

Product Monograph

Pr **CAYSTON[®]**

Aztreonam for Inhalation Solution

75 mg aztreonam / vial

Antibiotic

(ATC J01DF01)

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Date of Revision:
23 February 2018

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Control No.: 209680

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Pr **CAYSTON®**
(Aztreonam for Inhalation Solution)
75 mg aztreonam / vial

PART I. HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form/Strength | Nonmedicinal Ingredients |
|--------------------------------|---|---|
| Inhalation | Sterile lyophilized powder for reconstitution 75 mg aztreonam/vial | Lysine Diluent (0.17% sodium chloride) |

INDICATIONS AND CLINICAL USE

CAYSTON (aztreonam for inhalation solution) is indicated for the management of cystic fibrosis (CF) patients with chronic pulmonary *Pseudomonas aeruginosa* infections.

Safety and efficacy have not been demonstrated in patients with FEV₁ <25% or >75% predicted or in patients infected with *Burkholderia cepacia* complex.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of CAYSTON and other antibacterial drugs, CAYSTON should be used only to treat infections that are proven or strongly suspected to be caused by bacteria.

Sputum culture and susceptibility testing performed periodically will provide information on changing microbial flora and the possible emergence of bacterial resistance.

Geriatrics (>65 years of age):

Clinical studies with CAYSTON did not include sufficient numbers of patients aged 65 years old and over to determine whether they responded differently from younger patients.

Pediatrics (<18 years of age):

Safety and efficacy have not been studied in patients under the age of 6 years.

CONTRAINDICATIONS

CAYSTON (aztreonam for inhalation solution) is contraindicated in patients with a known allergy to aztreonam or to any ingredient in the formulation or any components of the container. For a complete listing see **DOSAGE FORMS, COMPOSITION, AND PACKAGING** section.

WARNINGS AND PRECAUTIONS

General

CAYSTON (aztreonam for inhalation solution) should only be used with the Altera® Nebulizer System manufactured by PARI Respiratory Equipment, Inc. CAYSTON is not for oral, intravenous, subcutaneous, intramuscular, or intrathecal administration.

CAYSTON has been specifically formulated with the amino acid lysine. Do not use other formulations of aztreonam (e.g., aztreonam for injection) in the Altera Nebulizer System. Aztreonam for injection has not been formulated for inhalation, and contains arginine, a substance known to cause pulmonary inflammation.

Certain antibiotics (eg. ceftazidime, imipenem) may induce high levels of beta-lactamase *in vitro* in some gram-negative aerobes such as *Enterobacter* and *Pseudomonas* sp., resulting in antagonism to many beta-lactam antibiotics including aztreonam. These *in vitro* findings suggest that such beta-lactamase inducing antibiotics should not be used concurrently with aztreonam lysine.

Immune

Allergic Reactions:

Severe allergic reactions have been reported following administration of aztreonam for injection (aztreonam arginine) to patients with no known history of exposure to aztreonam. CAYSTON is contraindicated in patients with a known history of aztreonam allergy. If an allergic reaction to CAYSTON does occur, stop administration of the drug and initiate treatment as appropriate. The occurrence of rash may be indicative of an allergic reaction to CAYSTON.

A history of allergy to beta-lactam antibiotics, such as penicillins, cephalosporins, and/or carbapenems, may be a risk factor for an allergic reaction to CAYSTON, since cross-reactivity may occur. Caution is advised when administering CAYSTON to patients if they have a history of beta-lactam allergy.

Respiratory

Bronchospasm:

Bronchospasm is a potential complication associated with nebulized therapies. In placebo-controlled trials, reduction of $\geq 15\%$ in forced expiratory volume in 1 second (FEV₁) immediately following administration of study medication after pretreatment with a bronchodilator was observed in 3% of patients treated with CAYSTON and 4% of patients receiving placebo.

Decreases in FEV₁ After 28-Day Treatment Cycle:

In clinical trials, patients with increases in FEV₁ during a 28-day course of CAYSTON were sometimes treated for pulmonary exacerbations when FEV₁ declined after the treatment period. Healthcare providers should consider a patient's baseline FEV₁ measured prior to

CAYSTON therapy and the presence of other symptoms when evaluating whether post-treatment changes in FEV₁ are caused by a pulmonary exacerbation.

Susceptibility/Resistance

Development of Drug Resistant Bacteria:

Prescribing CAYSTON in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

Special Populations

Pregnant Women:

No adequate and well-controlled studies of CAYSTON or aztreonam for injection (aztreonam arginine) have been conducted in pregnant women. Because animal reproduction studies are not always predictive of human response, CAYSTON should be used during pregnancy only if the potential benefit outweighs the risk.

Aztreonam for injection (aztreonam arginine) has been shown to cross the placenta and enter fetal circulation. No evidence of embryo- or fetotoxicity or teratogenicity has been shown in studies with pregnant rats and rabbits treated with daily doses up to 15 and 5 times, respectively, the human dose of aztreonam for injection (aztreonam arginine). The systemic concentration of aztreonam following inhaled administration of 75 mg CAYSTON (3 times a day) is approximately 1% of the concentration resulting from a 500 mg dose of aztreonam for injection (aztreonam arginine).

Nursing Women:

Following administration of aztreonam for injection (aztreonam arginine), aztreonam is excreted in human milk at concentrations that are less than 1 percent of those determined in simultaneously obtained maternal serum. Systemic concentration of aztreonam following inhaled administration of CAYSTON is approximately 1% of the concentration resulting from a standard dose of aztreonam for injection (aztreonam arginine). Therefore use of CAYSTON during breastfeeding is unlikely to pose a risk to infants.

Pediatrics (<18 years of age):

Safety and efficacy have not been studied in patients under the age of 6 years. Eighty-three patients between 6 and 18 years of age received CAYSTON in the controlled trials. No dose adjustments were made for pediatric patients. Pyrexia was more commonly reported in pediatric patients than in adult patients.

Geriatrics (>65 years of age):

Clinical studies with CAYSTON did not include sufficient numbers of patients aged 65 years old and over to determine whether they responded differently from younger patients.

Renal Impairment:

Aztreonam is known to be excreted by the kidney. Controlled clinical trials with CAYSTON excluded patients with abnormal baseline renal function (defined as serum creatinine greater

than 2 times the upper limit of normal range). Given the low systemic exposure of aztreonam following administration of CAYSTON, clinically relevant accumulation of aztreonam is unlikely to occur in patients with renal impairment. Therefore, CAYSTON may be administered to patients with mild, moderate and severe renal impairment with no dosage adjustment.

Hepatic Impairment:

There are no data on the use of CAYSTON in patients with severe hepatic impairment (ALT or AST greater than 5 times the upper limit of normal). No drug-related worsening of hepatic function was observed in patients in clinical trials with baseline ALT or AST less than 5 times the upper limit of normal. No dose adjustment is necessary in cases of hepatic impairment since the systemic concentration of aztreonam following inhaled administration of CAYSTON is very low (approximately 1% of the concentration resulting from a dose of 500 mg aztreonam for injection).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In the placebo-controlled studies, the most common adverse drug reaction (based on adverse events assessed by the Investigator to be possibly or probably related to study medication) was cough, occurring in 15% of patients treated with CAYSTON (aztreonam for inhalation solution) versus 10% of patients treated with placebo (Table 1). The majority of adverse reactions in CAYSTON-treated patients in the placebo-controlled Phase 3 studies were mild (21%) to moderate (8%) in severity, as judged by the Investigator. Adverse reactions of severe intensity were reported with the same incidence in both the placebo and CAYSTON treatment groups, 2%. Patient discontinuations due to adverse events occurred at a higher rate in placebo-treated patients (16%) vs. CAYSTON-treated patients (7%). Most study discontinuations were associated with signs and symptoms of pulmonary exacerbations. The most common adverse event resulting in study drug discontinuation in both treatment groups was cough.

Clinical Study Adverse Drug Reactions

Because clinical studies are conducted under very specific conditions the adverse reaction rates observed in the clinical studies may not reflect the rates observed in practice and should not be compared to the rates in the clinical studies of another drug. Adverse drug reaction information from clinical studies is useful for identifying drug-related adverse events and for approximating rates.

The safety of CAYSTON was evaluated in a total of 344 patients with CF and chronic *P. aeruginosa* in two Phase 3 placebo controlled studies and one Phase 3 uncontrolled, open-label follow-on study. Seventy-six patients were 6-17 years of age and 268 patients were 18 years of age and older.

In the placebo controlled studies 215 patients received CAYSTON 75 mg 2 times or 3 times a day for 28 days. In the uncontrolled, open-label follow-on study, 274 patients received

CAYSTON 75 mg 2 times or 3 times a day; 166 patients completed nine 28-day courses of CAYSTON.

Table 1 displays adverse reactions, assessed as at least possibly related to treatment by the investigator, reported in $\geq 1\%$ of patients treated with CAYSTON in Phase 3 placebo-controlled studies, compared with the incidence observed following multiple courses of therapy in the uncontrolled, open-label follow-on study.

