ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cayston 75 mg powder and solvent for nebuliser solution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains aztreonam lysine equivalent to 75 mg aztreonam. After reconstitution the nebuliser solution contains 75 mg aztreonam.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for nebuliser solution.

White to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cayston is indicated for the suppressive therapy of chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis (CF) aged 6 years and older.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

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 taking multiple inhaled therapies, the recommended order of administration is as follows:

1. bronchodilator
2. mucolytics
3. and lastly, Cayston.

Adults and children 6 years and older

The recommended dose for adults is 75 mg three times per 24 hours for 28 days.

Doses should be taken at least 4 hours apart.

Cayston may be taken in repeated cycles of 28 days on therapy followed by 28 days off Cayston therapy.

The dosing in children aged 6 years and older is the same as for adults.

Elderly

Clinical studies of Cayston did not include Cayston-treated patients aged 65 years and older to determine whether they respond differently from younger patients. If Cayston is to be prescribed to the elderly then the posology is the same as for adults.

Renal impairment

Aztreonam is known to be excreted renally and therefore administration of Cayston in patients with renal impairment (serum creatinine > 2 times upper limit of normal) should be undertaken with caution. No dose adjustment is necessary in cases of renal 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).

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 dose adjustment is necessary in cases of hepatic impairment.

Paediatric population

The safety and efficacy of Cayston in children younger than 6 years of age have not been established. Currently available data are described in section 5.1 but no recommendation on posology can be given.

Method of administration

For inhalation use.

Cayston should only be used with the Altera Nebuliser Handset and Altera Aerosol Head connected to an eBase Controller or an eFlow rapid Control Unit. For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Allergic reactions

If an allergic reaction to aztreonam does occur, stop administration of the medicinal product and initiate treatment as appropriate. The occurrence of rash may be indicative of an allergic reaction to aztreonam.

Cross-reactivity may occur in patients with a history of allergy to beta-lactam antibiotics, such as penicillins, cephalosporins, and/or carbapenems. Animal and human data demonstrate low risk of cross-reactivity between aztreonam and beta-lactam antibiotics. Aztreonam, a monobactam, is only weakly immunogenic. Caution is advised when administering Cayston to patients if they have a history of beta-lactam allergy.

The following rare and severe adverse reactions have been reported after parenteral use of other aztreonam containing products: toxic epidermal necrolysis, anaphylaxis, purpura, erythema multiforme, exfoliative dermatitis, urticaria, petechiae, pruritus, diaphoresis.

Bronchospasm

Bronchospasm (an acute reduction of ≥ 15% in FEV_1) is a complication associated with nebulised therapies. Bronchospasm has been reported after Cayston administration (see section 4.8). Patients should use a bronchodilator before each dose of Cayston. If a case of bronchospasm is suspected to be part of an allergic reaction appropriate measures should be taken (see "allergic reactions" paragraph above).

Haemoptysis

Inhalation of nebulised solutions may induce a cough reflex. The use of Cayston in paediatric CF patients has been associated with haemoptysis during treatment cycles and could have aggravated underlying conditions. Administration of Cayston in CF patients with active haemoptysis should be undertaken only if the benefits of treatment are considered to outweigh the risks of inducing further haemorrhage.

Other precautions

Efficacy has not been established in patients with FEV_1 > 75% predicted. Patients with *Burkholderia cepacia* isolated from sputum within the previous 2 years were excluded from the clinical studies.

Aztreonam for injection must not be used in the Altera or other nebulisers. Aztreonam for injection has not been formulated for inhalation, and contains arginine, a substance known to cause pulmonary inflammation.

Resistance to aztreonam, other antibiotics and treatment-emergent microorganisms

The development of antibiotic-resistant *P. aeruginosa* and superinfection with other pathogens represent potential risks associated with antibiotic therapy. Development of resistance during inhaled aztreonam therapy could limit treatment options during acute exacerbations. A decrease in *P. aeruginosa* susceptibility to aztreonam and other beta-lactam antibiotics was observed in clinical studies of Cayston. In a 24-week active-controlled clinical study of Cayston therapy, increases were observed in the MIC_{90} for all *P. aeruginosa* isolates as well as in the percentages of patients with *P. aeruginosa* resistant (MIC above the parenteral breakpoint) to aztreonam, to at least 1 beta-lactam antibiotic, and to all 6 beta-lactam antibiotics tested (see section 5.1). However, decreased *P. aeruginosa* susceptibility was not predictive of clinical efficacy of Cayston during the study. Among patients with multidrug-resistant *P. aeruginosa*, improvements in respiratory symptoms and pulmonary function were observed following treatment with Cayston. The emergence of parenteral *P. aeruginosa* resistance to aztreonam or other beta-lactam antibiotics may have potential consequences for the treatment of acute pulmonary exacerbations with systemic antibiotics.

An increased prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-sensitive *S. aureus* (MSSA), *Aspergillus* and *Candida* species was observed over time in patients treated with several Cayston treatment courses. An association between persistent isolation of MRSA and worse clinical outcome has been reported in the literature. During clinical studies of Cayston, isolation of MRSA did not result in worsening of lung function.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. However, no evidence of any drug interactions with aztreonam were identified from clinical studies in which Cayston was taken concomitantly with bronchodilators, dornase alfa, pancreatic enzymes, azithromycin, tobramycin, oral steroids (less than 10 mg daily/20 mg every other day) and inhaled steroids.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of aztreonam in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Systemic concentration of aztreonam following inhaled administration of Cayston is low compared to a standard dose of aztreonam for injection (approximately 1% of the concentration resulting from a dose of 500 mg aztreonam for injection).

Cayston should not be used during pregnancy unless the clinical condition of the woman requires treatment with aztreonam.

Breast-feeding

Following administration of aztreonam for injection, aztreonam is excreted in human milk at very low concentrations. Systemic concentration of aztreonam following inhaled administration of Cayston is approximately 1% of the concentration resulting from a standard dose of aztreonam for injection. Therefore, and because of low oral absorption, aztreonam exposure in breast-fed infants due to mothers receiving Cayston is likely to be extremely low.

Cayston can be used during breast-feeding.

Fertility

Non-clinical data for aztreonam for injection about fertility do not indicate any adverse effects.

4.7 Effects on ability to drive and use machines

Cayston has no or negligible influence on the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

Assessment of adverse reactions is based on experience in four Phase 3 clinical studies involving CF patients with chronic *P. aeruginosa* infection and post-marketing spontaneous reporting.

