

CEDAC FINAL RECOMMENDATION

AZTREONAM FOR INHALATION SOLUTION (Cayston – Gilead Sciences Canada, Inc.)

Indication: Cystic Fibrosis with Chronic Pulmonary *Pseudomonas Aeruginosa* Infections

Recommendation:

The Canadian Expert Drug Advisory Committee (CEDAC) recommends that aztreonam for inhalation solution be listed for the treatment of chronic pulmonary *Pseudomonas aeruginosa* infections when used as cyclic treatment (28-day cycles) in patients with moderate to severe cystic fibrosis (CF) and deteriorating clinical condition despite treatment with inhaled tobramycin.

Reasons for the Recommendation:

1. In one open-label randomized controlled trial (RCT) in tobramycin-experienced patients with moderate to severe lung disease, aztreonam for inhalation solution had a similar impact on hospitalizations and quality of life compared with inhaled tobramycin. In addition, aztreonam-treated patients had a statistically significant improvement in lung function and a statistically significant reduction in the incidence of intravenous antibiotic use compared with inhaled tobramycin.
2. Although the clinical trial data are limited and aztreonam is associated with additional cost compared with inhaled tobramycin, the Committee recognized patient input that stressed the need for additional antibiotic treatment options.

Background:

Aztreonam is a monobactam antibiotic. Aztreonam for inhalation solution has a Health Canada indication for the management of CF patients with chronic pulmonary *Pseudomonas aeruginosa* infections. It is available as a sterile lyophilized powder in single-use vials of 75 mg per vial, for reconstitution and inhalation. The Health Canada-recommended dose for patients six years of age and older is one single-use vial (75 mg) administered three times a day for a 28-day course (followed by 28 days without aztreonam for inhalation solution).

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Summary of CEDAC Considerations:

The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs of aztreonam for inhalation solution, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Clinical Trials

The systematic review included three double-blind RCTs comparing inhaled aztreonam with placebo (AIR-CF1, AIR-CF2, AIR-CF4) and one open-label RCT comparing inhaled aztreonam with tobramycin inhalation solution (GS-US-205-0110, hereafter referred to as study 0110).

AIR-CF4 was conducted in patients with mild CF (forced expiratory volume in one second [FEV₁] % predicted of greater than 75%) and AIR-CF1 and AIR-CF2 were conducted in patients with moderate to severe CF (FEV₁ % predicted of 25% to 75%). Study 0110 was conducted in patients with moderate to severe CF (FEV₁ % predicted of 75% or less). All trials included patients six years of age or older.

Placebo-controlled trials:

- AIR-CF1 (N = 166) and AIR-CF4 (N = 160) were multinational studies that randomized patients to inhaled aztreonam 75 mg three times daily or placebo; both trials included a 28-day treatment period and 14-day follow-up period. AIR-CF1 had high and differential withdrawal between treatment groups: 18% and 32% for aztreonam and placebo groups, respectively. Only a small percentage of patients in AIR-CF4 withdrew from the study: 3% and 2% for aztreonam and placebo groups, respectively.
- AIR-CF2 (N = 246) was a multi-centre (US only) study that included a 28-day run-in period wherein all patients received inhaled tobramycin 300 mg twice daily, after which patients received their randomized treatment for 28 days, followed by a 56-day follow-up period. Patients were randomized to one of four treatment groups: inhaled aztreonam 75 mg (either two or three times daily) or placebo (either two or three times daily). AIR-CF2 had high and differential study withdrawal (63% overall).

Active-controlled trial:

- Study 0110 (N = 273) was a multinational study that randomized patients to one of inhaled aztreonam 75 mg three times daily or tobramycin inhalation solution 300 mg twice daily; treatments were administered for 28 days, followed by 28 days off treatment. The study included three courses of treatment; total study duration was 24 weeks. Study withdrawal was more frequent for patients in the tobramycin group compared with aztreonam: 18% versus 9%, respectively.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: mortality, need for additional antibiotics, lung function as measured by the FEV₁, quality of life, withdrawal due to adverse events, and serious adverse events.

The primary outcomes for each of the trials were as follows:

- AIR-CF1: change in patient-reported respiratory symptoms as measured by the revised CF Questionnaire (CFQ-R) score.

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- AIR-CF2: time to need for additional inhaled or intravenous antipseudomonal antibiotics to treat exacerbation.
- AIR-CF4: change in patient-reported respiratory symptoms as measured by the CFQ-R score.
- Study 0110: co-primary end points were the relative change in the FEV₁ % predicted, from baseline to day 28 (non-inferiority outcome) and the average absolute change in FEV₁ % predicted from baseline over three treatment courses (superiority outcome). For the test of non-inferiority, aztreonam would be considered non-inferior to tobramycin if the upper bound of the 95% confidence interval of the between-treatment difference did not exceed 4%.

