

Product Monograph

Pr CAYSTON™

Aztreonam for Inhalation Solution

75 mg aztreonam / vial

Antibiotic

(ATC J01DF01)

CAYSTON™, indicated for the management of cystic fibrosis patients with chronic pulmonary *Pseudomonas aeruginosa* infections, has been issued marketing authorization with conditions, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization.

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Date of Preparation:

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Control No.: 120872

**This product has been authorized under the
Notice of Compliance with Conditions (NOC/c)
Policy for one or all of its indicated uses.**

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market authorization granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c Policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating disease. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

What will be different about this Product Monograph?

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol **NOC/c**. These sections may include, but are not limited to, the following:

- Indications and Clinical Use;
- Action;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials

Adverse Reaction Reporting and Re-Issuance of the Product Monograph

Health care providers are encouraged to report Adverse Reactions associated with normal use of these and all drug products to Health Canada's Health Product Safety Information Division at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c Policy, the conditions associated with market authorization will be removed.

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^{Pr}CAYSTON™
(Aztreonam for Inhalation Solution)

PART I. HEALTH PROFESSIONAL INFORMATION

CAYSTON™, indicated for the management of cystic fibrosis patients with chronic pulmonary *Pseudomonas aeruginosa* infections, has been issued marketing authorization with conditions, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization.

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)

NOC/c

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 (**see CLINICAL TRIALS**).

Demonstration of longer-term safety and efficacy of CAYSTON is limited to uncontrolled, open-label clinical trial data obtained over nine cycles of therapy (**see CLINICAL TRIALS**).

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

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 (**see CLINICAL TRIALS**).

NOC/c

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.

NOC/c

WARNINGS AND PRECAUTIONS

General

CAYSTON 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.

Carcinogenesis and Mutagenesis

A 104-week rat inhalation toxicology study of aztreonam lysine using dose levels 7 to 27 times the maximum human recommended dose demonstrated no drug-related increase in malignant tumors. Both aztreonam for injection (aztreonam arginine) and aztreonam lysine demonstrated no evidence of mutagenic potential in *in vitro* and *in vivo* laboratory models (see TOXICOLOGY).

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.^{1,2} 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. 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.

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:

The safety of CAYSTON in breast-fed infants of mothers who received CAYSTON has not been established.

Following administration of aztreonam for injection (aztreonam arginine), aztreonam is excreted in human milk at concentrations that are less than one 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, aztreonam exposure in breast-fed infants due to mothers receiving CAYSTON is likely to be extremely low.

Pediatrics (<18 years of age):

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

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 renally and therefore administration of CAYSTON in patients with renal impairment should be undertaken with caution.

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.

NOC/c

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In clinical studies, CAYSTON was generally well-tolerated with an adverse event profile consistent with the signs and symptoms of cystic fibrosis. In the placebo-controlled studies AIR-CF1 and AIR-CF2, 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 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.

Patients 6 years and older were included in clinical studies with CAYSTON. Fifty-five patients under 18 years of age received CAYSTON in the placebo-controlled studies. In CAYSTON clinical studies no dose adjustments were made for pediatric patients. Pyrexia was more commonly reported in pediatric than adult patients in the placebo-controlled studies.

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 344 patients from two Phase 3 placebo controlled studies (AIR-CF1 and AIR-CF2) and one Phase 3 uncontrolled open label follow-on study (AIR-CF3). In these studies patients with *P. aeruginosa* initiated treatment with doses of 75 mg of CAYSTON 2 or 3 times a day for 28 days. Seventy-nine patients were 6-17 years of age and 265 patients were 18 years of age and older. In the uncontrolled open label study, 171 patients initiated the ninth 28-day course of CAYSTON.

In studies AIR-CF1 and AIR-CF2, 215 CF patients received CAYSTON 75 mg 2 times or 3 times a day for 28 days. 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 (AIR-CF1 and AIR-CF2), compared with the incidence observed following multiple courses of therapy in the uncontrolled, open-label follow-on study (AIR-CF3).

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 (AIR-CF1 and AIR-CF2) and the Uncontrolled, Open-label Follow-on Study (AIR-CF3)^b

System Organ Class Preferred Term	Integrated AIR-CF1 and AIR-CF2		AIR-CF3 ^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): AIR-CF2 (28 + 56), AIR-CF1 (28 + 14).

Planned study duration for AIR-CF3: 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 AIR-CF3, dyspnea exertional (1.0%) and pleuritic pain (1.0%) were observed during course 4.

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%).

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.

DRUG INTERACTIONS

Drug-Drug Interactions

No formal clinical studies of drug interactions with CAYSTON 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.