In the two Phase 3 placebo-controlled clinical studies where patients received Cayston for 28 days, the most frequently occurring adverse reactions to Cayston were cough (58%), nasal congestion (18%), wheezing (15%), pharyngolaryngeal pain (13.0%), pyrexia (12%) and dyspnoea (10%).

An acute reduction of ≥ 15% in FEV_1 is a complication associated with nebulised therapies, including Cayston (see section 4.4).

Tabulated summary of adverse reactions

The adverse reactions considered at least possibly related to treatment from clinical study and post-marketing experience are listed below by body system organ class and frequency.

Frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1000 to < 1/100).

Respiratory, thoracic and mediastinal disorders:	
Very common:	cough, nasal congestion, wheezing, pharyngolaryngeal pain, dyspnoea
Common:	bronchospasm[1], chest discomfort, rhinorrhoea, haemoptysis[1]
Skin and subcutaneous tissue disorders:	
Common:	rash[1]
Musculoskeletal and connective tissue disorders:	
Common:	arthralgia
Uncommon:	joint swelling
General disorders and administration site conditions:	
Very common:	pyrexia
Investigations:	
Common:	lung function test decreased[1]

[1] See section Description of selected adverse reactions

Description of selected adverse reactions

Bronchospasm

Nebulised therapies, including Cayston, may be associated with bronchospasm (an acute reduction of ≥ 15% in FEV_1). Refer to section 4.4.

Haemoptysis

Inhalation of nebulised solutions may induce a cough reflex which could aggravate underlying conditions (see section 4.4).

Allergic reactions

Rash has been reported with the use of Cayston and may be indicative of an allergic reaction to aztreonam (see section 4.4).

Lung function test decreased

Lung function test decreased has been reported with use of Cayston, but was not associated with a sustained decrease in FEV_1 (see section 5.1).

The following rare and severe adverse reactions have been reported after parenteral use of other aztreonam containing products: toxic epidermal necrolysis, anaphylaxis, purpura, erythema multiforme, exfoliative dermatitis, urticaria, petechiae, pruritus, diaphoresis.

Paediatric population

A total of 137 paediatric patients aged 6 to 17 years with chronic *P. aeruginosa* infection and FEV_1 ≤ 75% predicted have received Cayston in Phase 2 and Phase 3 clinical studies (6-12 years, n = 35; 13-17 years, n = 102).

Pyrexia was observed at a higher incidence rate in paediatric patients aged 6 to 17 years compared to adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Adverse reactions specifically associated with overdose of Cayston have not been identified. Since the plasma concentration of aztreonam following administration of Cayston (75 mg) is approximately 0.6 µg/ml, compared to serum levels of 54 µg/ml following administration of aztreonam for injection (500 mg), no safety issues associated with aztreonam overdose are anticipated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, other beta-lactam antibacterials,
ATC code: J01DF01

Mechanism of action

Aztreonam exhibits activity *in vitro* against 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.

Mechanisms of resistance

Loss of 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/integron mediated genes.

Known mechanisms of resistance to aztreonam mediated by mutation of chromosomal genes include: hyperexpression of the Class C beta-lactamase AmpC and up-regulation of the efflux pump MexAB-OprM. The known mechanism of resistance to aztreonam mediated by acquisition of genes involves acquisition of extended spectrum beta-lactam enzymes (ESBLs) that hydrolyse the four-member, nitrogen-containing ring of aztreonam.

ESBLs from Class A, B and D beta-lactamases may have activity against aztreonam. Class A beta-lactamases reported to hydrolyse aztreonam include the VEB type (primarily Southeast Asia), PER type (Turkey), and GES and IBC types (France, Greece, and S. Africa). There are rare reports of organisms with metallo-beta-lactamases (MBLs), Class B, that are resistant to aztreonam, VIM-5 (*K. pneumoniae* and *P. aeruginosa* - Turkey), VIM-6 (*P. putida* - Singapore) and VIM-7 (*P. aeruginosa* - United States), however, it is possible that these organisms were expressing multiple resistance mechanisms and thus a MBL was not responsible for the observed resistance to aztreonam. There are rare reports of Class D beta-lactamases from clinical isolates of *P. aeruginosa*, OXA-11 (Turkey) and OXA-45 (United States) that hydrolyse aztreonam.

Microbiology

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, local aztreonam concentrations generally exceeded aztreonam MIC values for *P. aeruginosa*, regardless of the level of *P. aeruginosa* susceptibility.

Treatment with up to nine 28-day courses 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; no increases in *P. aeruginosa* MIC_{50} (± 2 dilution change) were observed,

whereas MIC_{90} increased intermittently to 4 times the initial MIC. In a 24-week active-controlled study of Cayston therapy, no increases in *P. aeruginosa* MIC_{50} (± 2 dilution change) were observed, whereas MIC_{90} increased to 4 times the initial MIC. At the end of the study, the percentage of patients with aztreonam MIC for *P. aeruginosa* above the parenteral breakpoint (> 8 µg/ml) increased from 34% at baseline to 49%, the percentage of patients with *P. aeruginosa* resistant to at least 1 beta-lactam antibiotic increased from 56% at baseline to 67%, and the percentage of patients with *P. aeruginosa* resistant to all 6 beta-lactam antibiotics tested increased from 13% at baseline to 18%. There is a risk that *P. aeruginosa* isolates may develop resistance to aztreonam or other beta-lactam antibiotics in patients treated with Cayston. The emergence of parenteral *P. aeruginosa* resistance to aztreonam and other beta-lactam antibiotics may have potential consequences for the treatment of acute pulmonary exacerbations with systemic antibiotics. However, similar improvements in lung function were seen after treatment with Cayston among patients with aztreonam susceptible or resistant *P. aeruginosa* isolates.

