SUMMARY/POSITION STATEMENTS

This policy addresses the coverage of Cayston (aztreonam) for the treatment of cystic fibrosis when appropriate criteria are met.

- Inhaled aztreonam is a formulation of the monobactam antibiotic aztreonam and is specifically approved for use in patients with CF.

- There are two FDA-approved inhaled antibiotics on the market for the management of CF in patients with Pseudomonas (P.) aeruginosa: inhaled aztreonam (Cayston) and inhaled tobramycin (TOBI, TOBI Podhaler) at the time of this writing. These agents are administered chronically to suppress the growth of P. aeruginosa and reduce the risk of CF exacerbation.

- There is a lack of comparative evidence or demonstrated clinical benefit in efficacy or safety of aztreonam for inhalation over tobramycin inhalation solution. Currently, the evidence supports inhaled aztreonam as an alternative to commonly used inhaled antibiotics to treat P. aeruginosa infections in patients with CF. Further studies are needed to confirm the drug’s effectiveness and safety as a part of long-term treatment regimens for patients with CF.

- Inhaled aztreonam may also be a valuable therapy option for patients who cannot tolerate tobramycin inhalation solution or colistin due to airway hypersensitivity. For patients with β-lactam allergies, inhaled aztreonam offers a viable treatment alternative, since there is a low incidence of allergic cross-reactivity with beta lactams such as penicillin, cephalosporins or carbapenems, and immunogenic reactions to aztreonam are rare.

- Inhaled aztreonam for patients with CF with airway infections may help to address the problematic increase in resistance of P. aeruginosa to tobramycin and colistin.

- There is insufficient long-term evidence available for aztreonam lysine for inhalation beyond a 28-day course.
  
  - There is insufficient long-term evidence available for the inhaled antibiotics and dornase alfa for Cystic Fibrosis which includes tobramycin (Tobi®), aztreonam (Cayston®), dornase alfa (Pulmozyme®). The longest study for dornase alfa (Pulmozyme®) is 2 years and tobramycin inhalation solution (Tobi®) is 33 months.
The American Thoracic Society (ATS) has published updated Cystic Fibrosis Pulmonary Guidelines in the April 2013 issue of American Journal of Respiratory and Critical Care Medicine. An evidence review of chronic medications for CF lung disease was performed in 2007 to provide policy to clinicians in evaluating and selecting appropriate treatment for individuals with this disease. The new guidelines have undertaken a new review of the literature to update the recommendations, including consideration of new medications and additional evidence on previously reviewed therapies.

- Chronic use of inhaled tobramycin (TOBI) and inhaled aztreonam (Cayston) at the same rating to reduce exacerbation for patients who are six years of age and older with persistent P. aeruginosa culture in the airways (strength of recommendation A for moderate to severe disease; strength of recommendation B for mild disease).
- Ivacaftor (Kalydeco™), a potentiator that activates defective CF transmembrane conductance regulator (CFTR) at the cell surface, has been added to the guidelines.
- For individuals with CF, six years of age and older, with at least one G551D CFTR mutation, the Pulmonary Clinical Practice Guidelines Committee strongly recommends the chronic use of ivacaftor to improve lung function and quality of life, and reduce exacerbations (strength of recommendation A). For individuals with CF, six years of age and older, without Pseudomonas aeruginosa persistently present in cultures of the airways, the CF Foundation recommends the chronic use of azithromycin should be considered to reduce exacerbations (strength of recommendation C).

The FDA approval of Cayston was based on a randomized, double-blind, placebo-controlled, multicenter trial in 164 subjects.