Table 1 Adverse Reactions^a Occurring in $\geq 1\%$ of CAYSTON Treated Patients over Multiple Courses of Therapy from the Placebo-controlled Phase 3 Studies (CP-AI-007, CP-AI-005) and the Uncontrolled, Open-label Follow-on Study (CP-AI-006)^b

| System Organ Class Preferred Term | Integrated CP-AI-007 and CP-AI-005 | | CP-AI-006 ^c | | | |
|--|---|---|---|---|---|---|
| | Placebo Pooled (N = 160) n (%) | CAYSTON Pooled (N = 215) n (%) | CAYSTON Pooled Course 1 (N = 274) n (%) | CAYSTON Pooled Course 3 (N = 246) n (%) | CAYSTON Pooled Course 6 (N = 188) n (%) | CAYSTON Pooled Course 9 (N = 171) n (%) |
| Respiratory, thoracic and mediastinal disorders | | | | | | |
| Cough | 16 (10.0) | 33 (15.3) | 31 (11.3) | 10 (4.1) | 7 (3.7) | 2 (1.2) |
| Wheezing | 5 (3.1) | 6 (2.8) | 2 (0.7) | 1 (0.4) | 1 (0.5) | 0 (0.0) |
| Chest discomfort | 2 (1.3) | 5 (2.3) | 7 (2.6) | 1 (0.4) | 1 (0.5) | 0 (0.0) |
| Pharyngolaryngeal pain | 4 (2.5) | 4 (1.9) | 6 (2.2) | 0 (0.0) | 1 (0.5) | 0 (0.0) |
| Crackles lung | 2 (1.3) | 3 (1.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Dysphonia | 3 (1.9) | 3 (1.4) | 1 (0.4) | 2 (0.8) | 0 (0.0) | 0 (0.0) |
| Dyspnea | 3 (1.9) | 3 (1.4) | 6 (2.2) | 2 (0.8) | 1 (0.5) | 1 (0.6) |
| Productive cough | 11 (6.9) | 3 (1.4) | 7 (2.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Throat irritation | 2 (1.3) | 3 (1.4) | 2 (0.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Hemoptysis | 4 (2.5) | 2 (0.9) | 7 (2.6) | 3 (1.2) | 1 (0.5) | 0 (0.0) |
| Nasal Congestion | 1 (0.6) | 2 (0.9) | 3 (1.1) | 0 (0.0) | 1 (0.5) | 0 (0.0) |
| Respiratory Tract Congestion | 5 (3.1) | 1 (0.5) | 1 (0.4) | 3 (1.2) | 0 (0.0) | 0 (0.0) |
| Musculoskeletal and connective tissue disorders | | | | | | |
| Arthralgia | 0 (0.0) | 0 (0.0) | 2 (0.7) | 4 (1.6) | 1 (0.5) | 1 (0.6) |
| Nervous system disorders | | | | | | |
| Headache | 1 (0.6) | 3 (1.4) | 4 (1.5) | 1 (0.4) | 1 (0.5) | 0 (0.0) |

^aAdverse reactions are those AEs judged by the investigator to have a causality of possible or probable. This does not include all AEs reported.

^bPlanned study durations in days (treatment + follow-up): CP-AI-005 (28 + 56), CP-AI-007 (28 + 14).

Planned study duration for CP-AI-006: up to nine 28-day courses, each course followed by 28 days off treatment.

^cIn addition to the events listed for courses 1, 3, 6, 9 for study CP-AI-006, dyspnea exertional (1.0%) and pleuritic pain (1.0%) were observed during course 4.

In one Phase 3 active-controlled, open-label study, 136 patients received Cayston 75 mg 3 times a day for three 28-day courses. During the extension phase of the study, an additional

65 patients who originally received active control (tobramycin inhalation solution [TIS]) rolled over to receive up to three 28-day courses of Cayston.

Less Common Clinical Trial Adverse Drug Reactions (>0.5% to <1%)

In addition to the events listed in Table 1, the following uncommon adverse reactions, assessed as at least possibly related to treatment by the Investigator, were reported in >0.5% to <1% of patients treated with CAYSTON in the Phase 3 placebo-controlled studies:

Respiratory, thoracic and mediastinal: Non-cardiac chest pain, sneezing, sputum discolored, dyspnea exacerbated, dyspnea exertional

Gastrointestinal: Diarrhea, vomiting

Investigations: Pulmonary function test decreased

In addition to the events listed above, other adverse events reasonably associated with treatment in placebo-controlled studies include: pyrexia (12%), rhinorrhea (8%), bronchospasm (3%) (see **WARNINGS AND PRECAUTIONS**) and rash (2%).

Adverse events were similar in nature in patients receiving CAYSTON in the active-controlled Study GS-US-205-0110 (Study 110).

Abnormal Hematologic and Clinical Chemistry Findings

No abnormal hematologic and chemistry findings were observed. However, reduction in elevated white blood cell and elevated neutrophil counts were observed in the CAYSTON treatment group relative to placebo, consistent with antibiotic therapy.

Post Market Adverse Drug Reactions

In addition to adverse reactions reported from clinical trials, the following possible adverse reactions have been identified during post-approval use of CAYSTON. Because these events have been reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS

Joint swelling

DRUG INTERACTIONS

Drug-Drug Interactions

No formal clinical studies of drug interactions with CAYSTON (aztreonam for inhalation solution) have been conducted. In clinical studies of CAYSTON, many patients used commonly prescribed CF therapies such as TOBI® (tobramycin inhalation solution), Pulmozyme® (dornase alfa), pancreatic enzymes, oral/inhaled steroids, and/or azithromycin concomitantly with CAYSTON.

Drug-Food Interactions

Interactions of CAYSTON with food have not been established.

Drug-Herb Interactions

Interactions of CAYSTON with herbs have not been established.

Drug-Laboratory Interactions

Interactions of CAYSTON with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

General

CAYSTON (aztreonam for inhalation solution) is administered by inhalation over a 2 to 3 minute period, using the Altera Nebulizer System. CAYSTON should only be used with an Altera Nebulizer System. CAYSTON should not be mixed with any other drugs in the Altera Nebulizer Handset. Do not put drugs other than Cayston in the Altera Nebulizer Handset. Patients should use a bronchodilator before each dose of CAYSTON. Short acting bronchodilators can be taken between 15 minutes and 4 hours and long acting bronchodilators can be taken between 30 minutes and 12 hours prior to each dose of CAYSTON. For patients receiving multiple inhaled therapies, the recommended order of administration is as follows: bronchodilator, mucolytics, and lastly, CAYSTON.

CAYSTON is for inhalation administration only.

Recommended Dose

The recommended dosage for both adults and pediatric patients 6 years of age and older is 1 single-use vial (75 mg) of CAYSTON reconstituted with a 1 mL ampule of sterile diluent administered 3 times a day for a 28-day course. Dosage is not based on weight or adjusted for age. All patients should be administered a 75 mg dose 3 times a day. Each dose should be taken at least 4 hours apart. Take CAYSTON in repeated cycles of 28 days on CAYSTON followed by 28 days off CAYSTON therapy.

Missed Dose

In case of a missed dose, the dose can still be taken provided there is a period of at least 4 hours between each dose.

CAYSTON Reconstitution

CAYSTON must be administered immediately after reconstitution. Do not reconstitute CAYSTON until ready to administer a dose.

Take 1 amber glass vial containing CAYSTON and 1 diluent ampule from the carton. To open the glass vial, carefully remove the metal ring by lifting or pulling the tab and remove

the gray rubber stopper. Twist the tip off the diluent ampule and squeeze the liquid into the glass vial. Replace the rubber stopper, then gently swirl the vial until contents have completely dissolved.

CAYSTON Administration

Remove the rubber stopper, then pour the reconstituted CAYSTON into the Altera Nebulizer Handset. Turn the unit on. Place the mouthpiece of the handset in your mouth and breathe normally only through your mouth. Administration takes between 2 and 3 minutes. Further instruction for patients on how to administer drug is provided in **Part III, CONSUMER INFORMATION**. Instructions for testing nebulizer functionality, cleaning and disinfecting the handset are provided in the Instructions for Use included with the Altera Nebulizer System.

OVERDOSAGE

Contact your regional Poison Control Centre should there be any concerns regarding the management of a suspected drug overdose with CAYSTON.

No overdoses have been reported with CAYSTON (aztreonam for inhalation solution) in clinical trials to date. In clinical trials, 225 mg doses of CAYSTON via inhalation were associated with higher rates of drug-related respiratory adverse reactions, particularly cough. Since the peak plasma concentration of aztreonam following administration of CAYSTON (75 mg) is approximately 0.6 mcg/ml compared to a serum concentration of 54 mcg/ml following administration of aztreonam for injection (500 mg), no systemic safety issues associated with CAYSTON overdose are anticipated.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Aztreonam exhibits activity *in vitro* against a broad spectrum of gram-negative aerobic pathogens including *P. aeruginosa*. Aztreonam binds to penicillin-binding proteins of susceptible bacteria, which leads to inhibition of bacterial cell wall synthesis, followed by filamentation and cell lysis.