In studies of up to nine 28-day courses of Cayston therapy, no increases of clinical significance were observed in the treatment-emergent isolation of other gram-negative bacterial respiratory pathogens (*Burkholderia* species, *Stenotrophomonas maltophilia* and *Alcaligenes* species). During the 6-month randomised phase of study GS-US-205-0110, treatment-emergent isolation of MSSA and MRSA was observed more commonly among aztreonam-treated patients than Tobramycin Nebuliser Solution (TNS)-treated patients. The majority of the treatment-emergent isolations were intermittent. Treatment-emergent persistent isolation (defined as absent at screening/baseline then present at 3 or more subsequent consecutive visits) of MSSA occurred in 6% of aztreonam-treated patients compared to 3% of TNS-treated patients. Treatment-emergent intermittent isolation of MRSA occurred in 7% of aztreonam-treated patients compared to 1% of TNS-treated patients and treatment-emergent persistent isolation of MRSA occurred in 3% of aztreonam-treated patients compared to no TNS-treated patients. An association between persistent isolation of MRSA and more severe disease and increased mortality has been reported in the literature. During clinical studies of Cayston, isolation of MRSA did not result in worsening of lung function.

Clinical efficacy and safety

Cayston was compared to TNS over three 28-day courses of treatment in a randomised, active-controlled, multicenter study (GS-US-205-0110). Patients participating in this study in Europe who completed at least 1 course of Cayston or TNS during the randomised phase could subsequently receive up to three 28-day courses of Cayston in an open-label extension phase. Entry criteria included CF, $FEV_1 \leq 75\%$ predicted, stable pulmonary disease, a recent positive sputum culture for *P. aeruginosa*, and previous treatment with aerosolised antibiotics without demonstration of drug intolerance.

Cayston was evaluated over a period of 28-days of treatment (one course) in two randomised, double-blind, placebo-controlled, multicentre studies (CP-AI-005 and CP-AI-007). Patients participating in these studies could subsequently receive multiple courses of Cayston in an open-label follow-on study (CP-AI-006). Entry criteria included CF, baseline FEV_1 between 25% and 75% predicted, and chronic *P. aeruginosa* lung infection.

Overall, 539 patients (78% adults) were treated in these studies. Studies were conducted using the Altera Nebuliser System to administer Cayston.

GS-US-205-0110

In GS-US-205-0110, 268 patients with CF and chronic *P. aeruginosa* lung infection were randomised and received Cayston (n = 136) or TNS (n = 132). Fifty-nine paediatric patients aged 6 to 17 years were included in the study. Patients were randomised in a 1:1 ratio to receive either aztreonam (75 mg) administered by inhalation 3 times a day or TNS (300 mg) administered 2 times a day. Treatments were administered for three cycles of 28 days on therapy followed by 28 days off therapy. The co-primary endpoints were non-inferiority of Cayston to TNS in relative change from baseline to Day 28 in FEV_1 % predicted and superiority of Cayston to TNS in actual change from baseline in

FEV_1 % predicted across 3 treatment courses (the average of the actual change in FEV_1 % predicted observed at the end of each treatment course).

The adjusted mean percent change from baseline to Day 28 in FEV_1 % predicted was 8.35 and 0.55 in the Cayston and TNS groups, respectively (treatment difference: 7.80; p = 0.0001; 95% CI: 3.86, 11.73). The adjusted mean actual change from baseline in FEV_1 % predicted across 3 treatment courses was 2.05 and -0.66 in the Cayston and TNS groups, respectively (treatment difference: 2.70; p = 0.0023; 95% CI: 0.98, 4.43). Patients treated with aztreonamexperienced a longer time to need for i.v. antipseudomonal antibiotics related to respiratory events compared to TNS-treated patients (p = 0.0025). The Kaplan-Meier estimates for this event rate at week 24 were 36% in aztreonam-treated patients and 54% in TNS-treated patients. Additionally, aztreonam-treated patients had fewer hospitalisations due to respiratory events (40 *versus* 58, p = 0.044) and fewer respiratory events requiring the use of i.v. or inhaled antipseudomonal antibiotics (84 *versus* 121, p = 0.004) than TNS-treated patients. Aztreonam-treated patients also demonstrated larger mean improvements in CFQ-R respiratory symptoms scores compared to TNS-treated patients across 3 treatment courses (6.30 *versus* 2.17, p = 0.019).

In the limited subgroup of patients who received inhaled tobramycin for less than 84 days in the previous 12 months (n = 40), lung function improvements at Day 28 and across three 28-day treatment courses were numerically smaller among aztreonam-treated patients than TNS-treated patients.

CP-AI-007

CP-AI-007 enrolled 164 adult (predominantly) and paediatric patients randomised in a 1:1 ratio comparing Cayston 75 mg (80 patients) or placebo (84 patients) administered 3 times a day for 28 days (one course). Patients were required to have been off antipseudomonal antibiotics for at least 28 days before treatment with study drug.

Pulmonary function and respiratory symptoms significantly improved from baseline to Day 28 in patients treated with one course of Cayston.

CP-AI-005

CP-AI-005 enrolled 246 adult (predominantly) and paediatric patients. All patients were treated with Tobramycin Nebuliser Solution (TNS) 300 mg, 2 times a day in the four weeks immediately prior to receiving Cayston or placebo either 2 or 3 times a day for 28 days. Patients continued on their baseline medications, including macrolide antibiotics. Patients were randomised in a 2:2:1:1 ratio to be treated with aztreonam 75 mg 2 or 3 times a day or volume-matched placebo 2 or 3 times a day for 28 days immediately following the 28-day lead-in course of open-label TNS.

Aztreonamtherapy resulted in significant improvements in pulmonary function and respiratory symptoms at Day 28 in the 66 patients treated with one course Cayston 75 mg 3 times a day.

CP-AI-006

CP-AI-006 was an open-label follow-on study to CP-AI-005 and CP-AI-007 evaluating the safety of repeated exposure to aztreonamand the effect on disease-related endpoints over multiple 28-day courses. Patients received Cayston at the same frequency (2 or 3 times a day) as they took Cayston or placebo in the randomised studies. Patients continued on their baseline medications and whenever indicated additional antibiotics were used in the majority of patients to treat exacerbations. Each 28-day course of Cayston was followed by a 28-day off drug period. Over nine 28-day courses of therapy, measures of pulmonary function (FEV_1), CFQ-R respiratory symptoms scores, and *P. aeruginosa* sputum density showed a trend to improvement while the patients were on treatment compared with off treatment. However, due to the uncontrolled nature of the study and concomitant medications no conclusion can be drawn on the sustainability of the observed short term benefit over subsequent courses of treatment.

