

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

Cayston contains aztreonam lysine (formed *in situ* from 75 mg aztreonam) as a sterile lyophilised powder in a vial and a 1 ml ampoule of sterile solvent (0.17% w/v sodium chloride). After reconstitution of the powder in the solvent, the nebuliser solution contains 75 mg aztreonam (as lysine).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for nebuliser solution.

White to off-white, lyophilised 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 18 years and older.

The primary support for this indication is based on two single 28-day course placebo-controlled studies. The data to support the sustainability of the observed short term benefit over subsequent courses of treatment are limited (see section 5.1). Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Patients should use a bronchodilator before each dose of Cayston. Short acting bronchodilators can be taken between 15 minutes and 4 hours and long acting bronchodilators can be taken between 30 minutes and 12 hours prior to each dose of Cayston.

For patients receiving several respiratory therapies, the recommended order is:

1. bronchodilator
2. dornase alfa
3. chest physiotherapy
4. other inhaled medicinal products
5. Cayston.

Adults

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.

Multiple course, controlled efficacy data are not yet available (see section 5.1). Additional courses, beyond the initial 28-day course, should be considered only at the discretion of the physician. If additional courses are prescribed, a minimum of 28 days without Cayston is recommended.

Paediatric population

Cayston is not recommended for use in children below the age of 18 years due to insufficient data on safety and efficacy (see section 5.1).

Elderly population

Clinical studies with Cayston did not include sufficient numbers of patients aged 65 years and over to determine whether they responded 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.

Method of administration

Cayston is only for inhalation use.

Cayston should only be used with the Altera Nebuliser Handset and Altera Aerosol Head connected to an Altera Control Unit 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.

4.4 Special warnings and precautions for use

Allergic reactions

If an allergic reaction to Cayston 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 Cayston.

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, although these have not been observed to date with Cayston, 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 is a complication associated with nebulised therapies. Patients were pre-treated with a bronchodilator before dosing with study therapy. An acute reduction of $\geq 15\%$ in forced expiratory volume in 1 second (FEV₁) following administration of study therapy was observed in 3% of patients treated with Cayston and 4% of patients receiving placebo despite pre-treatment with a bronchodilator before dosing with study therapy. 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).

Other precautions

In clinical studies, the efficacy and safety of Cayston were not tested in patients with FEV₁ % predicted < 25% or > 75%. 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.

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. In clinical studies of Cayston, no increases of clinical significance were observed in the prevalence of antibiotic-resistant *P. aeruginosa* or other bacterial respiratory pathogens among patients treated three times daily with Cayston. Among patients with multidrug-resistant *P. aeruginosa*, improvements in respiratory symptoms and pulmonary function were observed following treatment with Cayston. An increased prevalence of *Aspergillus* and *Candida* species were observed over time in patients treated with several Cayston treatment courses. The clinical significance of this finding is unknown.

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 Cayston 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 Pregnancy and lactation

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.

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.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, based on the safety profile and mechanism of action, Cayston is not expected to adversely affect the ability to drive or use machines.

4.8 Undesirable effects

The safety of Cayston was evaluated in three Phase 3 studies in 344 predominantly adult patients (77%) with chronic *P. aeruginosa*. In two Phase 3 placebo-controlled studies patients received Cayston 75 mg 2 times (69 patients) or 3 times a day (146 patients) for 28 days. In one Phase 3 open-label follow-on study 274 CF patients received up to nine 28-day treatment courses of Cayston 75 mg 2 times or 3 times a day.

The adverse reactions with suspected (at least possible) relationship to treatment in the placebo-controlled studies are listed below by body system organ class and frequency.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Frequencies are defined as follows: very common ($\geq 1/10$) and common ($\geq 1/100$ to $< 1/10$).

Respiratory, thoracic and mediastinal disorders

Very common: wheezing, cough, pharyngolaryngeal pain, nasal congestion

Common: non-allergic bronchospasm, chest discomfort, rhinorrhoea

Skin and subcutaneous tissue disorders

Common: rash

General disorders and administration site conditions

Very common: pyrexia

The following rare and severe adverse reactions, although these have not been observed to date with Cayston, have been reported after parenteral use of other aztreonam containing products: toxic epidermal necrolysis, anaphylaxis, purpura, erythema multiforme, exfoliative dermatitis, urticaria, petechiae, pruritus, diaphoresis.

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 $\mu\text{g/ml}$, compared to serum levels of 54 $\mu\text{g/ml}$ following administration of aztreonam for injection (500 mg), no safety issues associated with Cayston 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/integrin 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 generally have little or no 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 a 28-day course of 75 mg 3 times a day Cayston therapy resulted in clinically important improvements in respiratory symptoms, pulmonary function, and sputum *P. aeruginosa* CFU density, regardless of whether the highest aztreonam MIC for *P. aeruginosa* was above or below the established susceptibility breakpoint for intravenous aztreonam administration (8 µg/ml). Based on categorical analyses of the relationship between MIC and treatment response, a susceptibility breakpoint for Cayston cannot be established. Over 6 courses of Cayston therapy, *P. aeruginosa* MIC₅₀ and MIC₉₀ did not change (± 2 dilution change), however there is a theoretical risk that patients treated with Cayston may develop *P. aeruginosa* isolates resistant to aztreonam or other beta-lactam antibiotics.

In studies of up to six 28-day courses of Cayston therapy, no increases of clinical significance have been observed in the treatment-emergent isolation of other bacterial respiratory pathogens (*Stenotrophomonas maltophilia*, *Alcaligenes xylosoxidans*, and *Staphylococcus aureus*).

