonary function (FEV <sub>1</sub> ), chest X-ray, weight, height	Primary: FEV <sub>1</sub> declined by a median value of 7.6% during the two years before TSI treatment. After two years of TSI treatment, FEV <sub>1</sub> declined by 1.5% from baseline which represents a significant reduction in the decline of pulmonary function ( <i>P</i> =0.049).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
which the medication was administered and 28 days during which it was not administered)	lung disease (primarily FEV <sub>1</sub> ≥25% and ≤75% of predicted value), infected by <i>P aeruginosa</i>	2 years of TSI treatment)	Secondary: Not reported	TSI significantly delayed progression of pulmonary X-ray changes assessed by Brasfield score ( <i>P</i> =0.02).  Two years of TSI significantly improved body mass index ( <i>P</i> =0.02).  Secondary: Not reported
Hodson et al <sup>17</sup>  TSI 300 mg BID  vs  colistin (injection) 80 mg inhaled BID	RCT  Patients >6 years old with CF, FEV <sub>1</sub> >25% or predicted value, <i>P aeruginosa</i> positive sputum culture	N=115  4 weeks	Primary: Mean change from baseline to week four in FEV <sub>1</sub>  Secondary: Change in sputum <i>P aeruginosa</i> density, tobramycin and colistin MICs, safety	Primary: TSI produced a mean 6.7% improvement in lung function ( <i>P</i> =0.006), while there was no significant improvement in the colistin-treated patients (mean change, 0.37%; <i>P</i> =0.473).  Secondary: Both nebulized antibiotic regimens produced a significant decrease in the sputum <i>P aeruginosa</i> density (both <i>P</i> <0.05), and there was no development of highly resistant strains over the course of the study.  No significant difference was detected between groups with respect to incidence of adverse events ( <i>P</i> values not reported).

Drug regimen abbreviations: AZLI=aztreonam lysine for inhalation, BID=two times daily, IV=intravenous, TID=three times daily, TSI=tobramycin inhalation solution

Study abbreviations: DB=double-blind, MC=multicenter, MN=multinational, OL=open-labeled, OS=observational study, PC=placebo-controlled, RCT=randomized controlled trial

Miscellaneous abbreviations: BAL=bronchoalveolar lavage, CF=Cystic Fibrosis, CFQ-R=Cystic Fibrosis Questionnaire-Revised, CFU=colony forming units, FEV<sub>1</sub>=forced expiratory volume in one second, MCID=minimal clinically important differences, MIC=minimum inhibitory concentration, *P aeruginosa*=*Pseudomonas aeruginosa*

**Special Populations****Table 5. Special Populations**<sup>1,3</sup>

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Aztreonam lysine for inhalation	Clinical trials did not include patients who were ≥65 years of age.  Safety and effectiveness in children <7 years of age have not been established.	No dosage adjustment is required.	No dosage adjustment is required.	B	By injection <1% of aztreonam is excreted in human milk.  Use of inhalational product during breastfeeding is unlikely to pose a risk to infants.
Tobramycin solution for inhalation	No dosage adjustment required; use with caution in patients with known or suspected auditory, neuromuscular, renal or vestibular dysfunction.  Safety and effectiveness in children <6 years of age have not been established.	No dosage adjustment is required; use with caution	No dosage adjustment is required.	D	Unknown

**Adverse Drug Events****Table 6. Adverse Drug Events (%)**<sup>1,3</sup>

Adverse Event	Aztreonam Lysine for Inhalation	Tobramycin Solution for Inhalation
<b>Gastrointestinal</b>		
Abdominal pain	7	13
Anorexia	-	19
Diarrhea	-	6
Nausea	-	11
Taste perversion	-	7
Vomiting	6	14
Weight loss	-	10
<b>Respiratory</b>		
Asthma	-	16
Bronchospasm	3	-
Chest discomfort	8	-
Cough	54	46
Dyspnea	-	34
Epistaxis	-	7

Adverse Event	Aztreonam Lysine for Inhalation	Tobramycin Solution for Inhalation
Hemoptysis	-	19
Hyperventilation	-	5
Lower respiratory tract infection	-	6
Lung disorder	-	31
Lung function decreased	-	16
Nasal congestion	16	-
Pharyngitis	-	38
Pharyngolaryngeal pain	12	-
Rhinitis	-	35
Sinusitis	-	8
Sputum discoloration	-	21
Sputum increased	-	38
Wheezing	16	-
<b>Other</b>		
Asthenia	-	36
Back pain	-	7
Chest pain	-	26
Dizziness	-	6
Ear pain	-	7
Fever	13	33
Headache	-	27
Malaise	-	6
Pain	-	8
Rash	2	5
Tinnitus	-	3
Voice alteration	-	13

-Event not reported or incidence <5%.