NOC/c

DOSAGE AND ADMINISTRATION

General

CAYSTON 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 used with any other nebulizer. CAYSTON should not be mixed with any other drugs in the Altera Nebulizer Handset. Do not put other drugs in the Altera Nebulizer Handset. Patients should use a bronchodilator before each dose of CAYSTON (see **CLINICAL TRIALS**). 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 several respiratory therapies, the recommended order is: 1) bronchodilator 2) chest physiotherapy, 3) other inhaled medications, and 4) CAYSTON.

CAYSTON is for inhalation administration only.

Like all other nebulized treatments, the amount of CAYSTON delivered to the lungs will depend upon patient factors as well as the nebulization system used and its performance. Using the Altera Nebulizer System under *in vitro* conditions, the mean emitted dose (% nominal) was approximately 60 mg (80% of label dose) with a fine particle fraction of approximately 90% as measured by cascade impaction.

Recommended Dose

The recommended dosage for both adults and pediatric patients 6 years of age and older is one single-use vial (75 mg) of CAYSTON administered 3 times a day for a 28-day course (followed by 28 days without CAYSTON therapy). 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.

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 one amber glass vial containing CAYSTON and one diluent ampule from the carton. To open the glass vial, carefully remove the metal ring by 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 typically 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 and cleaning 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.

Adverse reactions specifically associated with overdose of CAYSTON have not been identified.

NOC/c

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.³

Pharmacokinetics

Absorption:

Sputum Concentrations

Individual patients' sputum aztreonam concentrations exhibited considerable variability. Ten minutes following a single dose of 75 mg CAYSTON, 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 increased accumulation of aztreonam following 3 times a day dosing.

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. Incubations were conducted at 3 and 50 µM to examine the metabolic stability of aztreonam by monitoring the rate of disappearance and also the formation of metabolites. Hepatocyte incubations were conducted in suspension for 6 hours at 37°C. Aztreonam is stable in pulmonary subcellular fractions in all species examined with little metabolism of the parent compound. As predicted by the high metabolic stability, no significant metabolites were observed by UV absorbance or high sensitivity linear ion trap LC/MS/MS. 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). 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 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).

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 one 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 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 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 two cartons each with a 14-day supply (42 vials of CAYSTON packaged in two trays and one tray of 44 diluent ampules). The four additional diluent ampules are provided in case of spillage.

PART II. SCIENTIFIC INFORMATION

CAYSTON™, indicated for the management of cystic fibrosis patients with chronic pulmonary *Pseudomonas aeruginosa* infections, has been issued marketing authorization with conditions, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization.

PHARMACEUTICAL INFORMATION

Drug Substance

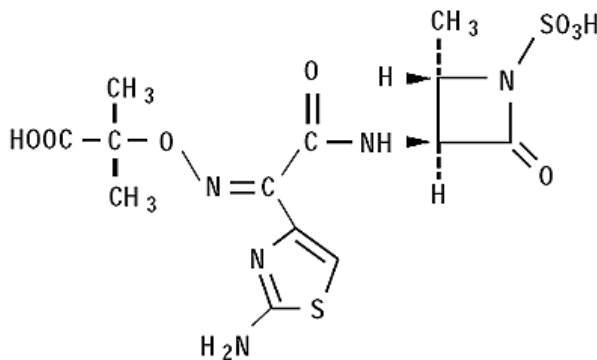
Common Name: aztreonam (INN)

Chemical Name: (Z)-2-[[[(2-amino-4-thiazolyl)[[(2S,-3S)-2-methyl-4-oxo-1-sulfo-3-azetidiny]l]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.

NOC/c

CLINICAL STUDIES

Study Demographics and Trial Design

***P. aeruginosa* in CF**

CAYSTON (aztreonam for inhalation solution) was evaluated over a period of 28 days of treatment (one course) in two randomized, double-blind, placebo-controlled, multicenter studies (AIR-CF1 and AIR-CF2) 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 (AIR-CF3) was conducted. AIR-CF1 was designed to evaluate improvement in respiratory symptoms as measured by the cystic fibrosis questionnaire-revised (CFQ-R) and AIR-CF2 was designed to evaluate the time to need for IV or inhaled antipseudomonal antibiotic therapy. Patients ≥ 6 years of age and with $FEV_1 \geq 25\%$ and $\leq 75\%$ predicted were enrolled in both studies. Patients participating in these studies could subsequently receive multiple courses of CAYSTON in AIR-CF3. All patients received CAYSTON on an outpatient basis administered with the Altera Nebulizer System (for clinical use was labeled as eFlow[®] Electronic Nebulizer). 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. Nearly all patients were taking drugs for obstructive airway diseases, many were taking pancreatic enzymes and vitamins, and a majority was taking mucolytics, drugs for acid related disorders, drugs for blood and blood forming organs, antihistamines, and analgesics. Concomitant Pulmozyme[®] was used by 65% and 85% of patients in studies AIR-CF1 and AIR-CF2, respectively.