- The subjects received either Cayston (75mg) or volume-matched placebo administered by inhalation 3 times a day for 28 days. Patients were required to have been off antibiotics for at least 28 days before treatment with study drug.
- The treatment difference at Day 28 between Cayston-treated and placebo-treated patients for percent change in FEV1 (L) was statistically significant at 10%. Improvements in FEV1 were comparable between adult and pediatric patients. Two weeks after completion of drug treatment, the difference in FEV1 between Cayston and placebo groups had decreased to 6%.
- Exclusion criteria included recent (within the previous 28 days) administration of antipseudomonal antibiotics, azithromycin, or aerosolized hypertonic saline solution; current oral corticosteroid; positive culture of Burkholderia cepacia within the previous two years; daily oxygen supplementation; monobactam antibiotic hypersensitivity; intolerance to short-acting beta2-agonists; lung transplantation; alanine transaminase (ALT) and aspartate aminotransferase (AST) levels more than five times the normal values; serum creatinine more than two times the normal value; pregnancy; lactation; recent change of antimicrobial, bronchodilator, anti-inflammatory, or corticosteroid medication; or new findings in the chest radiograph within the previous 90 days.
- The primary efficacy endpoint was improvement in respiratory symptoms on the last day of treatment with Cayston or placebo. The respiratory symptoms were determined by CF-Questionnaire-Revised Scale [CFQ-R], pulmonary function, P. aeruginosa density in sputum, and non-respiratory CFQ-R scales. Statistically significant improvements were seen in both adult and pediatric patients, but were substantially smaller in adult patients.
- Conclusion: At the end of the 28-day treatment, patients in the treatment arm had a higher mean CFQ-R respiratory score (9.7 points difference; p<0.001), improved pulmonary function (10.3 percent difference in FEV1 predicted, p<0.001), and less sputum P. aeruginosa density (28-day difference, -1.453 log10 CFU/g; p<0.001). Inhaled aztreonam was well-tolerated with similar adverse effects as the placebo group.

Aztreonam for inhalation was well-tolerated overall in clinical trials. Most adverse events were mild to moderate in severity, and the most commonly reported adverse events were associated with respiratory symptoms, such as cough, productive cough, nasal congestion, respiratory tract congestion, wheezing and pharyngolaryngeal pain. The observed respiratory symptoms are consistent with those generally seen in patients with cystic fibrosis lung disease, and there were no statistically significant differences between treatment groups in drug-related adverse events or serious adverse events.
FDA INDICATIONS

- **Cayston (aztreonam)** is indicated for the treatment of cystic fibrosis.

To improve respiratory symptoms in cystic fibrosis patients with Pseudomonas aeruginosa.

Safety and effectiveness have not been established in children younger than 7 years of age, patients with forced expiratory volume in 1 second (FEV1) less than 25% or greater than 75% predicted, or patients colonized with Burkholderia cepacia.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of aztreonam and other antibacterial drugs, only use aztreonam to treat patients with cystic fibrosis known to have P. aeruginosa in the lungs.

**Available as:** Cayston 75mg Powder for Inhalation Solution

**FDA Approved:** February 2010

Black Box Warnings: *None at the time of this writing*

**CLASSIFICATION:** Monobactam Antibacterials

**RECOMMENDATIONS/COVERAGE CRITERIA**

**Cayston (aztreonam)** may be authorized for members who meet ALL of the following criteria [ALL]

1. **Prescriber specialty [ONE]**
   - Prescribed by, or in consult with*, a board-certified pulmonologist or specialist with experience in treating cystic fibrosis. *Consultation notes required.

2. **Diagnosis/Indication [ONE]**
   **NOTE:** Documented diagnosis must be confirmed by portions of the individual’s medical record, which will confirm the presence of disease and may include, but not limited to, test reports, chart notes from provider’s office or hospital admission note.
   - Diagnosis of cystic fibrosis is confirmed by appropriate diagnostic or genetic testing
     - The sweat chloride test is the gold standard of CF diagnosis since it remains to be the most discriminatory test for this disorder. Values of chloride greater than 60 mEq/L in a sweat chloride concentration analysis are considered positive. CF can also be diagnosed by DNA analysis; however, a negative analysis result does not exclude the diagnosis of the disease.
   - Confirmation of *Pseudomonas aeruginosa* in cultures of the airways confirmed by a copy of a positive sputum culture
     **NOTE:** Sputum culture and susceptibility testing performed periodically will provide information on changing microbial flora and the possible emergence of bacterial resistance.
     - Prescribing aztreonam in the absence of known P. aeruginosa infection in patients with CF is unlikely to provide benefit and increases the risk of development of drug-resistant bacteria--to maintain the effectiveness of Cayston and other antibacterial drugs, Cayston should be used only to treat patients with CF known to have P. aeruginosa in the lungs.
   - Confirmation that member is not colonized with *Burkholderia cepacia*
     - Safety and effectiveness have not been established in patients colonized with Burkholderia cepacia.
3. Age/Gender/Other restrictions [ALL]

- 7 years of age or older
  - Safety and efficacy of inhaled aztreonam (Cayston) have not been established in pediatric patients less than seven years of age. No dose adjustment is required in pediatric patients.