**Contraindications/Precautions**

Aztreonam lysine for inhalation (AZLI) is contraindicated in patients with a known allergy to aztreonam. In clinical trials; some patients receiving AZLI experienced allergic reactions (e.g., facial rash, swelling, throat tightness). Immediate discontinuation of AZLI is recommended in the event of an allergic reaction. Caution should be exercised when administering AZLI in patients with a history of a beta-lactam allergy, as cross-sensitivity with agents like penicillins, cephalosporins and carbapenems may occur. However, in clinical trials, patients with a known beta-lactam allergy received AZLI, and no severe allergic reactions were reported.<sup>1</sup>

Tobramycin solution for inhalation (TSI) is contraindicated in patients with a known allergy to any aminoglycoside. Patients receiving concomitant parenteral aminoglycoside therapy should be monitored as clinically appropriate. TSI should be prescribed cautiously for patients with known or suspected auditory, vestibular, renal or neuromuscular dysfunction. During clinical studies, transient tinnitus was noted in 3% of patients receiving TSI. While ototoxicity was not reported with TSI during clinical studies, hearing loss was reported by patients during postmarketing experience. Some of these reports occurred in patients with previous or concomitant treatment with systemic aminoglycosides. An audiogram should be considered for patients who show any evidence of auditory dysfunction, or who are at increased risk for auditory dysfunction. Since tinnitus may be a sentinel symptom of ototoxicity, the onset of this symptom warrants caution. Nephrotoxicity was not seen during TSI clinical studies but has been associated with aminoglycosides as a class. If nephrotoxicity occurs in a patient receiving TSI, tobramycin therapy should be discontinued until the serum concentration falls <2 µg/mL. TSI should be used cautiously in patients with muscular disorders, such as myasthenia gravis or Parkinson's disease, since

aminoglycosides may aggravate muscle weakness because of a potential curare-like effect on neuromuscular function.<sup>3</sup>

Bronchospasm has been associated with nebulized therapies, including AZLI and TSI, and should be treated as medically appropriate.<sup>1,3</sup> A decrease in forced expiratory volume in one second (FEV<sub>1</sub>) of ≥15% immediately following administration of AZLI after pretreatment with a bronchodilator was observed in 3% of patients in clinical trials.<sup>1</sup> Additionally, patients with increases in FEV<sub>1</sub> during a 28-day course of AZLI were sometimes treated for pulmonary exacerbations after the treatment period had ended. As a result, healthcare providers should consider a patient's baseline FEV<sub>1</sub> prior to therapy and the presence of other symptoms when evaluating whether posttreatment changes in FEV<sub>1</sub> are caused by a pulmonary exacerbation. In clinical trials of TSI, changes in FEV<sub>1</sub> measured after the inhaled dose were similar in the TSI and placebo groups.<sup>3</sup> The safety and effectiveness of AZLI and TSI have not been established in patients with an FEV<sub>1</sub> <25% or >75% of predicted value.<sup>1,3</sup>

### Drug Interactions

At this time, no formal studies examining drug interactions with aztreonam lysine for inhalation have been conducted.<sup>1</sup> Concurrent and/or sequential use of tobramycin solution for inhalation with other drugs with neurotoxic or ototoxic potential should be avoided. Some diuretics can enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue. Tobramycin solution for inhalation should not be administered concomitantly with ethacrynic acid, furosemide, mannitol or urea.<sup>3</sup>

### Dosing and Administration

Table 7. Dosing and Administration<sup>1-3</sup>

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Aztreonam lysine for inhalation	<u>Cystic fibrosis:</u> 75 mg via Altera <sup>®</sup> Nebulizer (over about 2 to 3 minutes) TID for 28 days, then 28 days off therapy	Safety and effectiveness in children <7 years of age have not been established.	Solution for inhalation: 75 mg*
Tobramycin solution for inhalation	<u>Cystic fibrosis:</u> 300 mg via PARI LC PLUS <sup>®</sup> Reusable Nebulizer (over about 15 minutes) BID for 28 days, then 28 days off therapy	Safety and effectiveness in children <6 years of age have not been established.	Solution for inhalation: 300 mg/5 mL*

\*Available as a single use vial.  
 BID=twice daily, TID=three times daily

### Clinical Guidelines

Table 8. Clinical Guidelines

Clinical Guideline	Recommendations
Cystic Fibrosis Foundation: <b>Cystic Fibrosis Pulmonary Guidelines: Chronic Medications for Maintenance of Lung Health (2007)</b> <sup>5</sup>	<ul style="list-style-type: none"> <li>For cystic fibrosis (CF) patients ≥6 years of age and moderate to severe lung disease who persistently present with <i>Pseudomonas aeruginosa</i> in airway cultures, chronic use of inhaled tobramycin is strongly recommended to improve lung function and reduce exacerbations.</li> <li>For CF patients ≥6 years of age who are asymptomatic or have mild lung disease who persistently present with <i>P aeruginosa</i> in airway cultures, chronic use of inhaled tobramycin is recommended to reduce exacerbations.</li> <li>For CF patients ≥6 years of age who persistently present with <i>P aeruginosa</i> in airway cultures, there is insufficient evidence to recommend for or against routinely providing other chronically inhaled antibiotics (e.g., ceftazidime, colistin, gentamicin) to improve lung function and reduce exacerbations.</li> </ul>