Paediatric population

A total of 137 paediatric patients aged 6 to 17 years with chronic *P. aeruginosa* infection and FEV_1 ≤ 75% predicted have received Cayston in Phase 2 and Phase 3 clinical studies. Paediatric patients had clinical improvements with aztreonamas determined by an increase in FEV_1, improvement in CFQ-R respiratory symptoms scores and decline in *P. aeruginosa* sputum density. Cayston is indicated for use in paediatric patients aged 6 years and older with repeated cycles of 28 days on therapy followed by 28 days off Cayston therapy based on the above clinical experience.

In addition to the 137 paediatric patients with chronic *P. aeruginosa* infection, Cayston was studied in two clinical studies in paediatric patients with new onset *P. aeruginosa* infection/colonization:

GS-US-205-0162

In a Phase 2 open-label study (GS-US-205-0162), 105 paediatric patients aged 3 months to < 18 years (24 patients aged 3 months to < 2 years; 25 patients aged 2 to < 6 years; 56 patients aged 6 to < 18 years) with CF and documented initial/new onset *P. aeruginosa* infection/colonisation received Cayston 3 times a day for a single course of 28 days.

Of the 101 patients, all having a positive cultures for *P. aeruginosa* within 30 days of study enrolment, of whom 56 (55.4%) were free of *P. aeruginosa* at baseline who completed a 28-day treatment course 89.1% (n = 90) were free of *P. aeruginosa* at the end of treatment (Day 28) and 75.2% (n = 76) were free of *P. aeruginosa* 1 month after the end of treatment (Day 56). A total of 79 patients who completed a 28-day treatment course and who did not receive an additional antipseudomonal antibiotic during the treatment period were evaluable 6 months after the end of treatment; of these, 58.2% (n = 46) remained free of *P. aeruginosa* throughout this time period.

GS-US-205-1850

In a Phase 3b study (GS-US-205-1850), 149 paediatric patients aged 3 months to < 18 years (30 patients aged 3 months to < 2 years; 42 patients aged 2 to < 6 years; 77 patients aged 6 to < 18 years) with CF and new onset *P. aeruginosa* infection/colonisation received Cayston administered 3 times a day, randomised for 14 days (74 patients) and 28 days (75 patients) in a 1:1 ratio.

The 14-day treatment course did not demonstrate noninferiority to the 28-day treatment course; and therefore, a 28-day course of therapy remains the recommended treatment.

5.2 Pharmacokinetic properties

Absorption

Sputum concentrations

Individual patients' sputum aztreonam concentrations exhibited considerable variability. For the combined Phase 3 placebo-controlled studies, ten minutes following a single dose of 75 mg inhaled aztreonamon Days 0, 14, and 28, the mean sputum concentrations in 195 patients with CF were 726 µg/g, 711 µg/g, and 715 µg/g, respectively, indicating no increased accumulation of aztreonam following repeated dosing.

Plasma concentrations

Individual patients' plasma aztreonam concentrations exhibited considerable variability.

One hour following a single dose of 75 mg inhaled aztreonam (at approximately peak plasma concentration), the mean plasma level in patients with CF was 0.59 µg/ml. Mean peak plasma levels at Days 0, 14, and 28 of a course with 75 mg inhaled aztreonam 3 times a day were 0.55 µg/ml,

0.67 µg/ml, and 0.65 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 aztreonam for injection (500 mg) is approximately 54 µg/ml.

Plasma aztreonam concentrations in paediatric patients aged 3 months to < 6 years are comparable to those observed for children > 6 years, adolescents and adults.

Distribution

The protein binding of aztreonam in plasma is approximately 77% at clinically relevant plasma concentrations.

Metabolism

Aztreonam is not extensively metabolised. The principal metabolite (SQ26,992) is inactive and is formed by opening of the beta-lactam ring due to hydrolysis. Recovery data indicate that about 10% of the dose is excreted as this metabolite.

Elimination

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. Approximately 10% of the total inhaled aztreonamdose is excreted in the urine as unchanged drug, as compared to 60-65% following intravenous administration of aztreonam for injection. Systemically absorbed aztreonam is eliminated about equally by active tubular secretion and glomerular filtration.

Pharmacokinetics in special populations

Age and gender

There was no clinically relevant effect of age or sex on the pharmacokinetics of aztreonam.

Renal and hepatic impairment

Pharmacokinetic studies have not been performed in patients with renal or hepatic impairment.

Pharmacokinetic properties for aztreonam for injection

Peak levels of aztreonam are achieved at about one hour after i.m. administration. After identical single i.m. or i.v. doses, the serum concentrations are comparable at 1 hour (1.5 hours from the start of i.v. infusion), with similar slopes of serum concentrations thereafter. The serum half-life of aztreonam averaged 1.7 hours in subjects with normal renal function, independent of the dose and route. In healthy subjects 60-70% of a single i.m. or i.v. dose was recovered in the urine by 8 hours, and urinary excretion was essentially complete by 12 hours.

Paediatric population

The Phase 2 and 3 placebo-controlled, registrational studies permitted comparison of plasma concentrations 1 hour post dose of Cayston by age (6 to 12 years, 13 to 17 years, and ≥ 18 years). Data from these studies revealed minimal differences in mean plasma aztreonam concentrations between age groups in patients receiving Cayston 3 times a day.

Pooled sputum concentration data from the Phase 2 and 3 registrational studies revealed some evidence of lower mean sputum concentrations in patients aged 13 to 17 years following one dose of Cayston 3 times a day. However, all mean sputum concentration values were associated with relatively large standard deviations.

5.3 Preclinical safety data

A 104-week rat inhalation toxicology study to assess the carcinogenic potential of ascending doses of aztreonamdemonstrated no drug-related increase in malignant tumours.

Genotoxicity (Chromosomal aberration and mouse lymphoma mutation assay) studies with aztreonam were negative.

Fertility, teratology, perinatal and postnatal studies were conducted with aztreonam for i.v. injection in rats at daily doses up to 750 mg/kg without adverse effects. The survival rate during the lactation period was slightly reduced in the offspring of rats that received the highest dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

L-Lysine

Solvent

Sodium chloride
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Powder vial: 4 years.

Solvent: 3 years.

After reconstitution, immediate use of Cayston is recommended. If not used immediately, the reconstituted solution must be stored at 2°C - 8°C and used within 8 hours. In-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Powder vial and solvent ampoule: Store in a refrigerator (2°C - 8°C). May be stored outside a refrigerator but below 25°C for up to 28 days.

For storage conditions of the reconstitued medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder vial: Type I amber glass vial with siliconised grey rubber stopper and aluminium tear off overseal with a blue cap.