- FEV1 that is 25% to 75% of predicted (a forced expiratory volume in one second (FEV1) between 25% and 75% predicted)
  - Safety and effectiveness have not been established in patients with forced expiratory volume in 1 second (FEV1) less than 25% or more than 75% predicted.

4. Step/Conservative Therapy/Other condition Requirements [ALL: A, B]

- Susceptibility results indicating that aztreonam is the only inhaled antibiotic to which the Pseudomonas aeruginosa is sensitive
  
  OR

  At least one of the following is applicable. Documentation required: [ONE]
  - Previously use of TOBI® inhalation solution and experienced a clinically significant adverse drug reaction or an unsatisfactory therapeutic response
  - Contraindication/intolerance or medical condition(s) that prevents the use of TOBI® inhalation solution (e.g., patient is pregnant, allergy to tobramycin)
  - Sputum culture shows resistance to tobramycin

- Confirmation that member is not receiving treatment with other inhaled/nebulized antibiotics or inhaled/nebulized anti-infective agents, including alternating treatment schedules or as part of a cyclic rotation with TOBI® [MOLINA PHARMACY STAFF/REVIEWER TO VERIFY: Pharmacy claims data for other inhaled antibiotics/anti-infective agents within the last 30 days, OR for new members to Molina Healthcare, confirm inhaled antibiotics/anti-infective agents in medical chart history]
  - In the pivotal trials, patients were required to have been off antibiotics for at least 28 days before treatment with study drug.\(^\text{a-e}\)
  - There are no high quality clinical studies available for using Cayston in rotation with other inhaled antibiotics and/or in combination with other nonantibiotic therapies.
  - ‘It is not clear, from the data available to date, that an alternating treatment schedule is more effective than use of a single agent. There is reasonable theoretical foundation to suggest that such an approach might actually be associated more with emergence of antibiotic resistance. As there is not published experience adequately addressing the question, and as the decision to keep to a single agent versus alternating would be theoretical more than algorithm based (on a prospective basis), I find the current language presented for the coverage policy appropriate and defensible. As such, I do not recommend any changes in this section.’ AMR Reviewer (Board certified in Internal Medicine, Pulmonary Disease, Critical Care), 2010

- Member is prescribed an inhaled bronchodilator [e.g. albuterol solution, ProAir HFA, Proventil HFA, Maxair Autohaler, Ventolin HFA, Xopenex solution/HFA, Duoneb, Proventil, Accuneb, Alupent (Metaproterenol), Maxair, Serevent, Advair, Symbicort, Foradil, Perforomist, Dulera] to be utilized prior to administration of Cayston
  - A bronchodilator should be used before administration of Cayston.\(^\text{a-e}\)
5. **Contraindications/Exclusions/Discontinuations**
   Authorization will **not** be granted if ANY of the following conditions apply [ANY]
   - ☐ Non-FDA approved indications
   - ☐ Hypersensitivity to aztreonam or any of its components

   **Exclusions [ANY]**
   - ☐ < 7 years old
   - ☐ forced expiratory volume in 1 second (FEV1) < 25% or > 75% predicted
   - ☐ Colonized with Burkholderia cepacia

6. **Labs/Reports/Documentation required [ALL]**
   All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member’s medical records supporting the diagnosis. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCG are included.