Aztreonam activity is not significantly inhibited by sputum in the CF lung.

Pharmacokinetics

Absorption:

Sputum Concentrations

Individual patients' sputum aztreonam concentrations exhibited considerable variability. Ten minutes following a single dose of 75 mg CAYSTON (aztreonam for inhalation solution), the mean (range) sputum level in 195 patients with CF was 726 (0 – 6010) µg/g, which is approximately 10 times that of the aztreonam MIC₉₀ for all isolates of *P. aeruginosa* observed at baseline for patients treated with CAYSTON in the Phase 3 placebo-controlled

studies (64 µg/mL). Mean (range) sputum levels of aztreonam at Days 0, 14, and 28 of 75 mg 3 times a day CAYSTON dosing were 984 (8 – 6010) µg/g, 793 (2 – 2780) µg/g, and 715 (1 – 2800) µg/g, respectively, indicating no accumulation of aztreonam in sputum.

Plasma Concentrations

Individual patients' plasma aztreonam concentrations exhibited considerable variability. One hour following a single dose of 75 mg CAYSTON (at approximately peak plasma concentration), the mean (range) plasma level in patients with CF was 0.59 (0 – 2.92) µg/mL. Mean (range) peak plasma levels at Days 0, 14, and 28 of 75 mg 3 times a day CAYSTON dosing were 0.55 (0 – 1.62) µg/mL, 0.67 (0.01 – 1.66) µg/mL, and 0.65 (0 – 1.74) µg/mL, respectively, indicating no systemic accumulation of aztreonam following 3 times a day dosing. In contrast, the serum concentration of aztreonam following administration of a 500 mg dose of aztreonam for injection (aztreonam arginine) is approximately 54 µg/mL.

Distribution:

Local and systemic tissue distribution following inhalation exposure has not been clinically characterized.

Metabolism:

The *in vitro* metabolic stability and metabolism of aztreonam was demonstrated in pulmonary S9 fractions from healthy human donors as well as rats, dogs, and cynomolgus monkeys and pulmonary microsomes from human donors. Aztreonam is stable in pulmonary subcellular fractions in all species examined with little metabolism of the parent compound. No oxidative metabolites were observed in hepatocyte or pulmonary incubations and no glucuronide and sulfate conjugates or esterase hydrolysis products were detected.

Excretion:

The elimination half-life of aztreonam from serum is approximately 2.1 hours for inhalation administration, similar to what has been reported for aztreonam for injection (aztreonam arginine). Approximately 10% of the total CAYSTON dose is excreted in the urine as unchanged drug, as compared to 60–65% following intravenous administration of aztreonam for injection (aztreonam arginine). Systemically absorbed aztreonam is eliminated about equally by active tubular secretion and glomerular filtration.

Special Populations and Conditions

Age: There was no clinically relevant effect of age on the pharmacokinetics of CAYSTON.

Gender: There was no clinically relevant effect of gender on the pharmacokinetics of CAYSTON.

Hepatic Impairment: Pharmacokinetic studies have not been performed with CAYSTON in patients with hepatic impairment.

Renal Impairment: Pharmacokinetic studies have not been performed with CAYSTON in patients with renal impairment.

STORAGE AND STABILITY

Prior to Reconstitution:

CAYSTON (aztreonam for inhalation solution) vials should be stored in a refrigerator at 2 to 8°C (36 to 46°F) and may be stored by patients at room temperature (up to 25°C/77°F) for up to 28 days. Diluent ampules may be refrigerated or stored at room temperature (15 to 30°C /59 to 86 °F).

Do not use CAYSTON if it has been stored at room temperature for more than 28 days. Unused vials of CAYSTON stored at room temperature for more than 28 days should be discarded. Do not store back in the refrigerator. Do not use CAYSTON beyond the expiration date stamped on the vial. Do not use diluent beyond the expiration date embossed on the ampule.

Following Reconstitution:

CAYSTON should be used immediately upon reconstitution. Do not reconstitute more than 1 dose at a time.

Do not use diluent or reconstituted CAYSTON if it is cloudy or if there are particles in the solution.

SPECIAL HANDLING INSTRUCTIONS

The reconstituted solution should be used immediately and should not be stored. Do not reconstitute CAYSTON (aztreonam for inhalation solution) until ready to administer a dose (See Part III, CONSUMER INFORMATION, for detailed instructions for administration).

DOSAGE FORMS, COMPOSITION AND PACKAGING

A dose of CAYSTON (aztreonam for inhalation solution) consists of a single-use 2 mL vial of sterile, lyophilized powder (75 mg aztreonam and the non-medicinal ingredient lysine) and a low-density polyethylene ampule containing 1 mL of sterile diluent (0.17% sodium chloride). The formulations contain no preservatives. CAYSTON is reconstituted and administered by inhalation using the Altera Nebulizer System. Each kit of CAYSTON contains 84 sterile vials of CAYSTON and 88 sterile diluent ampules packed in 2 cartons each with a 14-day supply (42 vials of CAYSTON packaged in two trays and 1 tray of 44 diluent ampules). The 4 additional diluent ampules are provided in case of spillage.

PART II. SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

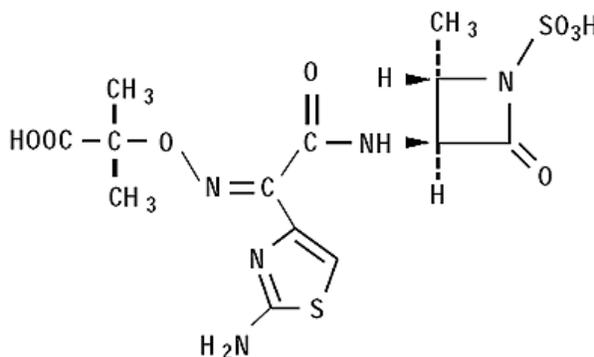
Common Name: aztreonam (INN)

Chemical Name: (Z)-2-[[[(2-amino-4-thiazolyl)[[(2*S*,-3*S*)-2-methyl-4-oxo-1-sulfo-3-azetidiny]caramoyl]methylene]amino]oxy]-2-methylpropionic acid

Empirical Formula: C₁₃H₁₇N₅O₈S₂

Molecular Weight: 435.43

Structural Formula:



Physicochemical Properties: Aztreonam is a white to off-white crystalline powder. The partition coefficient (log P) is -0.66 and aztreonam is soluble in buffered aqueous solutions at pH greater than 4. Aztreonam is produced as the α -polymorphic form, and is hygroscopic.

Drug Product

CAYSTON (aztreonam lyophilized powder) is a sterile white to off-white powder consisting of 75 mg aztreonam and the non-medicinal ingredient lysine. It is soluble in water and aqueous solutions. CAYSTON is sterile, hygroscopic, and light sensitive. Once reconstituted with the supplied diluent, the pH range is 4.5 to 6.0.

CLINICAL STUDIES

Study Demographics and Trial Design

CAYSTON (aztreonam for inhalation solution) was evaluated over a period of 28 days of treatment (1 course) in 2 randomized, double-blind, placebo-controlled, multicenter studies (CP-AI-007 and CP-AI-005) which enrolled patients with CF who had *P. aeruginosa*. To evaluate longer term safety and effects on disease related endpoints, an uncontrolled, open-label follow-on study (CP-AI-006) was conducted. CP-AI-007 was designed to evaluate improvement in respiratory symptoms as measured by the cystic fibrosis questionnaire-revised (CFQ-R) and CP-AI-005 was designed to evaluate the time to need for IV or inhaled antipseudomonal antibiotic therapy. Patients participating in these studies could subsequently receive multiple courses of CAYSTON in CP-AI-006. All patients received CAYSTON on an outpatient basis administered with the Altera Nebulizer System. All patients were required to take a dose of an inhaled bronchodilator (beta-agonist) prior to taking a dose of CAYSTON. The trial population was receiving standard care for CF.

Additionally, CAYSTON was compared to TIS over three 28-day courses of treatment (Study 110). This study was designed to evaluate improvement in pulmonary function over multiple courses of CAYSTON. The majority of patients had extensive previous inhaled antibiotic use with 85% of patients using inhaled tobramycin for ≥ 84 days (i.e. three 28 day courses) in the previous 12 months. All patients were required to take a dose of an inhaled bronchodilator (beta-agonist) prior to taking a dose of CAYSTON. Patients were receiving standard care for CF.

Patient reported outcomes were assessed using the CFQ-R, a validated, disease-specific questionnaire that measures health-related quality of life for children, adolescents, and adults with CF.

The trial design and patient demographics for the double-blind studies CP-AI-007 and CP-AI-005, the open-label study CP-AI-006, and the active-controlled, open-label study (Study 110) are summarized in Table 2 below.