Solvent: 1 ml low density polyethylene ampoule.

Each 28-day pack of Cayston contains 84 vials of lyophilised aztreonam and 88 solvent ampoules. The four additional solvent ampoules are provided in case of spillage.

The following pack sizes are available:
- 28-day pack of Cayston
- Pack containing one 28-day pack of Cayston plus one Altera Nebuliser Handset

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitution

Cayston should only be reconstituted with the solvent provided. Following reconstitution, Cayston is a clear, colourless to slightly coloured solution.

It is recommended that Cayston be administered immediately after reconstitution with solvent. Cayston should not be reconstituted until a dose is ready to be administered. One glass vial containing Cayston is opened by carefully removing the blue cap and the metal ring, and then the grey rubber stopper. The liquid is squeezed out of one solvent ampoule into the glass vial. The vial is then gently swirled until contents have completely dissolved. The reconstituted Cayston is then poured into the Altera Nebuliser Handset and the dose administered.

Cayston is administered by inhalation over a 2 to 3 minute period, using a Cayston specific Altera Nebuliser Handset and Altera Aerosol Head connected to an eBase Controller or an eFlow rapid Control Unit. Cayston should not be used with any other type of handset or aerosol head. Cayston should not be mixed with any other medicinal products in the Altera Nebuliser Handset. Do not put other medicinal products in the Altera Nebuliser Handset.

Do not reconstitute or mix Cayston with any other solvent or medicinal product. Do not reconstitute more than one dose at a time. Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/543/001
EU/1/09/543/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 September 2009
Date of latest renewal: 26 May 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Gilead Sciences Ireland UC
IDA Business & Technology Park
Carrigtohill
County Cork
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Periodic safety update reports (PSURs)

The requirements for submission of PSURsfor this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CAYSTON OUTER CARTON
(With a Blue box - Not for co-packaging with the Altera Nebuliser Handset)

1. NAME OF THE MEDICINAL PRODUCT

Cayston 75 mg powder and solvent for nebuliser solution
aztreonam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each powder vial contains 75 mg aztreonam.
After reconstitution, each ml of the nebuliser solution contains 75 mg aztreonam (as lysine).

3. LIST OF EXCIPIENTS

Powder vial also contains L-Lysine

Solvent ampoule contains sodium chloride, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for nebuliser solution

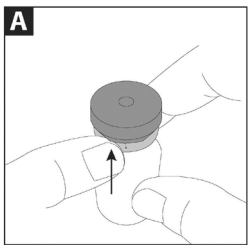
84 single-use vials
88 single-use 1 ml ampoules of solvent

5. METHOD AND ROUTE(S) OF ADMINISTRATION

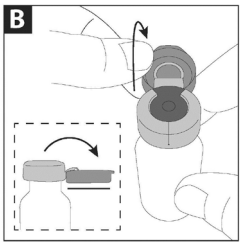
Read the package leaflet before use.

For inhalation use only. Reconstitute before use.

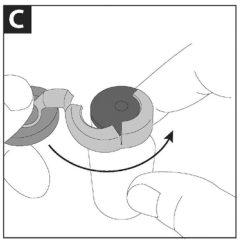
Powder should only be mixed with the solvent provided.



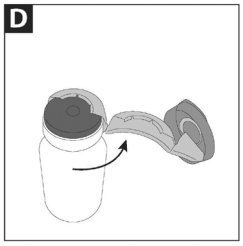
Step A: With the blue cap tab facing toward you, place the vial on a flat surface. Using one hand to hold the vial steady, use the other hand to slowly flip up the blue cap



Step B: Pull the blue cap down to a flat (horizontal) position (where the bottom of the blue cap faces up), to prepare the metal seal for removal. Do not completely tear through the metal seal.



Step C: While continuing to hold the vial steady with one hand, use the other hand to slowly pull the blue cap in a counterclockwise direction. Do not twist the blue cap.



Step D: When the metal seal opens, continue to slowly pull on the blue cap in a counterclockwise direction until the metal seal is completely removed.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. May be stored outside a refrigerator but below 25°C for up to 28 days.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/543/001: 28-day pack of Cayston

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cayston 75 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC {number}
SN {number}
NN {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON
(Outer carton containing one 28-day pack of Cayston and one Altera Nebuliser Handset with a Blue box)

1. NAME OF THE MEDICINAL PRODUCT

Cayston 75 mg powder and solvent for nebuliser solution
aztreonam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each powder vial contains 75 mg aztreonam.
After reconstitution, each ml of the nebuliser solution contains 75 mg aztreonam (as lysine).

3. LIST OF EXCIPIENTS

Powder vial also contains L-Lysine

Solvent ampoule contains sodium chloride, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for nebuliser solution

84 single-use vials
88 single-use 1 ml ampoules of solvent

This pack contains one Altera Nebuliser Handset.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

For inhalation use only. Reconstitute before use.

Powder should only be mixed with the solvent provided.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. May be stored outside a refrigerator but below 25°C for up to 28 days.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/543/002: 28-day pack of Cayston plus one Altera Nebuliser Handset

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cayston 75 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC {number}
SN {number}
NN {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CAYSTON OUTER CARTON
(No Blue box - for use only for co-packaging with Altera Nebuliser Handset)

1. NAME OF THE MEDICINAL PRODUCT

Cayston 75 mg powder and solvent for nebuliser solution
aztreonam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each powder vial contains 75 mg aztreonam.
After reconstitution, each ml of the nebuliser solution contains 75 mg aztreonam (as lysine).

3. LIST OF EXCIPIENTS

Powder vial also contains L-Lysine

Solvent ampoule contains sodium chloride, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for nebuliser solution

84 single-use vials
88 single-use 1 ml ampoules of solvent

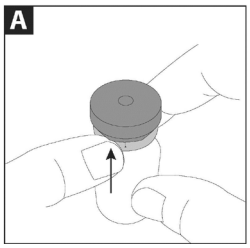
This pack is not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

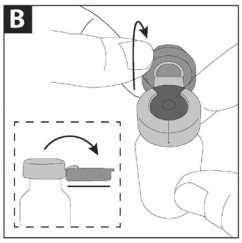
Read the package leaflet before use.

For inhalation use only. Reconstitute before use.

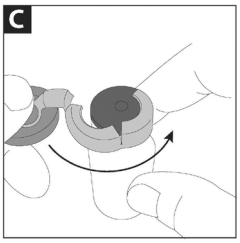
Powder should only be mixed with the solvent provided.