   **NOTE:** Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.
CONTINUATION OF THERAPY

Cayston (aztreonam) may be authorized for continuation of therapy if meet ALL of the following criteria are met:

1. Initial Coverage Criteria
   - Member currently meets ALL initial coverage criteria

2. Compliance [ALL]
   - Adherence to therapy at least 85% of the time as verified by Prescriber and member’s medication fill history (review Rx history for compliance), including: [MOLINA MEDICAL/PHARMACY STAFF TO VERIFY]
     - Compliance in taking the medication as prescribed
     - No intolerable adverse effects or drug toxicity
   
   NOTE: Therapy may be discontinued due to poor adherence upon recommendation of the Molina Medical Director when adherence < 85% has been demonstrated in at least two months during the course of therapy

3. Labs/Reports/Documentation required [ALL APPLICABLE]
   - Documentation of stabilization or improvement as evaluated by a board-certified pulmonologist or specialist with experience in treating cystic fibrosis
     - The CF foundation defines clinically meaningful endpoints as time to need for additional antipseudomonal antibiotics and hospitalization. The Cystic Fibrosis Questionnaire-Revised (CFQR) has been validated as a subjective measure to assess multiple domains of patient quality of life and is approved by the FDA as a patient reported outcome measure.

4. Discontinuation of Treatment [ANY]
   - Discontinue treatment if ANY of the following conditions applies: [ANY]
     - Intolerable adverse effects or drug toxicity
     - Persistent and uncorrectable problems with adherence to treatment
     - Poor response to treatment as evidenced by physical findings and/or clinical symptoms
     - Contraindications/Exclusions to therapy
       - Non-FDA approved indications
       - Hypersensitivity to aztreonam or any of its components
     - Exclusions [ANY]
       - < 7 years old
       - forced expiratory volume in 1 second (FEV1) < 25% or > 75% predicted
       - Colonized with Burkholderia cepacia

Monitoring
- All patients should have regular review of sputum microbiology to ensure continued appropriate ongoing treatment. If Pseudomonas has not been isolated or has been replaced by a new organism (i.e. Burkholderia cepacia) then a change of therapy should be considered.
- All patients should have a regular assessment of lung function to ensure ongoing treatment tolerance and identification of adverse effects. If there is evidence of bronchoconstriction associated with ongoing therapy, the inhaled antibiotic should be discontinued and an alternative considered.
1. Recommended Dosage [ALL]

☐ The recommended dosage for adults and children is ONE dose [one dose is a single-use vial (75mg) of lyophilized aztreonam mixed with one ampule of saline diluent (0.17% sodium chloride 1 mL)] taken 3 times a day by inhalation for a 28-day treatment course, followed by 28 days without the treatment. Use only with Altera® Nebulizer System, not with any other type of nebulizer.

- Cayston is administered by inhalation three times a day for a 28-day course, followed by 28 days off Cayston therapy. 
- Cayston is administered using the Altera® Nebulizer System only.
- Inhaled aztreonam requires no dose adjustment in patients with renal impairment.
- Patients taking several inhaled medications should be advised to use the medications in the following order of administration: bronchodilator, mucolytics, and lastly, Cayston.

2. Authorization Limit [ALL]

☐ Quantity limit: [ALL]

- **ONE (1) Cayston 28-day kit every 56 days** (84 vials per 56 days) for an administration cycle of 28 days of treatment followed by 28 days with no Cayston treatment

  **NOTE:** One Cayston® kit contains 84 vials (75mg/vial) of Cayston® and 88 ampules of diluent in two 14-day supply cartons

- Maximum daily dose: 75mg three times a day (225mg per day) via nebulizer after pre-treatment with a bronchodilator

☐ Dispensing limit: 3 vials per day, 28 days supply; 1 kit per 28 days

☐ Duration of initial authorization: 6 months (3 active 28-day courses)

☐ Continuation of treatment: Re-authorization for continuation of treatment is required every 6 months to determine continued need based on documented positive clinical response

3. Route of Administration [ALL]

☐ Cayston (aztreonam) is considered a self-administered medication

- Cayston is only approved for administration with the Altera hand set nebulizer system.
  - The FDA-approved labeling for Cayston states that it should only be administered with the Altera Nebulizer System.

- Administer a bronchodilator before administration of aztreonam
  - If member is on multiple inhaled therapies, administer bronchodilator first, then mucolytic, and lastly, aztreonam.