Table 2 CP-AI-007, CP-AI-005 (CAYSTON Compared with Placebo), CP-AI-006 (Uncontrolled, Open-label Follow-on), and Study 110 (Active-controlled, Open-label)

| Study Number | Trial Design | Dosage, Route of Administration and Duration | Study Subjects | Mean Age (Range) | Gender |
|------------------------|---|--|---|------------------|--------------------------|
| CP-AI-007 ⁴ | Randomized, double-blind, placebo-controlled, multicenter | <p>Arm 1: CAYSTON 75 mg 3 times a day</p> <p>Arm 2: Volume matched placebo 3 times a day</p> <p>Inhalation</p> <p>28 days of CAYSTON</p> | <p>N=80</p> <p>N=84</p> <p>Patients with cystic fibrosis; ≥ 6 years of age; FEV₁ $\geq 25\%$ and $\leq 75\%$</p> | 30 years (7-74) | Male: 57% Female: 43% |

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| | | treatment | predicted; mean FEV ₁ = 55% predicted | | |
|------------------------|---|--|--|--------------------|--------------------------|
| CP-AI-005 ⁵ | Randomized, double-blind, placebo-controlled, multicenter | <p>Arm 1: CAYSTON 75 mg 2 times a day</p> <p>Arm 2: CAYSTON 75 mg 3 times a day</p> <p>Arm 3: Volume matched placebo 2 times a day</p> <p>Arm 4: Volume matched placebo 3 times a day</p> <p>Inhalation 28 days of CAYSTON treatment</p> | <p>N=69</p> <p>N=66</p> <p>N=38</p> <p>N=38</p> <p>Patients with cystic fibrosis; ≥6 years of age; FEV₁ ≥ 25% and ≤ 75% predicted; mean FEV₁ = 55% predicted</p> | 26 years (7-65) | Male: 57% Female: 43% |

Table 2 (cont'd) CP-AI-007, CP-AI-005 (CAYSTON Compared with Placebo), CP-AI-006 (Uncontrolled, Open-label Follow-on) and Study 110 (Active-controlled, Open-label)

| Study Number | Trial Design | Dosage, Route of Administration and Duration | Study Subjects | Mean Age (Range) | Gender |
|------------------------|---|---|--|------------------|--------------------------|
| CP-AI-006 ⁶ | Open-label, uncontrolled, multicenter, follow-on study to CP-AI-007 and CP-AI-005 | <p>Arm 1: CAYSTON 75 mg 2 times a day</p> <p>Arm 2: CAYSTON 75 mg 3 times a day</p> <p>Inhalation</p> <p>Patients received CAYSTON at the same dose intervals (2 or 3 times a day) as they received CAYSTON or placebo in Studies CP-AI-007 or CP-AI-005.</p> <p>Repeated cycles of 28 days on and 28 days off treatment for 9 cycles of therapy.</p> | <p>N=85</p> <p>N=189</p> <p>Patients with cystic fibrosis; ≥6 years of age; previous participation in Studies CP-AI-007 or CP-AI-005; mean FEV₁ = 56% predicted</p> | 29 years (8-74) | Male: 55% Female: 45% |
| Study 110 | Randomized, active-controlled, open-label multicenter | <p>Arm 1: CAYSTON 75 mg 3 times a day</p> <p>Arm 2: TIS 300 mg 2 times a day</p> <p>Inhalation</p> <p>Repeated cycles of 28 days on and 28 days off treatment for 3 cycles of therapy. Total study period was 26 weeks.</p> | <p>N=136</p> <p>N=132</p> <p>Patients with cystic fibrosis; ≥6 years of age; FEV₁ ≤ 75% predicted; mean FEV₁ = 52% predicted</p> | 26 years (6-69) | Male: 50% Female: 50% |

Study Results

CP-AI-007:

Study results for the primary and key secondary endpoints for Study CP-AI-007 are provided in Table 3.

Table 3 Primary and Key Secondary Outcomes for Study CP-AI-007

| Endpoint | Treatment | | |
|---|---------------------|--|---|
| | Placebo (N = 84) | 75 mg CAYSTON 3 times a day (N = 80) | Treatment Difference (p-value; 95% CI) |
| Change in CFQ-R^a Respiratory Symptoms Score from Day 0 | | | |
| Day 28 | -2.6 | 7.1 | 9.7 (p = 0.0005; 4.3, 15.1) |
| Day 42 | -5.7 | 0.6 | 6.3 (p=0.0154; 1.2, 11.4) |
| Percent Change in FEV₁ [L] from Day 0 | | | |
| Day 28 | -2.4 | 7.9 | 10.3 (p<0.0001; 6.3, 14.3) |
| Day 42 | -2.6 | 3.1 | 5.7 (p=0.0024; 2.1, 9.4) |
| Mean Relative Change in FEV₁ % Predicted from Day 0 | | | |
| Day 28 | -1.8 | 8.3 | 10.2 (p<0.0001; 6.2, 14.2) |
| Day 42 | -2.2 | 3.5 | 5.7 (p=0.0026, 2.0, 9.4) |
| Change in Log₁₀ PA CFU/g Sputum from Day 0 | | | |
| Day 28 | 0.1 | -1.4 | -1.5 (p<0.0001; -2.1, -0.8) |
| Day 42 | 0 | -0.1 | -0.1 (p=0.8218; -0.7, 0.5) |
| Mean Change in Body Mass Index from Day 0 at Day 28 (kg/m²) | 0.01 | 0.21 | 0.20 (p=0.0054; 0.06, 0.34) |

PA = *P. aeruginosa*; CFU=Colony Forming Units

a The CFQ-R measures the impact of an intervention on several aspects of living with CF, including respiratory symptoms. Scores range from 0 to 100, with higher scores indicating fewer symptoms. The Respiratory Symptoms scale of the CFQ-R asks patients to report on symptoms such as difficulty breathing, coughing, wheezing, color of sputum, and nature of sputum production.

Adjusted means, p-values, estimates of treatment differences and confidence intervals from an Analysis of Covariance (ANCOVA) model including treatment, disease severity and baseline value of the endpoint as covariates

CP-AI-005:

Study results for the primary and key secondary endpoints for Study CP-AI-005 are presented in Table 4 and Table 5. All patients were treated with TOBI®, 300 mg, 2 times a day in the 4 weeks immediately prior to the 28-day course of CAYSTON or placebo.

Table 4 Use of Inhaled or IV Antipseudomonal Antibiotics Due to Pre-defined Symptoms (CP-AI-005)

| Endpoint | Treatment | | | |
|--|-----------------------|------------------------------------|------------------------------------|------------------------------|
| | Placebo Pooled (N=76) | 75 mg CAYSTON 2 times a day (N=69) | 75 mg CAYSTON 3 times a day (N=66) | 75 mg CAYSTON Pooled (N=135) |
| Median Time (Days) to Need for Inhaled or IV Antibiotics | 71 | NE ^a | 87 | 92 |
| Estimated ^b Percentage of Patients Requiring Inhaled or IV Antibiotics through Day 84 (%) | 56 | 27 | 40 | 33 |
| p-value for treatment vs. pooled placebo | -- | (p=0.0019) | (p=0.1816) | (p=0.0070) |

^aNot Estimable

^bKaplan-Meier Estimate

Table 5 Change at Day 28 from Baseline (following TOBI[®] run-in period) for Key Secondary Endpoints: CFQ-R Respiratory Symptoms Score, FEV₁ [L] (percent change), Log₁₀ PA CFU (CP-AI-005)

| Endpoint | Treatment | | | |
|---|-----------------------|------------------------------------|------------------------------------|------------------------------|
| | Placebo Pooled (N=76) | 75 mg CAYSTON 2 times a day (N=69) | 75 mg CAYSTON 3 times a day (N=66) | 75 mg CAYSTON Pooled (N=135) |
| Change in CFQ-R Respiratory Symptoms Score from Day 0 | -0.7 | 5.1 | 3.6 | 4.3 |
| Treatment Difference versus pooled placebo (p-value) | | 5.8 (0.0207) | 4.2 (0.0920) | 5.0 (0.0196) |
| Percent Change from Baseline in FEV ₁ [L] from Day 0 | -2.4 | 3.8 | 4.0 | 3.9 |
| Treatment Difference versus pooled placebo (p-value) | | 6.2 (0.0060) | 6.4 (0.0052) | 6.3 (0.0012) |
| Change in Log ₁₀ PA CFU/g Sputum from Day 0 | 0.2 | -0.5 | -0.4 | -0.4 |
| Treatment Difference versus pooled placebo (p-value) | | -0.7 (0.0106) | -0.6 (0.0313) | -0.7 (0.0059) |

PA = *P. aeruginosa*; CFU=Colony Forming Units

Adjusted means, p-values and estimates of treatment differences from an Analysis of Covariance (ANCOVA) model

CP-AI-006:

Over nine 28-day courses of therapy, measures of pulmonary function (FEV₁ (L)), CFQ-R Respiratory Symptoms score, and log₁₀ *P. aeruginosa* CFU showed a trend to improvement while the patients were on treatment compared with off treatment (see Table 6).