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 instrument encompasses both generic health-related quality of life and CF-specific domains including: Physical Functioning, Emotional Functioning, Social Functioning, Vitality, Health Perceptions, Body Image, Eating Disturbances, Treatment Burden, Role/School Functioning, Respiratory Symptoms, Digestive Symptoms, and Weight. 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. CFQ-R Respiratory Symptoms scores were categorized as improved, stable, or worsened depending on the magnitude and direction of change (change of ≥ 5 points was defined as the minimal clinically important difference).

AIR-CF1:

AIR-CF1 enrolled 164 patients with CF and *P. aeruginosa* in the US, Canada, Australia and New Zealand. These patients were randomized in a 1:1 ratio to receive either inhaled CAYSTON (75 mg) or volume-matched placebo administered 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 primary efficacy endpoint was improvement in respiratory symptoms as measured by the Respiratory Symptoms scale of the CFQ-R. The mean age was 30 years (range, 7 to 74 years), and the mean baseline FEV_1 % predicted was $55\% \pm 14\%$; 43% were females and 96% were Caucasian.

AIR-CF2:

AIR-CF2 was conducted in the US and enrolled and treated 211 patients with CF and *P. aeruginosa*. The primary efficacy endpoint was time to need for inhaled or IV antipseudomonal antibiotics with documented symptom(s) predictive of pulmonary exacerbation. In this study patients must have been treated with three or more 28 day courses of TOBI in the preceding year. Patients were permitted to continue taking certain CF treatments such as azithromycin and hypertonic saline regimens during the trial. The mean age was 26 years (range, 7 to 65 years), and the mean baseline FEV₁ % predicted was 55% ±15%; 43% were females and 92% were Caucasian. All patients were treated with TOBI, 300 mg, 2 times a day in the four weeks immediately prior to the 28-day course of CAYSTON or placebo. Patients were randomized in a 2:2:1:1 ratio to receive either inhaled CAYSTON (75 mg) or volume-matched placebo administered either 2 times or 3 times a day for 28 days. Following completion of the 28-day course of CAYSTON or placebo, patients were followed for up to 56 days to assess the need for IV or inhaled antibiotics for symptoms predictive of a pulmonary exacerbation.

Repeated Courses

AIR-CF3:

AIR-CF3 was an uncontrolled, open-label follow-on trial to AIR-CF1 and AIR-CF2, which evaluated the safety of repeated exposure to CAYSTON and its effect on disease related endpoints for up to nine 28-day courses. Patients received CAYSTON at the same frequency (2 times or 3 times a day) as they took CAYSTON or placebo in the randomized studies. Each 28-day course of CAYSTON was followed by 28 days off CAYSTON.

The trial design and patient demographics for the double-blind studies AIR-CF1 and AIR-CF2, as well as open-label study AIR-CF3 are summarized in Table 2 below.

Table 2 AIR-CF1, AIR-CF2 (CAYSTON Compared with Placebo) and AIR-CF3 (Uncontrolled, Open-label Follow-on)

Study Number	Trial Design	Dosage, Route of Administration and Duration	Study Subjects	Mean Age (Range)	Gender
AIR-CF1 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 treatment</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%
AIR-CF2 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</p> <p>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 $\geq 25\%$ and $\leq 75\%$</p>	26 years (7-65)	Male: 57% Female: 43%
AIR-CF3	Open-label, uncontrolled, multicenter, follow-on study to AIR-CF1 and AIR-CF2	<p>Arm 1: CAYSTON 75 mg 2 times a day</p> <p>Arm 2: CAYSTON 75 mg 3 times a day</p> <p>Patients received CAYSTON at the same frequency (2 or 3 times a day) that they received CAYSTON or placebo in Studies AIR-CF1 or AIR-CF2</p>	<p>N=85</p> <p>N=189</p> <p>Patients with cystic fibrosis; ≥ 6 years of age; previous participation in Studies AIR-CF1 or AIR-CF2</p>	29 years (8-74)	Male: 55% Female: 45%

Study Results

AIR-CF1:

Study results for the primary and key secondary endpoints for Study AIR-CF1 are provided in Table 3(a). Clinically significant improvements from baseline in CFQ-R Respiratory Symptoms score and pulmonary function (as measured by FEV1 [L] and FEV₁ % predicted) were observed for CAYSTON versus placebo at Day 28 and were maintained at Day 42, 14 days after cessation of treatment. Statistically significant reductions of *P. aeruginosa* sputum density were also observed for CAYSTON-treated patients at Day 28. Analysis of AIR-CF1 by baseline disease severity and age demonstrated consistent improvements in CFQ-R Respiratory Symptoms score and pulmonary function in both patients with less severe disease (FEV₁ > 50% and ≤ 75%) as well as in patients with more severe disease (FEV₁ ≤ 50% and ≥ 25%) and in patients <18 years of age and patients ≥ 18 years of age (Table 3(b)).