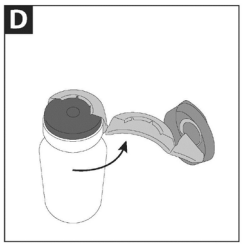
Step A: With the blue cap tab facing toward you, place the vial on a flat surface. Using one hand to hold the vial steady, use the other hand to slowly flip up the blue cap



Step B: Pull the blue cap down to a flat (horizontal) position (where the bottom of the blue cap faces up), to prepare the metal seal for removal. Do not completely tear through the metal seal.



Step C: While continuing to hold the vial steady with one hand, use the other hand to slowly pull the blue cap in a counterclockwise direction. Do not twist the blue cap.



Step D: When the metal seal opens, continue to slowly pull on the blue cap in a counterclockwise direction until the metal seal is completely removed.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. May be stored outside a refrigerator but below 25°C for up to 28 days.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/543/002: 28-day pack of Cayston plus one Altera Nebuliser Handset

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cayston 75 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CAYSTON INNER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Cayston 75 mg powder and solvent for nebuliser solution
aztreonam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each powder vial contains 75 mg aztreonam.
After reconstitution, each ml of the nebuliser solution contains 75 mg aztreonam (as lysine).

3. LIST OF EXCIPIENTS

Powder vial also contains L-Lysine

Solvent ampoule contains sodium chloride, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for nebuliser solution

42 single-use vials
44 single-use 1 ml ampoules of solvent

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

For inhalation use only. Reconstitute before use.

Powder should only be mixed with the solvent provided.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. May be stored outside a refrigerator but below 25°C for up to 28 days.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/543/001: 28-day pack of Cayston
EU/1/09/543/002: 28-day pack of Cayston plus one Altera Nebuliser Handset

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cayston 75 mg

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Cayston VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Cayston 75 mg powder for nebuliser solution
aztreonam

For inhalation use only.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

75 mg

6. OTHER

GILEAD

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SOLVENT AMPOULE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for Cayston
Sodium Chloride 0.17%

2. METHOD OF ADMINISTRATION

Inhalation use only

3. EXPIRY DATE

4. BATCH NUMBER

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

GILEAD SCIENCES

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Cayston 75 mg powder and solvent for nebuliser solution
aztreonam

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Cayston is and what it is used for

Cayston contains the active substance aztreonam. Caystonis an antibiotic used to suppress chronic lung infection caused by the bacteria *Pseudomonas aeruginosa* in patients aged 6 years and older with cystic fibrosis. Cystic fibrosis, also known as mucoviscidosis, is a life-threatening inherited disease that affects the mucus glands of internal organs, especially the lungs, but also of the liver, pancreas, and the digestive system. Cystic fibrosis in the lungs leads to clogging them with thick sticky mucus. This makes it hard to breathe.

2. What you need to know before you take Cayston

Do not take Cayston

- **if you are allergic** to aztreonam or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor before taking Cayston:
- if you are **allergic to any other antibiotics** (such as penicillins, cephalosporins, and/or carbapenems)
- if you do not tolerate or have chest tightness from taking other inhaled medicines
- if you have **kidney problems**
- if you have ever **coughed up any blood**
- if you have ever had **low lung function tests**.

If any of these apply to you **tell your doctor** before using Cayston.

As an inhaled medicine, Cayston could cause you to cough and this could lead to coughing up blood. If you have ever coughed up blood you should only use Cayston if your doctor thinks the benefit of taking this medicine outweighs the risk of coughing up blood.

You may get a temporary lowering of lung function test result during treatment with Cayston, but this is typically not a lasting effect.

Children

Cayston is not for use in children under the age of 6 years.

Other medicines and Cayston

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

There are no clinical data on the use of Cayston in pregnant women, therefore you should not take Cayston during pregnancy unless specifically discussed with your doctor.

If you plan to breast-feed ask your doctor for advice before taking Cayston. You can breast-feed during treatment with Cayston because the amount of Cayston likely to be passed to your child during breast-feeding will be extremely small.

Driving and using machines

Cayston is not expected to affect your ability to drive or use machines.

3. How to take Cayston

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is:

- **Take Cayston 3 times a day in repeated cycles of 28 days on therapy followed by 28 days off Cayston therapy.** Each of the three doses should be taken by inhalation at least four hours apart, using an Altera Nebuliser Handset. You can use either an eBase Controller or an eFlow rapid Control Unit with the Altera Handset.

- Each dose consists of one vial of Cayston mixed with one ampoule of solvent. Cayston needs to be mixed with a solvent before being inhaled through the Altera Nebuliser.

Put the prepared Cayston solution in the Altera Nebuliser Handset (see below). Each treatment takes about 2 to 3 minutes to inhale.

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.

If you are using other inhaled therapies to treat cystic fibrosis, the recommended order of use is as follows:

1. bronchodilator
2. mucolytics (a medicine that helps to dissolve the thick mucous produced in the lungs) and finally:
3. Cayston.

Do not mix Cayston with any other medicines in the Altera Nebuliser Handset.
- Do not put other medicines in the Altera Nebuliser Handset.
- Do not put the intravenous (injectable) form of aztreonam in the Altera Nebuliser Handset. Intravenous aztreonam is not suitable for inhalation.

How to take Cayston using the Altera Nebuliser Handset

You will need the following:
- One amber-coloured vial of Cayston with a blue cap.
- One plastic ampoule of solvent (0.17% w/v sodium chloride). The information that appears on the solvent ampoule is provided in English only (see section 6).
- An Altera Nebuliser Handset containing an Altera Aerosol Head connected to an eFlow Control Unit of the type 178 (eFlow rapid) or type 678 (eBase Controller).

You must use the Cayston specific Altera Nebuliser Handset containing an Altera Aerosol Head. Do not try to take Cayston using any other type of nebuliser handset (including the eFlow rapid handset).

Check that your nebuliser works properly before starting your treatment with Cayston. Read the manufacturer's instructions for use provided with your Altera Nebuliser System carefully.

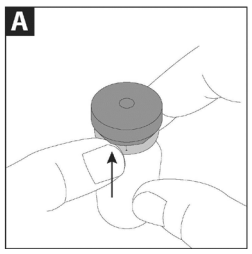
Preparing your Cayston for inhalation

- Do not prepare Cayston until you are ready to administer a dose.
- Do not use Cayston if you notice that the package has been tampered with.
- Do not use Cayston if it has been stored outside a refrigerator for more than 28 days.
- Do not use the solvent or prepared Cayston if it is cloudy or if there are particles in the solution.