FEV₁ (L), CFQ-R Respiratory Symptoms score, and log₁₀ *P. aeruginosa* CFU showed a dose response over the nine courses, with patients dosed 3 times a day demonstrating greater improvements than those dosed 2 times a day.

Table 6 CP-AI-006: Mean Change in Disease-Related Endpoints from Study Baseline Following Repeated 28-Day Exposures to CAYSTON (75 mg, 3 times a day)

| | Change in CFQ-R Respiratory Symptoms Score Mean (SD) | Percent change in FEV ₁ [L] Mean (SD) | Change in Log ₁₀ <i>P. aeruginosa</i> CFU/g Sputum Mean (SD) |
|--|--|--|---|
| CAYSTON Course 1 (N=189) ^a Off Treatment | 6.83 (17.38) | 7.98 (16.51) | -0.81 (1.76) |
| | 1.34 (15.95) | 0.71 (14.51) | -0.28 (1.79) |
| CAYSTON Course 3 (N=169) ^a Off Treatment | 7.34 (18.52) | 6.04 (16.49) | -0.53 (2.12) |
| | 3.06 (19.29) | 0.72 (15.20) | -0.07 (1.83) |
| CAYSTON Course 6 (N=135) ^a Off Treatment | 5.26 (18.62) | 4.78 (17.85) | -0.55 (2.00) |
| | 1.70 (18.61) | -1.43 (15.97) | -0.29 (1.99) |
| CAYSTON Course 9 (N=124) ^a Off Treatment | 6.01 (17.94) | 3.98 (17.90) | -0.60 (2.07) |
| | 3.80 (15.41) | -1.05 (17.68) | -0.48 (2.25) |

SD = Standard Deviation

^aN refers to the number of patients at the start of the course

Observed means and standard deviations are reported, unadjusted for treatment, disease severity or baseline values

Study 110:

Study results for the co-primary endpoints for Study 110 are presented in Table 7.

Table 7 Change from Baseline in FEV₁% Predicted at Day 28 and Across 3 Treatment Courses, Co-Primary Endpoints (Study 110)

| Endpoint | 75 mg CAYSTON 3 times a day (N = 136) | 300 mg TIS 2 times a day (N = 132) | Treatment Difference p-value (95% CI) |
|--|--|--|---|
| Relative change from baseline in FEV ₁ % predicted at Day 28 (adjusted mean) | 8.35 | 0.55 | 7.80 p=0.0001 (3.86, 11.73) |
| Actual change from baseline in FEV ₁ % predicted across 3 treatment courses (adjusted mean) | 2.05 | -0.66 | 2.70 p=0.0023 (0.98, 4.43) |

Treatment differences in relative change from baseline in FEV₁% predicted at Day 28 and actual change from baseline in FEV₁% predicted across 3 treatment courses for CAYSTON compared to TIS were significantly greater in the subset of patients who had received inhaled tobramycin for ≥ 84 days in the 12 months prior to entering the trial.

Results for additional key efficacy outcomes of Study 110 are presented in Table 8.

Table 8 Additional Key Efficacy Outcomes (Study 110)

| Endpoint | 75 mg CAYSTON 3 times a day (N = 136) | 300 mg TIS 2 times a day (N = 132) | Treatment Difference p-value (95% CI) |
|--|--|--|---|
| Time to need for IV antipseudomonal antibiotics for respiratory event among all subjects (Kaplan-Meier event rates at Week 24) | 36% | 54% | 18% p=0.0025 |
| Total number of respiratory hospitalizations | 40 | 58 | p=0.044 |
| Total number of respiratory events requiring IV and/or inhaled antipseudomonal antibiotics (Adjusted mean) | 84 | 121 | p = 0.004 |
| Actual change from baseline in CFQ-R respiratory symptoms score across 3 treatment courses (Adjusted mean) | 6.30 | 2.17 | 4.13 p=0.0189 (0.69, 7.57) |

DETAILED PHARMACOLOGY

Animal Pharmacology

Pharmacodynamics

Safety Pharmacology

Electrocardiographic assessments were performed during the 28-day and 90-day aztreonam lysine inhalation toxicology studies in dogs. Recordings were taken at pretreatment, Day 2 and 28 for the 28 day study and pretreatment, Day 2 and Week 7 and 13 for the 90 day study. The mean achieved dose levels for the 28 and 90 day studies were 53, 94 and 195 mg/kg/day and 34, 73 and 133 mg/kg/day respectively. Interval data (P-R, QRS and Q-T) and heart rate were unaffected by treatment with aztreonam lysine when measured approximately 15 minutes post dose which fell within the range of the T_{max} . The geometric mean (CV%) aztreonam plasma C_{max} ($\mu\text{g/mL}$) were 1.55 (102.1), 2.94 (260.6) and 4.83 (39.4) for the 28 day study and 5.79 (98.0), 12.72 (35.7), and 6.34 (989.8) for the 90-day study.

Additionally, a cardiovascular/respiratory safety pharmacology study was conducted in beagle dogs to assess the possible pharmacological effects of aerosolised aztreonam on hemoglobin oxygen saturation, blood pressure, heart rate, lead II electrocardiography (ECG), core body temperature and respiratory function parameters (respiratory rate, tidal volume and respiratory minute volume). Vehicle (30 mM NaCl) or aztreonam lysine was administered to 4 male beagle dogs by inhalation (60 min duration each occasion) in a cross-over design. The mean achieved dose levels of aztreonam were 0, 40, 102 and 163 mg/kg in the vehicle, low, medium and high dose groups, respectively. There were no treatment-related findings on cardiovascular or respiratory parameters measured at any dose level of aztreonam lysine.

Pharmacokinetics

Tissue distribution of aztreonam lysine following inhalation has not been studied. The following tables summarize the steady state plasma pharmacokinetics of aztreonam lysine in rat and dog following inhalation for 90 days.

Table 9 Pharmacokinetic Parameters^a at Steady State (Week 7) for Rats following Inhalation of Aztreonam Lysine (90-Day Study)

| Parameter (units) | Males | | | Females | | |
|---|--------|-------|-------|---------|-------|-------|
| | Week 7 | | | | | |
| Dose (mg/kg) | 30 | 60 | 120 | 30 | 60 | 120 |
| Estimated Achieved Dose (mg/kg) | 32 | 62 | 121 | 32 | 62 | 121 |
| C _{max} (µg/mL) | 3.88 | 6.6 | 7.57 | 4.28 | 6.68 | 8.57 |
| AUC _{0-t} (µg.h/mL) | 6.57 | 15.56 | 26.26 | 7.35 | 14.89 | 32.55 |
| T _{max} (obs) (h) ^b | 0.98 | 1.92 | 3.92 | 0.87 | 1.65 | 3.73 |
| T _{1/2el} (h) | 1.16 | 0.94 | 1.15 | 1.15 | 0.98 | 0.91 |
| CL/F (mL/h/kg) | 4482 | 3830 | 4532 | 4019 | 3976 | 3670 |
| Vd/F (mL/kg) | 7538 | 5180 | 7484 | 6684 | 5604 | 4826 |

^a PK parameters were calculated from mean plasma concentration data. As such no statistics could be calculated.

^b T_{max} was measured from the start of dosing with the duration of inhalation dosing increasing with dose level.

Table 10 **Pharmacokinetic Parameters^a at Steady State (Week 7) for Dogs following Inhalation of Aztreonam Lysine (90-Day Study)**

| Parameter (units) | Males | | | Females | | |
|------------------------------------|------------------------------|------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| | Week 7 | | | | | |
| Dose (mg/kg) | 35 | 70 | 140 | 35 | 70 | 140 |
| Estimated Achieved Dose (mg/kg) | 34 | 73 | 133 | 34 | 73 | 133 |
| C_{max} (µg/mL) ^b | 1.25 (0.69) | 5.01 (1.85) | 11.8 (2.85) | 2.60 (0.99) | 5.26 (2.09) | 15.0 (5.43) |
| AUC_{0-t} (µg.h/mL) ^c | 2.34 (137.6) [1.0-5.1] | 11.9 (42.0) [6.8-18.4] | 30.5 (26.4) [25.3-27.4] | 6.62 (39.7) [3.98-10.0] | 14.7 (29.4) [10.1-20.1] | 37.4 (44.0) [27.8-52.4] |
| T_{max} (obs) (h) ^{b,d} | 0.48 (0.02) | 0.80 (0.10) | 1.23 (0.12) | 0.60 (0.17) | 0.85 (0.13) | 1.02 (0.08) |
| $T_{1/2el}$ (h) ^b | 8.00 (8.9) | 5.27 (1.3) | 9.07 (4.9) | 4.73 (0.78) | 7.23 (1.6) | 7.23 (4.6) |
| CL/F (mL/h/kg) ^b | 8970 (1103) | 6264 (2419) | 4727 (1348) | 5584 (2100) | 4925 (1448) | 4036 (1790) |
| Vd/F (mL/kg) ^b | 102065 (115386) | 31982 (9858) | 62966 (38451) | 38533 (17209) | 52067 (22514) | 50263 (54201) |

^a Based on values for individual animals using WinNonlin Non-Compartment Analysis.