Table 3(a) Primary and Key Secondary Outcomes for Study AIR-CF1

Endpoint	Treatment		
	Placebo (N = 84)	75 mg CAYSTON 3 times a day (N = 80)	Treatment Difference (p-value; 95% CI)
Change in CFQ-R 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 Sputum Log₁₀ PA CFUs 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)

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

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

Table 3(b) Primary and Key Secondary Outcomes for Study AIR-CF1 by Subgroup: Baseline Disease Severity; Age Group

	Placebo (N = 84)	75 mg CAYSTON 3 times a day (N = 80)	Treatment Difference (p-value; 95% CI)
Change at Day 28 in CFQ-R Respiratory Symptoms Score from Day 0			
FEV₁ ≤ 50% (N)	30	30	
Adjusted mean	-4.0	4.2	8.3 (p = 0.0839; -1.1, 17.6)
FEV₁ > 50% (N)	53	50	
Adjusted mean	-0.8	10.1	10.9 (p = 0.0018; 4.2, 17.6)
Age < 18 years (N)	16	21	
Adjusted mean	-6.2	12.7	18.9 (p = 0.0006; 8.8, 29.1)
Age ≥ 18 years (N)	67	59	
Adjusted mean	-1.5	4.8	6.4 (p = 0.0495; 0.0, 12.7)
Percent Change at Day 28 in FEV₁ [L] from Day 0			
FEV₁ ≤ 50% (N)	30	30	
Adjusted mean	-4.0	6.3	10.3 (p = 0.0061; 3.1, 17.6)
FEV₁ > 50% (N)	54	50	
Adjusted mean	-0.6	9.5	10.1 (p < 0.0001; 5.3, 14.9)
Age < 18 years (N)	16	21	
Adjusted mean	-2.9	7.5	10.4 (p = 0.0790; -1.3, 22.1)
Age ≥ 18 years (N)	68	59	
Adjusted mean	-2.4	8.1	10.5 (p < 0.0001; 6.4, 14.7)

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

Nonrespiratory CFQ-R domains that demonstrated significant improvement over placebo were Physical Functioning, Emotional Functioning, Health Perceptions and Vitality. Mean increase in weight and body mass index at Day 28 was significantly larger in CAYSTON-treated patients than placebo-treated patients (Table 4).

Table 4 Changes in Weight and Body Mass Index at Day 28 from Day 0 (AIR-CF1)

Parameter	Treatment		
	Placebo (N = 84)	75 mg CAYSTON 3 times a day (N = 80)	Treatment Difference (p-value; 95% CI)
Percent Change in Weight (kg)	0.07	1.09	1.01 (p=0.0039; 0.33, 1.69)
Mean Change in Body Mass Index (kg/m ²)	0.01	0.21	0.20 (p=0.0054; 0.06, 0.34)

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

AIR-CF2:

Study results for the primary and key secondary endpoints for Study AIR-CF2 are presented in Table 5 and Table 6. All patients were treated with TOBI[®], 300 mg, 2 times a day in the four weeks immediately prior to the 28-day course of CAYSTON or placebo.

The median time to antibiotic need was prolonged among patients treated with CAYSTON compared to placebo treated patients and the proportion of CAYSTON-treated patients using IV or inhaled antibiotics was less than placebo-treated patients (Table 5).

Table 5 Use of Inhaled or IV Antipseudomonal Antibiotics Due to Pre-defined Symptoms (AIR-CF2)

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 of 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

CAYSTON therapy resulted in significant improvements in CFQ-R Respiratory Symptoms score, FEV₁ [L], and log₁₀ *P. aeruginosa* CFUs in sputum versus placebo at Day 28 (Table 6).

Table 6 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 CFUs (AIR-CF2)

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 FEV₁ [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 Sputum Log₁₀ PA CFUs 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

AIR-CF3:

Over nine 28-day courses of therapy, measures of pulmonary function (FEV₁ (L)), CFQ-R Respiratory Symptoms score, and log₁₀ *P. aeruginosa* CFUs showed a trend to improvement while the patients were on treatment compared with off treatment (see Table 7).

