Canadian Expert Drug Advisory Committee
Final Recommendation – Plain Language Version

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 Cayston, which is also called aztreonam for inhalation solution, be listed by Canada's publicly funded drug plans for the treatment of chronic lung infections with *Pseudomonas aeruginosa* bacteria, when used as cyclic treatment (28-day cycles) in patients with moderate to severe cystic fibrosis (CF) and worsening clinical condition despite treatment with inhaled tobramycin.

Reasons for the Recommendation:

1. In one study of patients with moderate to severe lung disease who had previously been treated with inhaled tobramycin, Cayston was similar to inhaled tobramycin in the occurrence of hospitalizations and effect on quality of life. As well, Cayston-treated patients had more improvement in lung function and less intravenous (given in the vein) antibiotic use compared with patients treated with inhaled tobramycin.
2. Although there are few data from medical studies and Cayston costs more than inhaled tobramycin, the Committee recognized patient input that emphasized the need for additional antibiotic treatment options.

Background:

Cayston belongs to a class of drugs called monobactam antibiotics. It works by binding to certain *Pseudomonas aeruginosa* proteins and interferes with the development of the bacterial cell wall, causing the cell wall to break and killing the bacteria. By decreasing the number of *Pseudomonas aeruginosa* bacteria living in the lungs, lung infection is reduced, and the respiratory symptoms and lung function are improved.

Cayston 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 (mixing with liquid) and inhalation. The Health Canada-recommended dose for patients six years of age and older is one single-use vial (75 mg) inhaled three times a day for 28 days (followed by 28 days without Cayston).

Summary of CEDAC Considerations:

To make their decision, the Committee considered the following information prepared by the Common Drug Review (CDR): a review of the medical studies of Cayston, and a review of economic information prepared by the manufacturer of Cayston. Also, CEDAC considered information that patient groups submitted about outcomes and issues important to patients who have the condition for which the drug is indicated or who might use the drug.

Clinical Trials

CEDAC reviewed four studies conducted in patients with CF. The review included three studies (AIR-CF1, AIR-CF2, AIR-CF4) comparing Cayston with placebo (an inhalation with no active medication) and one study comparing Cayston 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 [FEV_1] % predicted of greater than 75%) and AIR-CF1 and AIR-CF2 were conducted in patients with moderate to severe CF (FEV_1 % predicted of 25% to 75%). Study 0110 was conducted in patients with moderate to severe CF (FEV_1 % predicted of 75% or less). All studies included patients six years of age or older.

The studies comparing Cayston with placebo:

- In AIR-CF1 (with 166 patients) and AIR-CF4 (with 160 patients), patients either inhaled Cayston 75 mg three times daily or placebo. Both studies had a 28-day treatment period and a 14-day follow-up period. AIR-CF1 had a large percentage of patients who stopped participating during the study and this percentage was different depending on which treatment the patient was receiving; 18% and 32% for Cayston and placebo groups, respectively. Only a small percentage of patients in AIR-CF4 stopped taking part during the study; 3% and 2% for Cayston and placebo groups, respectively. These studies took place in more than one country
- In AIR-CF2 (with 246 patients), all patients received inhaled tobramycin 300 mg twice daily for 28 days before being assigned to receive one of the following four treatments for another 28 days: Cayston 75 mg (inhaled either two or three times daily) or placebo (inhaled either two or three times daily). Then there was a 56-day follow-up period. AIR-CF2 had had a large proportion of patients who stopped participating during the study (63% overall) and this percentage was different depending on which treatment the patient was receiving. This study took place in various locations in the US.

The study comparing Cayston with tobramycin inhalation solution:

- In study 0110 (with 273 patients), patients received either Cayston 75 mg inhaled three times daily or tobramycin inhalation solution 300 mg twice daily; treatments were given for 28 days, followed by 28 days without treatment. The study included three courses of treatment and lasted a total of 24 weeks. A greater proportion of tobramycin patients stopped taking part in the study compared to Cayston patients; 18% versus 9%, respectively. This study took place in more than one country.

Outcomes

Outcomes of interest were defined in advance in the CDR review protocol. Of these, the Committee discussed the following: mortality (death), need for additional antibiotics, lung function as measured by the FEV_1, quality of life, stopping participation due to side effects, and serious side effects.

The main purpose for each of the studies was as follows:

- AIR-CF1 – change in lung symptoms (reported by the patient) as measured by the revised CF Questionnaire (CFQ-R) score.
- AIR-CF2 – amount of time before patients needed additional treatment with antibiotics active against *Pseudomonas* bacteria (either inhaled or intravenous) because of a worsening of their condition.
- AIR-CF4 – change in lung symptoms (reported by the patient) as measured by the CFQ-R score.
- Study 0110 – this study had two main purposes: (i) to see if Cayston was not worse than inhaled tobramycin. Cayston would be considered not worse than inhaled tobramycin if the percentage improvement in the FEV_1 % predicted, from start of the study to day 28, was not likely to be more than 4% less for Cayston compared with inhaled tobramycin, and (ii) the average numerical change in FEV_1 % predicted from start of the study over three courses of treatment.