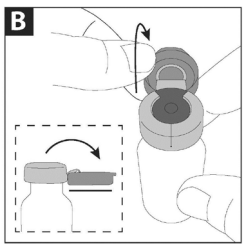
1. **Take one amber vial of Cayston and one ampoule of solvent** from the box. Solvent ampoules must be separated by gently pulling them apart.

2. **Gently tap the amber vial** containing the Cayston so that the powder settles at the bottom. This helps to ensure that you get the proper dose of medicine.

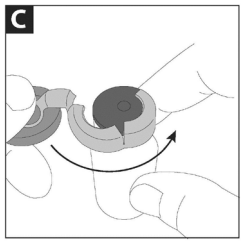
3. **Follow Step A to D in Figure 1 below to open the amber vial:**



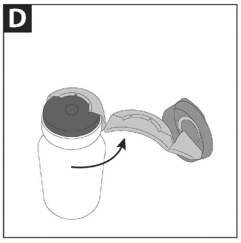
Step A: With the blue cap tab facing toward you, place the vial on a flat surface. Using one hand to hold the vial steady, use the other hand to slowly flip up the blue cap.



Step B: Pull the blue cap down to a flat (horizontal) position (where the bottom of the blue cap faces up), to prepare the metal seal for removal. Do not completely tear through the metal seal.



Step C: While continuing to hold the vial steady with one hand, use the other hand to slowly pull the blue cap in a counterclockwise direction. Do not twist the blue cap.



Step D: When the metal seal opens, continue to slowly pull on the blue cap in a counterclockwise direction until the metal seal is completely removed.

Figure 1

4. Safely dispose of the metal seal. Carefully remove (but do not yet discard) the rubber stopper.

5. **Open the ampoule of solvent** by twisting off the tip. Squeeze out the contents completely into the vial (Figure 2). Next, gently swirl the vial until the powder has completely dissolved and the liquid is clear.

It's best to use Cayston immediately after you have made up the solution. But, if you cannot use the prepared dose straight away, replace the stopper in the vial and store in a refrigerator. Use the prepared solution within 8 hours.

Figure 2

Preparing the Altera Nebuliser to take your Cayston

1. **Make sure the Altera Nebuliser Handset** is on a flat, stable surface.

2. **Remove the medicine cap** by twisting anticlockwise.

3. **Pour all of the prepared Cayston from the vial** into the Altera Nebuliser Handset medicine reservoir (Figure 3a). Be sure to completely empty the vial. Gently tap the vial against the side of the medicine reservoir if necessary.

4. **Close the medicine reservoir** by aligning the tabs of the medicine cap with the slots on the reservoir. Press down and turn the cap clockwise as far as it will go (Figure 3b).

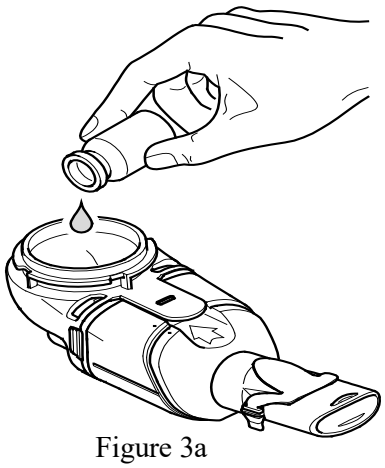


Figure 3a

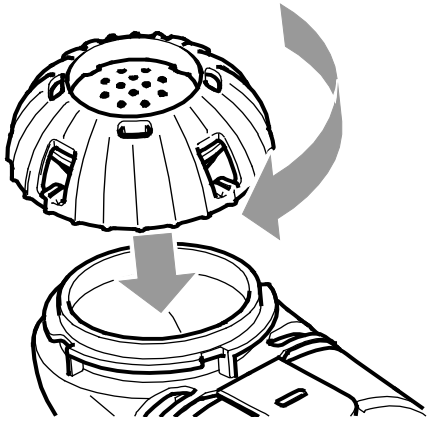


Figure 3b

Using the Altera Nebuliser to take your Cayston

1. **Begin your treatment.** Sit in a relaxed, upright position. Hold the handset level and place the mouthpiece in your mouth and close your lips around it (Figure 4).

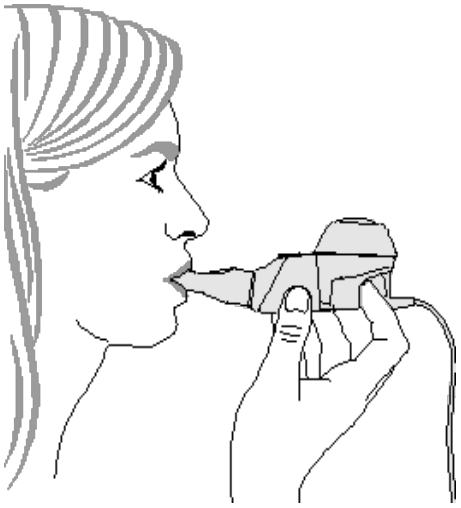


Figure 4

Keep the handset level.

2. **Press and hold the On/Off button** on the Control Unit for a few seconds. You will hear one "beep" and the status light will turn green.

3. **After a few seconds,** an aerosol mist will begin to flow into the Aerosol Chamber of the Altera Nebuliser Handset. If aerosol mist does not begin to flow, please refer to the Altera manual for information.

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

5. **When all of the medicine has been delivered,** you will hear a tone that means "treatment complete" (2 beeps).

6. **When treatment is complete,** open the medicine cap to ensure that all medicine has been used. A few drops of medicine may remain in the reservoir at the end of treatment. If there is more than a few drops of liquid left, replace the medicine cap and restart treatment.

7. **Once treatment is complete,** disconnect the Control Unit and take apart the Altera Nebuliser Handset for cleaning and disinfecting. For complete details on cleaning and disinfecting refer to the manufacturer's instructions for use provided with your Altera Nebuliser Handset.

What if I need to stop my treatment before I've finished?

8. If for any reason you must stop the treatment before you have finished, press and hold the On/Off button for one full second. To re-start the treatment, press and hold the On/Off button for one full second and then restart the treatment.