FEV₁ (L), CFQ-R Respiratory Symptoms score, and log₁₀ *P. aeruginosa* CFUs 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 7. AIR-CF3: 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> CFUs Mean (SD)
CAYSTON Course 1 (N=189) ^a	6.83 (17.38)	7.98 (16.51)	-0.81 (1.76)
Off Treatment	1.34 (15.95)	0.71 (14.51)	-0.28 (1.79)
CAYSTON Course 3 (N=169) ^a	7.34 (18.52)	6.04 (16.49)	-0.53 (2.12)
Off Treatment	3.06 (19.29)	0.72 (15.20)	-0.07 (1.83)
CAYSTON Course 6 (N=135) ^a	5.26 (18.62)	4.78 (17.85)	-0.55 (2.00)
Off Treatment	1.70 (18.61)	-1.43 (15.97)	-0.29 (1.99)
CAYSTON Course 9 (N=124) ^a	6.01 (17.94)	3.98 (17.90)	-0.60 (2.07)
Off Treatment	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

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} (µg/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 8 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 9 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 10) 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 10 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.

NOC/c

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.

In clinical studies with CAYSTON, *in vitro* antimicrobial susceptibility testing was performed on all phenotypically distinguishable *P. aeruginosa* isolates using the broth microdilution technique according to standard procedures for testing patient isolates.

In an effort to determine a therapeutic breakpoint specific to CAYSTON, treatment response (measured by improvement in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Symptoms score, FEV₁ [L] and log₁₀ *P. aeruginosa* CFUs in sputum following a 75 mg 3 times a day, 28-day course of CAYSTON) was evaluated in terms of baseline *P. aeruginosa* susceptibility to aztreonam for study AIR-CF1. Among patients with highest baseline

aztreonam MIC above the parenteral breakpoint ($> 8 \mu\text{g/mL}$), 29/31 (93.5%) patients responded to CAYSTON treatment in comparison with 33/38 (86.8%) patients with highest baseline aztreonam MIC below the parenteral breakpoint ($\leq 8 \mu\text{g/mL}$). Among patients with highest baseline aztreonam MIC $\geq 256 \mu\text{g/mL}$ ($n = 7$), all patients responded to CAYSTON treatment in comparison with 55/62 (88.7%) patients with MIC $< 256 \mu\text{g/mL}$. Accordingly, the parenteral breakpoint does not predict the clinical efficacy of CAYSTON therapy.

Further categorical analyses for the relationship between MIC and treatment response provided insufficient evidence to establish a susceptibility breakpoint for CAYSTON. The highest baseline aztreonam MIC may shorten the duration of lung function improvements in response to CAYSTON treatment. In the Phase 3 placebo-controlled studies, patients with highest baseline aztreonam MIC above or below the parenteral breakpoint demonstrated similar improvements in FEV₁ [L] following a 28-day course of CAYSTON therapy. Two weeks following cessation of CAYSTON therapy, patients with MIC $\leq 8 \mu\text{g/mL}$ retained substantial improvement in FEV₁; however, FEV₁ dropped to below baseline levels for patients with MIC $> 8 \mu\text{g/mL}$.

Development of Resistance

No changes in the susceptibility of *P. aeruginosa* to aztreonam were observed following a single 28-day course of 75 mg CAYSTON in the Phase 3 placebo-controlled studies. In the open-label follow-on study, treatment with up to nine 28-day courses (with 28 days between courses) of 75 mg CAYSTON administered 3 times a day has not been shown to affect the overall susceptibility of *P. aeruginosa* to aztreonam. The MIC₅₀ of aztreonam for the *P. aeruginosa* isolate with the highest MIC from each patient, as well as all *P. aeruginosa* isolates, remained unchanged (± 2 fold change) from baseline following 28-day courses of 75 mg CAYSTON administered 3 times a day. Only transient increases from baseline were observed in the MIC₉₀ of aztreonam for *P. aeruginosa* following repeated CAYSTON courses. At the end of the 18-month study (Course 9 Off Treatment), all MIC values were considered unchanged (± 2 fold change) from the baseline value (Table 11).

Administration of 75 mg CAYSTON 3 times a day over repeated cycles appears to offer a microbiological advantage over 2 times a day dosing. The susceptibility of *P. aeruginosa* to aztreonam and other antibiotics appears to decrease more readily over time with 2 times a day dosing than 3 times a day dosing.

Table 11 MIC₅₀ and MIC₉₀ of Aztreonam (µg/mL) for the *P. aeruginosa* Isolate with the Highest MIC from Each Patient (AIR-CF3)

	n	MIC ₅₀ ^a	MIC ₉₀ ^a
Baseline	171	8	256
CAYSTON Course 1	171	8	256
Off Treatment	163	8	256
CAYSTON Course 2	157	8	512
Off Treatment	161	8	256
CAYSTON Course 3	144	16	512
Off Treatment	147	8	256
CAYSTON Course 4	128	8	512
Off Treatment	133	8	512
CAYSTON Course 5	127	8	512
Off Treatment	121	8	256
CAYSTON Course 6	119	16	1024
Off Treatment	118	8	512
CAYSTON Course 7	115	8	512
Off Treatment	117	8	256
CAYSTON Course 8	110	8	512
Off Treatment	111	16	512
CAYSTON Course 9	110	8	1024
Off Treatment	107	8	512

Data for 75 mg CAYSTON administered 3 times a day from the open-label follow-on study, each course 28 days long.
n = number of patients with available data.