The CFQ-R is a good health-related quality of life measure for CF, and includes three sections; quality of life (including both general and disease-specific areas), symptoms (including lung, bowel, and weight scales), and health awareness. Each results in a score from 0 to 100, with higher scores being better. The smallest change which makes a difference for patients with stable CF is 4 points on the CFQ-R respiratory symptoms score, and 8.5 points for patients during a period of a worsening of their condition.

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

Results

Efficacy or Effectiveness

The studies comparing Cayston with placebo:

- In patients with mild CF (AIR-CF4), there were no real differences in the percentage of patients who needed antibiotics for a worsening of their condition, quality of life, or the percentage of school days missed. The observed difference in lung function (based on FEV_1 % predicted) between Cayston and placebo was not considered to be an important difference.
- AIR-CF1 and AIR-CF2 Cayston-treated patients with moderate to severe CF had greater improvements in quality of life (CFQ-R respiratory symptom score) and lung function (FEV_1 % predicted) compared with placebo. The improvement in CFQ-R scores was at a level that made a difference for the patients in AIR CF1 and AIR CF2 (results for patients treated two and three times a day were combined to compare Cayston with placebo).

The study comparing Cayston with tobramycin inhalation solution:

- In study 0110, compared with tobramycin, a smaller percentage of Cayston patients needed intravenous antibiotics. Also, the time it took until intravenous antibiotics were needed was longer for Cayston patients compared with tobramycin. The occurrence of hospitalizations was about the same for Cayston and tobramycin patients.
- Cayston improved lung function (based on FEV_1 % predicted) compared with tobramycin at four weeks and over the three courses of treatments.

Harms (Safety and Tolerability)

- The percentage of patients having side effects and serious side effects was similar between Cayston and placebo, and between Cayston and tobramycin. The most common side effects were lung related and included cough, shortness of breath, congestion, and throat pain.
- In study 0110, it was noted that over the six months of the study patients' bacteria became more resistant to Cayston. None of the studies were long enough, or contained enough patients, to be able to assess the importance of bacterial resistance to Cayston.

Cost and Cost-Effectiveness

The manufacturer submitted economic information to compare Cayston with tobramycin inhalation solution in patients with CF suffering from *Pseudomonas aeruginosa* treated as outpatients to evaluate the health benefit over a one-year time horizon. The manufacturer's economic assessment was based on results from study 0110. Cayston costs more than tobramycin ($26,160 versus $18,346, annually), but these costs were in part offset by lower rates (and, therefore, costs) of hospitalizations for CF ($16,385 versus $23,590, annually). The manufacturer reported that, over a one-year time horizon, Cayston cost more than tobramycin ($42,545 versus $41,936).

A number of possible problems were noted with 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. If this had been taken into account, then the difference between the cost of Cayston and tobramycin would have been even greater. The manufacturer claimed that Cayston is linked to improvements in the severity of the lung disease, but there is no data supporting this in study 0110. Cayston decreased hospitalizations related to lung problems compared with tobramycin, but Cayston did not decrease total hospitalizations compared with tobramycin.

The daily cost of Cayston ($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 lower the quality of life for patients with CF were noted, including: the time it takes to get treatments; missed school, work, or social activities; and the need for hospitalization.

- Parent caregivers can have financial problems because of loss of income (due to the time spent in caregiving) and treatment costs.
- Treatments that take less time to give are expected to greatly increase quality of life for patients and caregivers.
- Patients expect that Cayston will be an alternative treatment for patients who cannot take other treatments, or who develop resistance to other treatments (i.e., other treatments stop working).

Other Discussion Points:

- The Committee took into account the patient input, which emphasized the need for other antibiotic treatment options, and that Cayston belongs to a different class of antibiotics than 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:

The information contained within this plain language version of the Canadian Expert Drug Advisory Committee (CEDAC) Recommendation about this drug is based on the information found within the corresponding technical version of the CEDAC Recommendation.

In making its recommendation, CEDAC considered the best clinical and pharmacoeconomic evidence available, up to that time. Health care professionals and those requiring more detailed information are advised to refer to the technical version available in the CDR Drug Database on the CADTH website (www.cadth.ca).

Background on CEDAC

CEDAC is a committee of the Canadian Agency for Drugs and Technologies in Health (CADTH). The committee is made up of drug evaluation experts and public members. CEDAC provides recommendations about whether or not drugs should be listed for coverage through the participating publicly funded drug plans; however, the individual drug plans make their own decision about whether or not to cover a drug.

In making its recommendations, CEDAC decides if the drug under review ought to be covered by the participating public drug plans based on an evidence-informed review of the medication's effectiveness and safety, and based on an assessment of its cost-effectiveness in comparison with other available treatments. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CEDAC deliberations.

The CEDAC Recommendation neither takes the place of a medical professional providing care to a particular patient, nor is it intended to replace professional advice. CADTH is not legally responsible for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.

The statements, conclusions, and views expressed herein do not necessarily represent the views of Health Canada, the federal government, any provincial or territorial government, or any pharmaceutical manufacturer.

The manufacturer has reviewed this document and has not requested the deletion of any confidential information.