^b Mean (SD)

^c Geometric Mean (CV%) [range]

^d T_{max} was measured from the start of dosing with the duration of inhalation dosing increasing with dose level.

Total distribution of radioactivity and unchanged aztreonam in the tissues of male and female rats was evaluated after a single intramuscular injection of 50 mg/kg [14C] aztreonam. Radioactivity was well distributed throughout the body (Table 11) with no major differences between sexes. Generally, the mean concentration of total radioactivity was higher than the serum concentration for kidneys, large intestine and its contents, liver, lymph nodes (females only), meninges, muscle (injection site), small intestine (females only) and its contents, stomach, and urinary bladder. Whole body autoradiography essentially confirmed the results of distribution of [14C] aztreonam as determined by liquid scintillation counting. Radioactivity was eliminated from the tissues at a slower rate than from serum and, with time, there appeared to be more radioactivity in the excretory organs (kidney, liver, and gastrointestinal tract) than the serum. Based on the slower elimination of radioactivity from the tissues than in serum, the duration of activity of aztreonam in many target tissues might be longer than that predicted by the rate of decline in the serum.

Table 11 Concentrations of Unchanged Aztreonam Following Administration of 50 mg/kg Aztreonam

| | Aztreonam concentration (µg/g tissue) ^a | | | |
|-----------------------|--|-------------|-------------|-------------|
| | 0.25 h | 2 h | 6 h | 24 h |
| Males | | | | |
| Serum | 85 ± 13 | 8.7 ± 2.6 | 0.15 ± 0.04 | 0.01 ± 0.00 |
| Kidney | 115 ± 20 | 10 ± 5.6 | 0.71 ± 0.04 | 0.42 ± 0.07 |
| Liver | 53 ± 1.5 | 13 ± 4.9 | 1.7 ± 0.3 | 0.18 ± 0.05 |
| Lung | 24 ± 1.1 | 2.1 ± 0.5 | 0.07 ± 0.01 | 0.03 ± 0.01 |
| Sm intestine contents | 5.0 ± 1.2 | 94 ± 2.6 | 47 ± 22 | 0.20 ± 0.06 |
| Lg intestine contents | 0.13 ± 0.09 | 0.07 ± 0.02 | 68 ± 19 | 8.3 ± 1.2 |
| Females | | | | |
| Serum | 77 ± 10 | 15 ± 4.5 | 0.09 ± 0.01 | 0.02 ± 0.01 |
| Kidney | 119 ± 39 | 8.8 ± 2.9 | 0.42 ± 0.05 | 0.27 ± 0.06 |
| Liver | 75 ± 16 | 12 ± 2.7 | 1.2 ± 0.31 | 0.10 ± 0.04 |
| Lung | 24 ± 1.6 | 3.1 ± 1.2 | 0.17 ± 0.07 | 0.05 ± 0.02 |
| Sm intestine contents | 5.2 ± 1.9 | 46 ± 16 | 0.53 ± 0.20 | 1.7 ± 1.1 |
| Lg intestine contents | 0.17 ± 0.06 | 0.06 ± 0.02 | 57 ± 4.1 | 11 ± 6.3 |

^a Uncorrected data representing minimum values with a detection limit of 0.01 µg/mL.

MICROBIOLOGY

Mechanism/Mode of Action

The active ingredient in CAYSTON is aztreonam, a monobactam. The monobactams are structurally different from beta-lactam antibiotics (e.g., penicillins, cephalosporins, carbapenems) due to a unique monocyclic nucleus (see PHARMACEUTICAL INFORMATION), but have a similar mechanism of action. Aztreonam binds to penicillin-binding proteins of susceptible bacteria, which leads to inhibition of bacterial cell wall synthesis, followed by filamentation and cell lysis.

Spectrum of Activity

Aztreonam is active *in vitro* against a variety of aerobic gram-negative bacteria, including *P. aeruginosa*, but is relatively inactive against gram-positive and anaerobic bacteria.

Susceptibility Testing

A single sputum sample from a CF patient may contain multiple isolates of *P. aeruginosa* and each isolate may have a different level of *in vitro* susceptibility to aztreonam. The *in vitro* antimicrobial susceptibility test methods used for parenteral aztreonam therapy can be used to monitor the susceptibility of *P. aeruginosa* isolated from CF patients.

In the Phase 3 placebo-controlled studies of Cayston, sputum aztreonam concentrations generally exceeded aztreonam MIC values for *P. aeruginosa*, regardless of the level of *P. aeruginosa* susceptibility.

Treatment with a 28-day course of 75 mg 3 times a day Cayston therapy resulted in clinically important improvements in respiratory symptoms, pulmonary function, and sputum *P. aeruginosa* CFU density, regardless of whether the highest aztreonam MIC for *P. aeruginosa*

was above or below the established susceptibility breakpoint for intravenous aztreonam administration (8 µg/ml). Based on categorical analyses of the relationship between MIC and treatment response, a susceptibility breakpoint for Cayston cannot be established. Over 9 courses of Cayston therapy, *P. aeruginosa* MIC₅₀ and MIC₉₀ did not change (± 2 dilution change), however there is a theoretical risk that patients treated with Cayston may develop *P. aeruginosa* isolates resistant to aztreonam or other beta-lactam antibiotics.

Development of Resistance

Decreases in susceptibility to aztreonam in CF patients with *P. aeruginosa* occurs either through selection of strains with mutations located on the chromosome or rarely through acquisition of plasmid/integrin mediated genes.

No changes in the susceptibility of *P. aeruginosa* to aztreonam or cross-resistance to other classes of antibiotics, including aminoglycosides, quinolones, and beta-lactams, have been observed following up to nine 28-day courses of 75 mg CAYSTON administered 3 times a day.

Effects on Respiratory Flora

No concerning trends in the treatment-emergent isolation of other bacterial respiratory pathogens (*B. cepacia* complex, *S. maltophilia*, *A. xylosoxidans*, and *S. aureus*) have been observed following up to nine 28-day courses of CAYSTON therapy.

TOXICOLOGY

Inhalation Toxicity Studies

The systemic and local tolerability of inhaled aztreonam lysine was evaluated in single-dose and repeat-dose toxicity studies in rats and dogs for up to 90 days. There were no treatment-related adverse local or systemic effects in dogs administered a single dose up to 169 mg/kg (38 times the maximum recommended human dose [MRHD]) or repeated doses over 90 days at dose levels up to 133 mg/kg/day (30 times MRHD), the highest dose tested. No adverse treatment-related systemic effects were observed in rats for up to 90 days at dose levels up to 129 mg/kg/day (8 times MRHD). At higher dose levels following nose only exposure, local histopathological effects were noted in the rat that included minimal to mild squamous metaplasia of the arytenoid cartilage in the larynx and minimal to mild olfactory epithelial atrophy. As these effects, observed at high multiples (4 to 8 times) of the anticipated clinical dose, are unique to the species and a result of exposure to an irritant and the intranasal route of administration, their clinical significance is unknown. In these toxicology studies, up to 90 days duration by the inhalation route, no treatment-related adverse effects were seen at levels that represent 2 to 43 times the MRHD on a mg/kg basis or 6.5 to 38.5 times the MRHD based on plasma C_{max} levels.

Carcinogenesis

A 104-week rat inhalation toxicology study to assess the carcinogenic potential of ascending doses (31, 56 and 120 mg/kg/day) of aztreonam lysine demonstrated no drug-related increase in malignant tumors. These dose levels represent 7 to 27 times the maximum recommended human dose (MRHD) on a mg/kg basis or 7 to 18 times the MRHD based on plasma C_{max} levels. The only evidence of aztreonam lysine-related carcinogenicity was a small increase in the incidence of benign C-cell thyroid tumors in females at 120 mg/kg/day. There was no such effect at 56 or 31 mg/kg/day.

Mutagenesis

Genetic toxicology studies performed *in vitro* and *in vivo* with aztreonam for injection (aztreonam arginine) as well as with aztreonam lysine in several standard laboratory models revealed no evidence of mutagenic potential at the chromosomal or gene level.

Reproductive Toxicity

No reproductive or developmental toxicity studies have been performed with CAYSTON (aztreonam lysine).

Reproductive and developmental toxicity studies were conducted with aztreonam for injection (aztreonam arginine) in rats at daily doses up to 20 times the maximum recommended human dose (MRHD). Aztreonam for injection (aztreonam arginine) before and during gestation and lactation produced no evidence of impaired fertility. The survival rate during the lactation period was slightly reduced in the offspring of rats that received the highest dose.