^aValues at end of treatment course; ± 2-fold change in MIC is considered *unchanged*.

Further, no cross-resistance to other classes of antibiotics, including aminoglycosides, quinolones, and beta-lactams, has 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, as summarized in Tables 12 and 13. There were no adverse clinical signs or treatment-related effects observed on body weight, food consumption, laboratory investigations, ophthalmoscopy or necropsy. At higher dose levels following nose only exposure, local histopathological effects were noted in the rat that included squamous metaplasia of the arytenoid cartilage in the larynx and minimal to mild olfactory epithelial atrophy (see Tables 12 and 13), effects unique to the species and a result of exposure to an irritant and the intranasal route of administration. In general toxicology studies up to 90 days duration by the inhalation route, no treatment-related adverse effects were seen at plasma C_{max} levels that were 6.5 to 38.5 fold the clinical C_{max}.

Table 12 7-Day and 28-Day Inhalation Studies of Aztreonam Lysine

Study Number	Duration of Dosing; Species	Estimated Achieved Doses (mg aztreonam/kg/day)	Mean Cmax ^a (µg/mL) Male and Female [Multiple of Cmax at MHRD at NOAEL] ^b	AUC _(0-t) µg.h/mL Male and Female (Geometric Mean)	Biologically Significant Treatment-Related Findings ^c
663166	Single dose; Male dogs	0 44 108 169	- 4.6 M 5.4 M 12.1 M [20.2]	- 12.6 M 19.2 M 35.6 M	In one of two dogs in the high dose group the following was found on Day 2: nasal cavity goblet cell hyperplasia, anterior; tracheal squamous metaplasia, focal, carina; and on Day 15 (in one of two dogs) trachea stratified epithelium, focal, carina. These findings were considered typical of spontaneously arising background lesions seen in dogs at the testing laboratory. NOAEL = 169 mg/kg/day [Multiple of MRHD ^d at NOAEL = 38]
663632	7-Day; Rat	0 34 144	-	-	An increase in prostate weights for Groups 2 and 3 animals which was still apparent following correction for body weight. This increase (57%) attained statistical significance (p<0.01) in the Group 3 animals. A much smaller non-statistically significant increase (13%) was noted in the Group 2 animals. NOAEL = 34 mg/kg/day [Multiple of MRHD ^d at NOAEL = 2]
663559	28-Day; Rat	0 38 76 157	- 3.5 M, 3.8 F 5.9 M, 6.2 F 11.1 M, 12.0 F [18.5 – 20.0]	- 5.4 M, 6.7 F 11.9 M, 14.5 F 30.1 M, 32.1 F	Increased thyroid gland weights for Group 3 and 4 male animals and Group 2, 3 and 4 female animals which was still reflected in the covariance adjusted values, without dose-relationship or histopathological correlates. Increased incidence (Group 4) in squamous metaplasia (with keratinization) of the arytenoid cartilage in the larynx (an adaptive response to an irritant at a site of predilection to rats) was noted which returned to a background level after the 14 day recovery period. NOAEL was 157 mg/kg/day [Multiple of MRHD ^d at NOAEL = 10]

Study Number	Duration of Dosing; Species	Estimated Achieved Doses (mg aztreonam/kg/day)	Mean C _{max} ^a (µg/mL) Male and Female [Multiple of C _{max} at MHRD at NOAEL] ^b	AUC _(0-t) µg.h/mL Male and Female (Geometric Mean)	Biologically Significant Treatment-Related Findings ^c
668117	28-Day: Rat (Degraded formulation)	0 119 102 ^e	- 9.1 M, 9.1 F 3.4 M, 4.6 F ^e [15.2]	- 30.8 M, 30.3 F 14.7 M, 18.0 F ^e	Increased thyroid gland weights (absolute, relative, covariate adjusted) for groups 2 (119 mg/kg/day) and group 3 (102 mg/kg/day) females, without histopathological correlates. Decreased heart weights (relative, covariate adjusted) for Groups 2 and 3 males. Increased incidence (Groups 2 and 3) in squamous metaplasia of the laryngeal epithelium (an adaptive response to an irritant at a site of predilection to rats) was noted after 4 weeks of treatment and after 2 weeks recovery. Atrophy of the olfactory epithelium in the nasal cavity (Groups 2 and 3) was noted after 4 weeks of treatment but not after 2 weeks recovery. Results support an NOAEL of 119 mg/kg/day aztreonam and 102 mg/kg/day degraded aztreonam. [Multiple of MRHD ^d at NOAEL = 7]
663496	28-Day; Dog	0 53 94 195	- 5.6 M, 3.4 F 6.9 M, 7.1 F 23.1 M, 8.6 F [14.3 – 38.5]	- 11.2 M, 6.8 F 20.3 M, 17.8 F 55.6 M, 25.9 F	None. NOEL was 195 mg/kg/day [Multiple of MRHD ^d at NOAEL = 43]