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> <li>For CF patients <math>\geq 6</math> years of age who persistently present with <i>P aeruginosa</i> in airway cultures, chronic azithromycin is recommended in order to improve lung function and reduce the number of exacerbations.</li> <li>The CF Foundation does note that the definition of “chronic” for each treatment regimen is not necessarily clear. As a result, the CF Foundation recommends that clinicians closely monitor each patient and decide whether a particular therapy continues to benefit the patient. If the regimen is no longer beneficial, then the clinician should determine whether or not the therapy needs to be discontinued.</li> </ul>
Cystic Fibrosis Foundation: <b>Cystic Fibrosis Pulmonary Guidelines: Treatment of Pulmonary Exacerbations (2009)</b> <sup>6</sup>	<ul style="list-style-type: none"> <li>There is insufficient evidence to recommend for or against continued use of inhaled antibiotics in patients treated with the same antibiotics intravenously for the treatment of an acute exacerbation of pulmonary disease.</li> <li>The decision to continue an inhaled antibiotic in conjunction with the same intravenous antibiotic should be determined on a case-by-case basis.</li> </ul>

### Conclusions

There are two agents in the therapeutic class review called “Inhaled Cystic Fibrosis Agents” and they are aztreonam lysine for inhalation (AZLI) and tobramycin solution for inhalation (TSI). These inhaled agents are Food and Drug Administration (FDA) approved for the management of patients with cystic fibrosis (CF) complicated by *Pseudomonas aeruginosa*.<sup>1-3</sup> Neither of these inhalational products is available generically. Since TSI has been on the market for more than 10 years while AZLI was FDA approved in February 2010, there is more published efficacy and safety data with TSI than AZLI.

Several studies have demonstrated the ability of AZLI and TSI to significantly improve lung function and decrease the density of *P aeruginosa* in the sputum of CF patients.<sup>8,11</sup> AZLI also increased the time before additional antipseudomonal antibiotics were required.<sup>9</sup> TSI significantly decreased hospitalization rates and reduced the need for additional antipseudomonal antibiotics.<sup>10</sup> Prospective studies have reported continued benefit with TSI for up to two years.<sup>11</sup> *P aeruginosa* susceptibility decreased slightly, but the average number of hospitalizations and antibiotic courses did not increase over time. The most recent guidelines from the CF Foundation recommend the chronic use of inhaled tobramycin for asymptomatic and symptomatic CF patients  $\geq 6$  years of age who persistently present with *P aeruginosa* in airway cultures to improve lung function and/or reduce exacerbations.<sup>5</sup> These guidelines were published prior to the FDA approval of AZLI. At this time, there are no published clinical studies evaluating the long-term efficacy and safety of AZLI (beyond a 28-day course of therapy) or comparing the efficacy and safety of AZLI to TSI.

Both AZLI and TSI are administered via nebulizer; however, AZLI is dosed three times daily (with each dose administered over two to three minutes) and TSI is dosed twice daily (with each dose administered over 15 minutes).<sup>1-3</sup> At this time, it is not known if the differences in administration schedules lead to significant differences in patient compliance or clinical outcomes. During clinical trials, AZLI and TSI were generally well tolerated with cough reported as the most common adverse event. Since there are no head-to-head trials comparing the safety of AZLI to TSI or long-term experience with AZLI, at this time it is not known if one agent is safer than the other. The manufacturer warns that TSI should be prescribed cautiously in patients with known or suspected auditory, neuromuscular, renal, or vestibular dysfunction.<sup>3</sup> During postmarketing experience, hearing loss was reported in patients receiving TSI. Efficacy and safety have not been established for the use of AZLI in patients  $< 7$  years of age and TSI in patients  $< 6$  years of age.<sup>1,3</sup> AZLI and TSI are classified as pregnancy categories B and D, respectively.

**Appendix I: Utilization Within This Drug Class for DVHA: October 1, 2010 to December 31, 2010**

Medication	# of Rx's	Market Share (%)	Plan Cost \$	Avg \$/Rx
TOBI	23	%	\$82,370.85	\$3,581.34
Cayston	6	%	\$22,799.70	\$3,799.95
<b>Class Total:</b>	<b>29</b>	<b>100%</b>	<b>\$105,170.55</b>	<b>\$3,626.57</b>

**Recommendations**

In recognition of the following factors:

- The established short- and long-term efficacy and safety of TOBI® (tobramycin solution for inhalation), and the established short-term efficacy and safety of Cayston® (aztreonam lysine for inhalation).
- The limited treatment options available for patients with cystic fibrosis with Pseudomonas aeruginosa and the association of this bacterium with a more rapid decline in pulmonary function.
- The current recommendations from the clinical guidelines.

...it is recommended that the current Department of Vermont Health Access (DVHA) approval criteria remain unchanged (see below).

Cayston®:

- The diagnosis or indication is cystic fibrosis.
- Quantity limit: 84 vials/56 days; maximum days supply = 56 days

TOBI® is the preferred agent, available without a prior authorization at a quantity limit of 56 vials/56 days and a maximum days supply of 56 days.

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