Local Tolerance

The local effects of aztreonam lysine on the eyes and skin were evaluated in two studies in rabbits (Table 12). No adverse effects were induced by aztreonam lysine in either study.

Table 12 Local Tolerance Studies using Aztreonam Lysine

| Species | Method of Administration | Dose (mg/mL) | Number and Gender per Group | Results |
|----------------|---------------------------------|---------------------|------------------------------------|----------------|
| NZW Rabbits | Eye | 100 | 3F | Non-irritating |
| NZW Rabbits | Dermal | 100 | 3F | Non-irritating |

Special Studies

The allergenicity potential of aztreonam lysine through potential induction of bronchoconstriction and/or pulmonary eosinophilia was evaluated following intratracheal administration of aztreonam to Guinea pigs sensitized to aztreonam. While the positive control group (ovalbumin) exhibited a profound increase in pulmonary resistance and a significant increase in eosinophils in the broncho-alveolar lavage (BAL) fluids, no such response was observed in the aztreonam lysine-treated group. At levels calculated to be approximately five times the estimated clinical dose, aztreonam sensitized and challenged Guinea pigs did not exhibit evidence of the production of reagenic antibodies which would elicit an allergic reaction.

Table 13 Studies of the Allergenic Potential of Aztreonam Lysine

| Species | Method of Administration | Duration of Dosing | Dose (mg) | Number and Gender per Group | Results |
|---------------------------|---|---------------------------|---|------------------------------------|--|
| Dunkin-Hartley Guinea Pig | IP for Sensitization; IT for challenge | 3 weeks | 0, 25 for sensitization; 0, 10 for challenge | 10M | No adverse effects on pulmonary compliance and no effects on eosinophils in sensitized Guinea pigs administered aztreonam lysine |

IP = Intraperitoneal; IT = Intratracheal

REFERENCES

1. Soto Alvarez J, Sacristan del Castillo JA, Sampedro Garcia I, Alsar Ortiz MJ. Immediate hypersensitivity to aztreonam. *Lancet* 1990;335(8697):1094.
2. Iglesias Cadarso A, Saez Jimenez SA, Vidal Pan C, Rodriguez Mosquera M. Aztreonam-induced anaphylaxis. *Lancet* 1990;336(8717):746-7.
3. Gibson RL, Retsch-Bogart GZ, Oermann C, et al. Microbiology, safety, and pharmacokinetics of aztreonam lysinate for inhalation in patients with cystic fibrosis. *Pediatr Pulmonol* 2006;41(7):656-65.
4. Retsch-Bogart, G. Z., A. L. Quittner, R. L. Gibson, C. M. Oermann, K. S. McCoy, A. B. Montgomery, and P. J. Cooper. Efficacy and safety of inhaled aztreonam lysine for airway *Pseudomonas* in cystic fibrosis. *Chest*. 2009; 135:1223-1232.
5. McCoy KS, Quittner AL, Oermann CM, Gibson RL, Retsch-Bogart GZ, Montgomery AB. Inhaled aztreonam lysine for chronic airway *Pseudomonas aeruginosa* in cystic fibrosis. *Am J Resp Crit Care Med*. 2008; 178:921–928.
6. Oermann CM, Retsch-Bogart GZ, Quittner AL, Gibson RL, McCoy KS, Montgomery AB, Cooper PJ. An 18-month study of the safety and efficacy of repeated courses of inhaled aztreonam lysine in cystic fibrosis. *Pediatr Pulmonol*. 2010, DOI 10.1002/ppul.21301.

PART III. CONSUMER INFORMATION

Pr **CAYSTON**[®]
(aztreonam for inhalation solution)
75 mg aztreonam / vial

This leaflet is Part III of a three-part “Product Monograph” published when CAYSTON was authorized for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about CAYSTON. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is used for:**

CAYSTON is an inhaled antibiotic prescribed for the management of cystic fibrosis patients with chronic *Pseudomonas aeruginosa* (*P. aeruginosa*) lung infections. The safety and efficacy of CAYSTON in patients below the age of 6 years has not been established.

Antibacterial drugs like CAYSTON treat only bacterial infections. They do not treat viral infections such as the common cold. Although you may feel better early in treatment, CAYSTON should be used exactly as directed. Misuse or overuse of CAYSTON could lead to the growth of bacteria that will not be killed by CAYSTON (resistance). This means that CAYSTON may not work for you in the future. Do not share your medicine.

What it does:

When you inhale CAYSTON, it will enter your lungs and come in contact with the *P. aeruginosa* bacteria that are present. CAYSTON binds to certain *P. 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 *P. aeruginosa* bacteria living in your lungs, lung infection is reduced and your respiratory symptoms and lung function are improved.

When it should not be used:**Do not take CAYSTON if:**

- you are allergic to aztreonam or to any ingredient in this formulation (**See: What the important non-medicinal ingredients are**).

What the medicinal ingredient is:

Aztreonam

What the important non-medicinal ingredients are:

Lysine
 Sterile diluent (0.17% sodium chloride solution)

What dosage forms it comes in:

CAYSTON is available as a freeze-dried powder that needs to be reconstituted (converted to liquid form) by adding a sterile diluent (0.17% sodium chloride) before inhaling it through your Altera[®] Nebulizer System manufactured by PARI Respiratory Equipment, Inc. CAYSTON is designed to be delivered specifically with the Altera Nebulizer System. A dose of CAYSTON consists of a single-use glass vial of sterile powder (75 mg aztreonam and the non-medicinal ingredient lysine) and a 1 mL ampule of sterile diluent (0.17% sodium chloride). Each kit of CAYSTON contains 84 vials of CAYSTON and 88 diluent ampules packed in 2 carton inserts each with a 14-day supply (42 vials of lyophilized CAYSTON packaged in two trays and one tray of 44 diluent ampules). The four additional diluent ampules are provided in case of spillage.

WARNINGS AND PRECAUTIONS**BEFORE you use CAYSTON tell your doctor if:**

- you are allergic to any antibiotics
- you are taking certain antibiotics (cefoxitin, imipenem) as these may interfere with the action of CAYSTON
- you are pregnant or planning to become pregnant
- you are nursing or planning to nurse
- you have kidney or liver problems

Contact your doctor if the following occur while taking **CAYSTON**:

- you have a rash because this could mean that you have an allergic reaction to CAYSTON.
- you have difficulty in breathing (bronchospasm) immediately after inhalation. Bronchospasm is a potential side effect with inhalation therapies such as CAYSTON.

INTERACTIONS WITH THIS MEDICATION

Let your doctor know if you are taking any other medications.

No formal studies of drug interaction have been done with CAYSTON.

PROPER USE OF THIS MEDICATION

Usual Dose:

- The recommended dosage for both adults and children 6 years of age and older is one single-use vial (75 mg) of CAYSTON reconstituted with one ampule of saline diluent taken 3 times a day by inhalation for a 28-day treatment course. Each of the 3 daily doses should be taken at least 4 hours apart (e.g. morning, after school or work and before bed). The dosage of CAYSTON is the same for patients regardless of age or weight. The safety and efficacy of CAYSTON in patients below the age of 6 years has not been established.
- An inhaled bronchodilator should be used prior to taking a dose of CAYSTON. Short acting bronchodilators can be taken between 15 minutes and 4 hours and long acting bronchodilators can be taken between 30 minutes and 12 hours prior to each dose of CAYSTON.
- If you are receiving several respiratory therapies, the recommended order is: 1) bronchodilator 2) mucolytics (medicines to help clear mucus from your lungs and, 3) CAYSTON.
- CAYSTON is formulated for inhalation in your drug-specific Altera Nebulizer System (PARI Respiratory Equipment, Inc.). CAYSTON should only be used in your Altera Nebulizer System. Do not use aztreonam for injection in your Altera Nebulizer System, as it has not been formulated for inhalation use. Do not use any medications other than CAYSTON in your Altera Nebulizer System.

Treatment Schedule

You should take CAYSTON in prescribed courses of 28 days on CAYSTON followed by at least 28 days without CAYSTON, as directed by your physician. CAYSTON should be taken 3 times a day during the 28-day period on drug. You can take your treatments at home, school, work, or any place where you are able to carry out the steps described below. Each treatment should take approximately 2 to 3 minutes. You must complete the entire 28-day course (3 times daily) of CAYSTON prescribed by your doctor for it to be fully effective.

Can I use my existing nebulizer with CAYSTON?

Only the Altera Nebulizer System should be used for taking CAYSTON. The Altera Nebulizer System is the only device to demonstrate safety and efficacy with CAYSTON. Other nebulizers or handsets may give a sub-optimal therapeutic result. Do not mix CAYSTON with any other medications in the Altera Nebulizer System.