☐ If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare. Self-administered medications may not be dispensed for self-administration and billed through the medical benefit by a provider; they must be dispensed through a participating pharmacy.
COVERAGE EXCLUSIONS

All other uses of Cayston (aztreonam) that are not an FDA-approved indication or not included in the ‘Coverage Criteria’ section of this policy are considered experimental/investigational or not a covered benefit of this policy. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

SUMMARY OF EVIDENCE

Cystic Fibrosis (CF) is a rare genetic disease which can affect multiple organs, in which lung disease is responsible for approximately 85% of the mortality. CF is the second most common inherited life-threatening disease in the U.S. after sickle cell disease. There is no cure, but aggressive prevention and treatment of complications have led to improved survival. It is estimated that CF affects approximately 30,000 children and adults in the U.S. and about 70,000 people worldwide. More than 1,000 individuals are diagnosed with CF annually, with 53 percent of patients being diagnosed by six months of age and 74 percent by two years of age.8

CF is an autosomal recessive disorder caused by mutations on both alleles of chromosome 7, affecting the gene encoding for cystic fibrosis transmembrane conductance regulator (CFTR) gene located on that particular chromosome. It is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) protein, a complex chloride channel and regulatory protein found in exocrine tissues. Transport of chloride, sodium, and bicarbonate are disrupted, which may lead to thick, viscous secretions in the lungs, pancreas, liver, intestine, and reproductive tract, and to increased salt content in sweat gland secretions.

There is currently no curative treatment. The disease is characterized by episodes of pulmonary infection associated with inflammation, which lead to worsening respiratory function, respiratory failure and ultimately death. The typical manifestation of CF involves progressive obstructive lung disease that has been associated with impaired mucus clearance, difficulty clearing pathogens, and risk of chronic pulmonary infection and inflammation. As a result respiratory failure is the common cause of death in patients with CF with the median expected survival age of 36 years. CF also manifests as pancreatic insufficiency that has been associated with fat and protein malabsorption and, consequently, malnutrition.

Bacterial colonization of the airway secretions with Pseudomonas aeruginosa, Haemophilus influenza, Staphylococcus aureus or Burkholderia cepacia may occur in patients with CF. P. aeruginosa is the most common pathogen in CF patients, and chronic colonization may cause respiratory insufficiency and eventual respiratory failure. Consequences in this patient population include increased morbidity and mortality. Therefore, therapies that may decrease or eliminate colonization in addition to treating exacerbations are essential to improving outcomes.

The primary goals of CF treatment include: 1) maintaining lung function as near to normal as possible by controlling respiratory infection and clearing airways of mucus, 2) administering nutritional therapy (i.e., enzyme supplements, multivitamin and mineral supplements) to maintain adequate growth, and 3) Managing complications. Medications used to treat patients with cystic fibrosis may include pancreatic enzyme supplements, multivitamins (particularly fat-soluble vitamins), mucolytics, antibiotics (including inhaled, oral, or parenteral), bronchodilators, anti-inflammatory agents, and CFTR potentiators [i.e. ivacaftor (Kalydeco)]. Since pulmonary infection is the main source of morbidity and mortality, antibiotics play a crucial role in CF therapy to control the progression of the disease.

There are two inhaled antibiotic agents FDA-approved for the management of patients with CF that is complicated by Pseudomonas aeruginosa, inhaled aztreonam (Cayston) and inhaled tobramycin (TOBI), at the time of this writing. Inhaled antibiotics help reduce exacerbations and improve lung function by reducing P.aeruginosa concentrations.

Inhaled aztreonam (Cayston) is a beta-lactamase-resistant monobactam antibiotic that only has activity against aerobic gram-negative bacteria, including Pseudomonas aeruginosa. Aztreonam exerts its effect by binding penicillin-binding protein of susceptible bacteria, forming elongated filamentous cells that eventually lyse and die.
formulated for administration by inhalation through a nebulizer so that the drug is concentrated in the airway. A bronchodilator, and any other cystic fibrosis inhaled therapies should be taken before the administration of aztreonam.

**DEFINITIONS**

N/A

**APPENDIX**

N/A

**CODING INFORMATION:** THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

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**REFERENCES**

**Package Insert, FDA, Drug Compendia**


Clinical Trials, Definitions, Peer-Reviewed Publications


Government Agencies, Professional Societies, and Other Authoritative Publications


DISCLAIMER

This Medical Policy is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusions or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern.
In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the following website: http://www.cms.hhs.gov/center/coverage.asp.

The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina medical coverage policy (MCP) document and provide the directive for all Medicare members.