-: Not Measured

^a C_{max} values from Day 27 for Study No. 663559 and Day 28 for Study No. 668117 and 663496

^b Multiple of the Maximum Recommended Human Dose (MRHD) was calculated by comparing the C_{max} at the NOAEL from animal studies to the C_{max} (0.6 µg/mL) in the human studies.

^c Observations made for all studies include: viability, clinical signs, body weight, food consumption (except Study No. 663632 that looked at water consumption), hematology, coagulation, clinical chemistry, urinalysis, necropsy, organ weights, and histopathology including respiratory tract. Study 663559 also included ophthalmoscopy and water consumption and Study 663496 also included ophthalmoscopy and electrocardiography.

CAYSTON™ (aztreonam for inhalation solution)
Product Monograph

- ^d Multiple of the Maximum Recommended Human Dose (MRHD) was calculated by comparing the pulmonary dose in humans and animals at the NOAEL determined from animal studies. The MRHD is 225 mg or 4.5 mg/kg for a 50 kg patient. Pulmonary deposition using the eFlow is approximately 25% or a 1.125 mg/kg pulmonary dose. The pulmonary dose level from the animal studies assumed 7% of the achieved dose level in the rat and 25% of the achieved dose level in dogs.
- ^e Degraded formulation

Table 13 90-Day Inhalation Studies of Aztreonam Lysine

Study Number	Duration of Dosing; Species	Estimated Achieved Doses (mg aztreonam/kg/day)	Mean C _{max} ^a (µg/mL) Male and Female [Multiple of C _{max} at MHRD at NOEL] ^b	AUC _(0-t) µg.h/mL Male and Female (Geometric Mean)	Biologically Significant Treatment-Related Findings ^c
664348	90-Day; Rat	0	-	-	Decreased neutrophils in Group 2, 3, 4 and 5 animals during weeks 7 and 13; increased red blood cell parameters (Hb, RBC and Hct) in Group 3 and 4 females during week 13. Adverse histological effects were seen in the nasal cavities (olfactory epithelial atrophy and/or rhinitis) in groups 3, 4 and 5 and larynx (squamous metaplasia of the arytenoid or the U-shaped cartilage) in groups 3 and 4. Following a 28 day recovery period, the adverse effects in the nasal cavity and larynx were still present, as well as increased numbers of eosinophilic globules in the nasal cavity in 3/5 males and 2/5 females from Group 4 and in 3/5 females from Group 5. NOAEL was 32 mg aztreonam/kg/day. [Multiple of MRHD ^e at NOAEL = 2]
		32	3.9 M, 4.3 F	6.6 M, 7.4 F	
		62	6.6 M, 6.7 F	15.6 M, 15.0 F	
		121	7.6 M, 8.6 F	26.3 M, 32.5 F	
		129 ^d	7.6 M, 10.0 F ^d	28.1 M, 31.9 F ^d	
664353	90-Day; Dog	0	-	-	None. NOEL was 133 mg/kg/day [Multiple of MRHD ^e at NOAEL = 30]
		34	1.3 M, 2.6 F	2.3 M, 6.6 F	
		73	5.0 M, 5.3 F	11.9 M, 14.7 F	
		133	11.8 M, 15.0 F	30.5 M, 37.4 F	
			[19.7 – 25]		

^a C_{max} values from Week 7

^b Multiple of the Maximum Recommended Human Dose (MRHD) was calculated by comparing the C_{max} at the NOAEL from animal studies to the C_{max} (0.6 µg/mL) in the human studies.

^c Observations made for both studies include: viability, clinical signs, body weight, food and water consumption, ophthalmoscopy, hematology, coagulation, clinical chemistry, urinalysis, necropsy, organ weights, and histopathology including respiratory tract. Study 664353 also included electrocardiography.