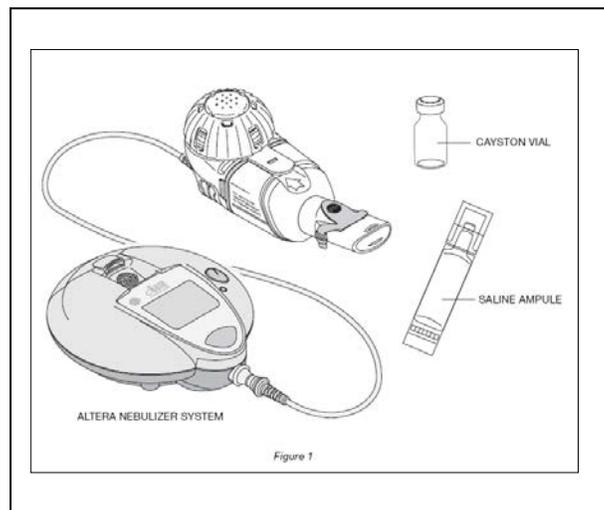
Administering CAYSTON using the Altera Nebulizer System

THIS LEAFLET SUMMARIZES THE MOST IMPORTANT INFORMATION ABOUT CAYSTON. PLEASE CONSULT WITH YOUR PHYSICIAN FOR MORE INFORMATION ABOUT PROPERLY TAKING CAYSTON OR USING YOUR ALTERA NEBULIZER SYSTEM.

You will need the following supplies (Figure 1):

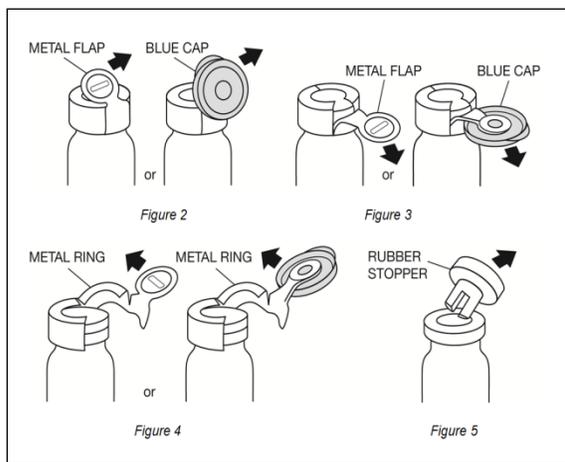
- One amber colored CAYSTON vial covered by a metal seal with a blue cap or a metal seal only
- One ampule of diluent (0.17% sodium chloride)
- Altera Nebulizer System

Check that your Altera Nebulizer System works properly before starting your treatment with CAYSTON. Refer to the manufacturer's instructions for use provided with your Altera Nebulizer System for complete details on the assembly, preparation, use, cleaning, disinfecting, and care of your Altera Nebulizer System.

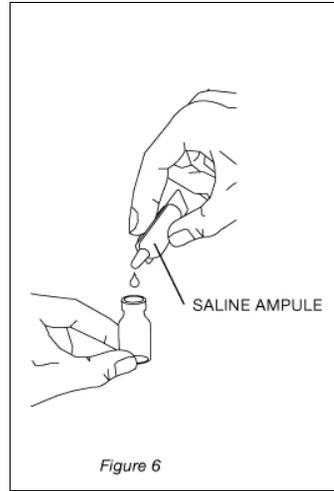


Preparing your CAYSTON for Inhalation

1. **Reconstitute CAYSTON only when ready to take a dose.** Take one amber vial of CAYSTON and one ampule of diluent from the carton. Diluent ampules must be separated by gently pulling apart.
2. Gently tap the vial so that the powder settles to the bottom of the vial. This helps you get the proper dose of medication. Open the amber drug vial by lifting up the metal flap or blue cap on the top (Figure 2) and pulling down (Figure 3) to carefully remove the entire metal ring and overcap from the vial (Figure 4). Safely dispose of the ring. Carefully remove the rubber stopper (Figure 5).
You will receive one of two different types of drug product vials in your CAYSTON package:
 - (i) A drug product vial with a metal cap and flap; or
 - (ii) A drug product vial with a blue cap over the metal cap and flap.



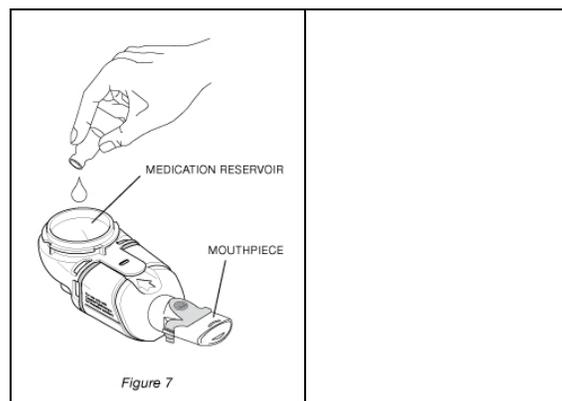
3. Open the ampule of diluent by twisting off the tip. Squeeze out the contents completely into the vial (Figure 6). Next, replace the rubber stopper and gently swirl the vial until the powder has completely dissolved and the liquid is clear. **Use CAYSTON immediately following reconstitution.**

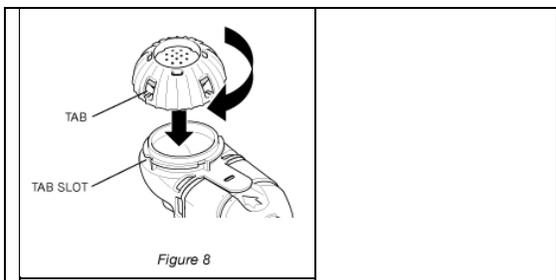


Taking your CAYSTON Treatment

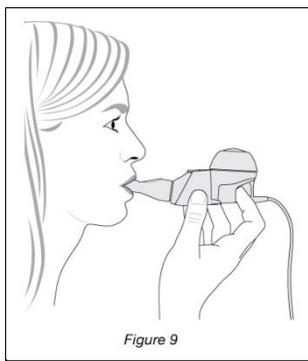
Refer to the manufacturer's instructions for use provided with your Altera Nebulizer System for complete instructions on Taking a Treatment, as well as complete details on cleaning and disinfecting your Altera Nebulizer Handset.

1. Make sure the handset is on a flat, stable surface.
2. Remove the rubber stopper, then pour all of the reconstituted CAYSTON into the Medication Reservoir of the handset (Figure 7). Be sure to completely empty the vial, gently tapping the vial against the side of the Medication Reservoir if necessary. Close the Medication Reservoir (Figure 8).





3. Begin your treatment by sitting in a relaxed, upright position. Holding the handset level, place the Mouthpiece in your mouth and close your lips around it (Figure 9).



4. Breathe normally through the Mouthpiece. **Avoid breathing through your nose.** Continue to inhale and exhale comfortably until the treatment is finished.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

It is important that you do not miss any doses. **If you miss a dose, you can still take all 3 daily doses as long as there is a period of at least 4 hours between each dose.**

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects with CAYSTON include:

- cough
- nasal congestion
- wheezing
- sore throat
- fever

- chest discomfort
- runny nose

Less common side effects include rash, bronchospasm (difficulty in breathing) immediately after inhalation, shortness of breath, and swelling or pain of joints. Patients with cystic fibrosis can have many possible symptoms. Some of these symptoms may be related to your medications. If you have new or worsening symptoms, you should tell your doctor. If you believe you are experiencing an allergic reaction to CAYSTON, tell your doctor immediately.

This list of side effects is **not complete** at this time because CAYSTON is still being studied. If you have questions about side effects, ask your doctor, nurse, or pharmacist.

HOW TO STORE IT

- Keep CAYSTON and all other medications out of reach and sight of children.
- CAYSTON vials should be stored in a refrigerator at 2 to 8°C (36 to 46°F), however, vials may be stored by the patient at room temperature (up to 25°C/77°F) for up to 28 days. Diluent ampules may be refrigerated or stored at room temperature (15 to 30°C/59 to 86°F).
- Do not use CAYSTON if it has been stored at room temperature for more than 28 days. Unused vials of CAYSTON stored at room temperature for more than 28 days should be discarded. Do not store back in the refrigerator.
- Do not use CAYSTON beyond the expiration date stamped on the vial. Do not use diluent beyond the expiration date embossed on the ampule.
- CAYSTON should be used immediately upon reconstitution. Do not reconstitute more than one dose at a time.
- Do not use diluent or reconstituted CAYSTON if it is cloudy or if there are particles in the solution.

REPORTING SUSPECTED SIDE EFFECTS
You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at:**
www.healthcanada.gc.ca/medeffect
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting form and:**
 - **Fax toll-free to 1-866-678-6789, or**
 - **Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, ON K1A 0K9**

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph prepared for health professionals can be found at: www.gilead.ca
or by contacting Gilead Sciences Canada, Inc., at: 1-866-207-4267

This leaflet was prepared by Gilead Sciences, Inc.

Last revised: February 23, 2018

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