The CFQ-R is a validated health-related quality of life measure for CF that includes three modules: quality of life module (including both generic and disease-specific domains), symptoms (including respiratory, digestive, and weight scales), and health perception. Each scale yields a standardized score from 0 to 100, with higher scores indicating better quality of life. A minimally clinically important difference (MCID) of 4 points on the CFQ-R Respiratory Symptoms score has been established for patients with stable CF, and 8.5 points for patients during an exacerbation.

Outcomes that patients highlighted were hospitalization, time lost from work or school, time spent administering treatments, and quality of life.

Results

Efficacy or Effectiveness

Placebo-controlled trials:

- In patients with mild CF (AIR-CF4), there were no statistically significant differences in the proportion of patients requiring antibiotics for an exacerbation, quality of life, or the percentage of school days missed. The observed difference in lung function (based on FEV₁ % predicted) between aztreonam and placebo was not considered clinically important.
- In AIR-CF1 and AIR-CF2, aztreonam-treated patients with moderate to severe CF had statistically significantly greater improvements in quality of life (CFQ-R respiratory symptom score) and lung function (FEV₁ % predicted) compared with placebo. The improvement in CFQ-R scores exceeded the MCID in AIR-CF1 and AIR-CF2 (pooled twice and three times daily aztreonam versus placebo).

Active-controlled trial:

- In the open-label study 0110, compared with tobramycin, aztreonam statistically significantly reduced the proportion of patients who required intravenous antibiotics and delayed the time to intravenous antibiotics, but the incidence of hospitalization was similar between treatments.
- Aztreonam statistically significantly increased lung function (based on FEV₁ % predicted) compared with tobramycin at four weeks and over the three treatment courses.

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Harms (Safety and Tolerability)

- The frequency of adverse events and serious adverse events was similar between aztreonam and comparators. Adverse events reported were primarily respiratory, such as cough, dyspnea, respiratory tract congestion, and oropharyngeal pain.
- An increase in antimicrobial resistance to aztreonam was noted in study 0110 over the six months of the study. The clinical trials are of insufficient size and follow-up duration to assess the importance of aztreonam resistance.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-effectiveness analysis comparing aztreonam with tobramycin inhalation solution in patients with CF suffering from *Pseudomonas aeruginosa*, treated as outpatients, over a one-year time horizon. The model was based on clinical data from a single head-to-head trial of the two treatments (study 0110). Drug acquisition costs were considerably higher for aztreonam (\$26,160 versus \$18,346), but these were in part offset by lower rates (and, therefore, costs) of CF-related hospitalization (\$16,385 versus \$23,590). The manufacturer reported that over a one-year horizon, aztreonam was associated with greater costs (\$42,545 versus \$41,936) and similar life-years (0.9959 versus 0.9960) compared with tobramycin inhalation solution.

A number of limitations were noted regarding the manufacturer's economic analysis. The manufacturer did not consider the use of intravenous tobramycin for inhalation, which is reimbursed by a number of participating drug plans. The lower cost of intravenous tobramycin would increase the relative cost of aztreonam. The manufacturer's claim that aztreonam is associated with improvements in lung disease was not supported by study 0110. A reduction in respiratory hospitalizations was observed even though a reduction in overall hospitalizations was not observed.

The daily cost of aztreonam (\$144) is greater than tobramycin inhalation solution (\$101) and intravenous tobramycin used for inhalation (\$36).

Patient Input Information:

The following is a summary of information provided by one patient group that responded to the CDR Call for Patient Input:

- Patients may spend two or more hours per day receiving treatments.
- A number of factors that contribute to reduced quality of life for patients with CF were noted, including treatment time; missed school, work, or social activities; and the need for hospitalization.
- Parent caregivers face financial challenges because of loss of income (due to the time spent in caregiving) and treatment costs.
- Treatments that have reduced administration times are expected to vastly increase quality of life for patients and caregivers.
- Patients expect that inhaled aztreonam will be an alternative treatment for patients who cannot tolerate, or develop resistance to, alternative treatments.

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Other Discussion Points:

- The Committee considered patient input that stressed the need for additional antibiotic treatment options, and aztreonam belongs to a different class of antibiotics from tobramycin.

CEDAC Members:

Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Dr. Doug Coyle, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, Dr. Yvonne Shevchuk, and Dr. James Silvius.

June 15, 2011 Meeting**Regrets:**

Two CEDAC members did not attend

Conflicts of Interest:

None

About this Document:

CEDAC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CEDAC made its recommendation. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CEDAC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final CEDAC Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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