^d Degraded formulation

^e Multiple of the Maximum Recommended Human Dose (MRHD) was calculated by comparing the pulmonary dose in humans and animals at the NOAEL determined from animal studies. The MRHD is 225 mg or 4.5 mg/kg for a 50 kg patient. Pulmonary deposition using the eFlow is approximately 25% or a 1.125 mg/kg pulmonary dose. The pulmonary dose level from the animal studies assumed 7% of the achieved dose level in the rat and 25% of the achieved dose level in dogs.

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 14). No adverse effects were induced by aztreonam lysine in either study.

Table 14 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 15 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

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PART III. CONSUMER INFORMATION

**PrCAYSTON™
(aztreonam for inhalation solution)**

CAYSTON™, for use in the management of cystic fibrosis patients with chronic *Pseudomonas aeruginosa* lung infections, has been authorized with conditions, pending the results of studies to verify its clinical benefit. For more information, patients are advised to contact their health care provider.

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market authorization granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada’s NOC/c Policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating disease. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

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.

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 nursing your baby
- 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) chest physiotherapy 3) other inhaled medications, and 4) 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.

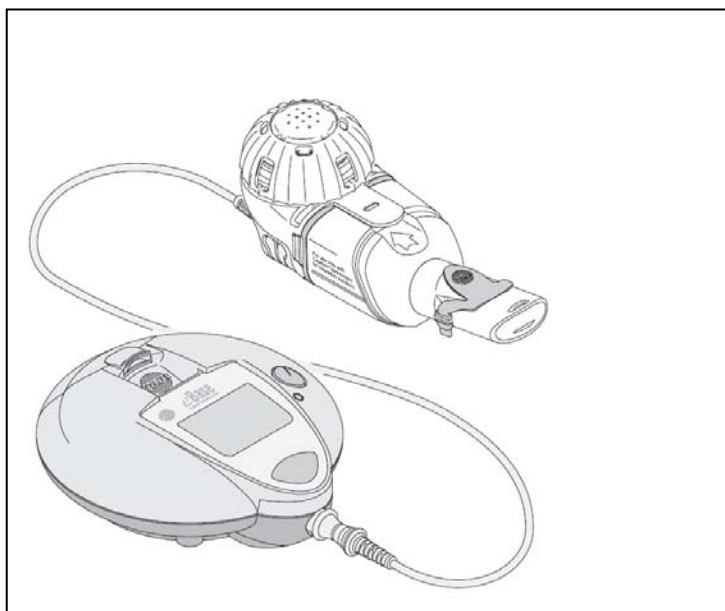
Administering CAYSTON using the Altera Nebulizer System

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:

- One amber colored CAYSTON vial
- 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, and care of your Altera Nebulizer System.



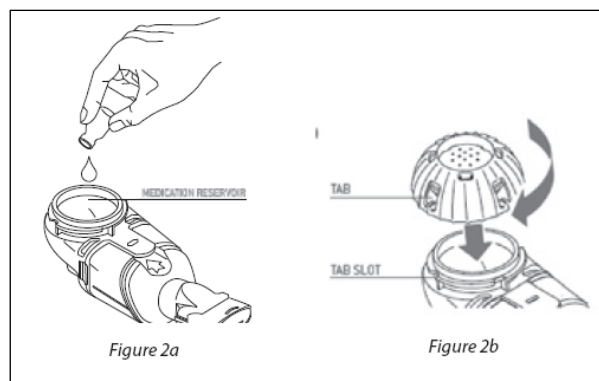
Taking your CAYSTON Treatment

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 2a). Be sure to completely empty the vial, gently tapping the side of the Medication Reservoir if necessary. Close the Medication Reservoir (Figure 2b).

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 on the top (Figure 1a) and pulling down (Figure 1b) to carefully remove the entire metal ring and overcap from the vial (Figure 1c). Safely dispose of the ring. Carefully remove the rubber stopper.
3. Open the ampule of diluent by twisting off the tip. Squeeze out the contents completely into the vial (Figure 1d). 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.**



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 3).

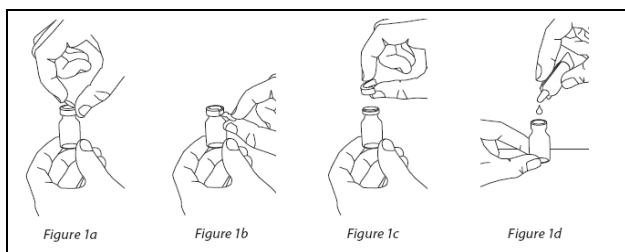


Figure 3

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

Overdosage:

If you suspect that you took more than the prescribed dose of CAYSTON, contact your doctor, local poison control center or emergency room right away. As with all medicines, CAYSTON should be kept out of reach of children.

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 and bronchospasm (difficulty in breathing) immediately after inhalation. 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 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 (15-30°C).

- 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 0701C
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

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