Replacing the Altera Nebuliser Handset

The Altera Nebuliser Handset is designed to last for three 28-day courses of Cayston when used as directed. After this time replace your Altera Nebuliser Handset, including the aerosol head. If you notice that the performance has changed before this time (for instance, if it takes longer to produce a mist, more than 5 minutes), please refer to the Altera Nebuliser instructions for use.

If you take more Cayston than you should

If you have taken more Cayston than you should, talk to a doctor or pharmacist immediately.

If you forget to take Cayston

If you miss a dose, you can still take all 3 daily doses as long as they are at least 4 hours apart. If you can't leave a gap of 4 hours just skip the missed dose.

If you stop taking Cayston

Do not stop taking Cayston without first talking to your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you get a rash, tell your doctor immediately because this could mean that you have an allergic reaction to Cayston.

Very common side effects (affects more than 1 user in 10)
- Cough
- Blocked nose
- Wheezing
- Sore throat
- Shortness of breath
- High temperature. This may be more common in children than in adults.

Common side effects (affects 1 to 10 users in 100)
- Difficulty breathing
- Chest discomfort
- Runny nose
- Coughing up blood
- Rash

- Joint pain
- Lower lung function test results

Uncommon side effects (affects 1 to 10 users in 1000)
- Joint swelling

The following side effects have been observed after the use of aztreonam for injection, but not after taking Cayston: swelling of the face, lips, tongue and/or throat with difficulty in swallowing or breathing, sweating, skin irritation and flaking, itchy rash, flushing, small red spots and very rarely, blistering of the skin. All these may be signs of an allergic reaction.

Tell your doctor if you have any of these effects.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Cayston

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial label, solvent ampoule and the carton. The expiry date refers to the last day of that month.

Powder vial and solvent ampoule:
Store in a refrigerator (2°C - 8°C). The unopened vials may also be stored outside the refrigerator but below 25°C for up to 28 days.

Use this medicine immediately after preparation. If not used immediately, the prepared solution must be stored at 2°C - 8°C and used within 8 hours. Do not prepare more than one dose at a time.

Do not use this medicine if you notice that the package has been tampered with.

Do not use this medicine if it has been stored outside a refrigerator for more than 28 days.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Cayston and the solvent contain

- The powder vial contains 75 mg aztreonam (as lysine).
- The solvent ampoule contains water for injections and sodium chloride. The ampoule is imprinted in English only. The information that appears on the ampoule is presented below:

Solvent for Cayston Sodium Chloride 0.17%
Inhalation use only
1 ml
GILEAD SCIENCES

What Cayston looks like and contents of the pack

Cayston is a white to off-white powder and solvent for nebuliser solution.

Cayston is contained in a 2 ml amber glass vial with a grey rubber stopper and aluminium tear-off overseal with a blue cap.

The 1 ml solvent is contained in a plastic ampoule.

Each 28-day pack of Cayston contains 84 vials of lyophilised Cayston and 88 solvent ampoules. The four additional solvent ampoules are provided in case of spillage.

The following pack sizes are available:
- 28-day pack of Cayston
- Pack containing one 28-day pack of Cayston plus one Altera Nebuliser Handset

Not all pack sizes may be marketed.

Marketing Authorisation Holder:

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

Manufacturer:

Gilead Sciences Ireland UC
IDA Business & Technology Park
Carrigtohill
County Cork
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Gilead Sciences Belgium SRL-BV
Tél/Tel: + 32 (0) 2 401 35 50

България
Gilead Sciences Ireland UC
Тел.: + 353 (0) 1 686 1888

Česká republika
Gilead Sciences s.r.o.
Tel: + 420 910 871 986

Danmark
Gilead Sciences Sweden AB
Tlf: + 46 (0) 8 5057 1849

Deutschland
Gilead Sciences GmbH
Tel: + 49 (0) 89 899890-0

Lietuva
Gilead Sciences Ireland UC
Tel: + 353 (0) 1 686 1888

Luxembourg/Luxemburg
Gilead Sciences Belgium SRL-BV
Tél/Tel: + 32 (0) 2 401 35 79

Magyarország
Gilead Sciences Ireland UC
Tel: + 353 (0) 1 686 1888

Malta
Gilead Sciences Ireland UC
Tel: + 353 (0) 1 686 1888

Nederland
Gilead Sciences Netherlands B.V.
Tel: + 31 (0) 20 718 36 98

Eesti
Gilead Sciences Ireland UC
Tel: + 353 (0) 1 686 1888

Ελλάδα
Gilead Sciences Ελλάς Μ.ΕΠΕ.
Τηλ: +30 210 8930 100

España
Gilead Sciences, S.L.
Tel: + 34 91 378 98 30

France
Gilead Sciences
Tél: + 33 (0) 1 46 09 41 00

Hrvatska
Gilead Sciences Ireland UC
Tel: + 353 (0) 1 686 1888

Ireland
Gilead Sciences Ireland UC
Tel: +353 (0) 214 825 999

Ísland
Gilead Sciences Sweden AB
Sími: + 46 (0) 8 5057 1849

Italia
Gilead Sciences S.r.l.
Tel: + 39 02 439201

Κύπρος
Gilead Sciences Ελλάς Μ.ΕΠΕ.
Τηλ: + 30 210 8930 100

Latvija
Gilead Sciences Ireland UC
Tel: + 353 (0) 1 686 1888

Norge
Gilead Sciences Sweden AB
Tlf: + 46 (0) 8 5057 1849

Österreich
Gilead Sciences GesmbH
Tel: + 43 1 260 830

Polska
Gilead Sciences Poland Sp. z o.o.
Tel: + 48 22 262 8702

Portugal
Gilead Sciences, Lda.
Tel: + 351 21 7928790

România
Gilead Sciences (GSR) S.R.L.
Tel: +40 31 631 18 00

Slovenija
Gilead Sciences Ireland UC
Tel: + 353 (0) 1 686 1888

Slovenská republika
Gilead Sciences Slovakia s.r.o
Tel: + 421 232 121 210

Suomi/Finland
Gilead Sciences Sweden AB
Puh/Tel: + 46 (0) 8 5057 1849

Sverige
Gilead Sciences Sweden AB
Tel: + 46 (0) 8 5057 1849

United Kingdom (Northern Ireland)
Gilead Sciences Ireland UC
Tel: + 44 (0) 8000 113700

This leaflet was last revised in .

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.