Clinical Experience:

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 FEV₁ % predicted between 25% and 75% and chronic *P. aeruginosa* lung infection. Overall, 344 predominantly adult patients (77%) were treated in these studies. Studies were conducted using the Altera Nebuliser System.

CP-AI-007

CP-AI-007 enrolled 164 adult (predominantly) and paediatric patients randomised in a 1:1 ratio comparing inhaled 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 Cayston 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.

Cayston therapy 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 Cayston and 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 six 28-day courses of therapy, measures of pulmonary function (FEV₁), CFQ-R respiratory symptoms scores, and log₁₀ *P. aeruginosa* CFUs 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.

This medicinal product has been authorised under a so-called “conditional approval” scheme.

This means that further evidence on this medicinal product is awaited.

The European Medicines Agency (EMA) will review new information on the product every year and this SPC will be updated as necessary.

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 Cayston on 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 Cayston (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 Cayston 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.

Elimination

The elimination half-life of aztreonam from serum is approximately 2.1 hours following inhalation administration, similar to what has been reported for aztreonam for injection. Systemically absorbed aztreonam is eliminated by both 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 Cayston.

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.

5.3 Preclinical safety data

A 104-week rat inhalation toxicology study to assess the carcinogenic potential of ascending doses (31, 56 and 120 mg/kg/day) of Cayston demonstrated no drug-related increase in malignant tumours. The only evidence of Cayston-related carcinogenicity was a small increase in the incidence of benign C-cell adenomas in females at 120 mg/kg/day. The clinical relevance of this effect is unknown. No such added effect was observed at 56 mg/kg/day in which exposures exceeded 2.2 to 9 times the human exposure, based on AUC or C_{max} respectively.

Genotoxicity (Chromosomal aberration and mouse lymphoma mutation assay) studies with aztreonam were negative indicating that the mechanism of benign C-cell adenomas in female rats was not genotoxically mediated.

Fertility, teratology, perinatal and postnatal studies were conducted with aztreonam for 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 vial

L-Lysine

Solvent ampoule
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: 2 years.

Solvent: 4 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 reconstituted 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.

Solvent: 1 ml low density polyethylene 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.

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 flipping up the metal tab, the metal ring is removed by carefully pulling the tab (tweezers or small pliers may be used to remove the metal ring if necessary) and the grey rubber stopper removed. 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 an Altera Nebuliser System (consisting of a Cayston specific Altera Nebuliser Handset and Altera Control Unit). Cayston should only be used with the Altera Nebuliser Handset and Altera Aerosol Head connected to an Altera Control Unit 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 International Limited
Granta Park
Abington
Cambridge
CB21 6GT
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/543/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 September 2009

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

- A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**
- C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER**

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

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

B. CONDITIONS OF THE MARKETING AUTHORISATION

• CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

Medicinal product subject to medical prescription.

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

Not applicable.

• OTHER CONDITIONS

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, as described in version 1.0 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 1.0 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER

The Marketing Authorisation Holder shall complete the following programme of studies within the specified time frame. The results of which shall be taken into account in the risk benefit balance during the assessment of the application for a renewal.

Clinical aspects

1. The applicant commits to submit the results of study GS-US-205-0110 and other available long term data by July 2010.

2. Ongoing studies (ages 6 years and older):

Study GS-US-205-0110: Open-label, randomized Phase 3 study to evaluate the efficacy and safety of AZLI *versus* Tobramycin Nebulizer Solutions (TNS) in an intermittent aerosolized regimen in patients with CF. The final clinical study report will be available by July 2010.

Study GS-205-0117: Phase 3, double-blind, multi-center, multinational randomized, placebo-controlled trial evaluating AZLI in patients with cystic fibrosis, mild lung disease, and PA. The final clinical study report will be available by December 2009.

A review of all paediatric data from controlled studies will be provided by September 2010.

The applicant commits to a paediatric development of the product consisting of well controlled trials to support short-term and long-term repeated use in this patient group. Protocols will be drafted by March 2010 (after availability of results from GS-US-205-0110), with the studies anticipated to be completed within 3 years following finalisation of the protocol.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER 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

84 single-use vials

88 single-use 1 ml ampoules of solvent

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For inhalation use only. Reconstitute before use.

Read the package leaflet before use.

Powder should only be mixed with the solvent provided.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C). 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

Do not dispose of medicines via wastewater or household waste. Ask your pharmacist about proper disposal of medicines.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences International Ltd
Granta Park
Abington
Cambridge
CB21 6GT
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/543/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Cayston 75 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

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

For inhalation use only. Reconstitute before use.

Read the package leaflet before use.

Powder should only be mixed with the solvent provided.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C). 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

Do not dispose of medicines via wastewater or household waste. Ask your pharmacist about proper disposal of medicines.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences International Ltd
Granta Park
Abington
Cambridge
CB21 6GT
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/543/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

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.

- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Cayston is and what it is used for
2. Before you take Cayston
3. How to take Cayston
4. Possible side effects
5. How to store Cayston
6. Further information

1. WHAT CAYSTON IS AND WHAT IT IS USED FOR

Cayston is an antibiotic used to suppress chronic lung infection caused by the bacteria *Pseudomonas aeruginosa* in adult patients 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. BEFORE YOU TAKE CAYSTON

Do not take Cayston

- **if you are allergic** (hypersensitive) to aztreonam or any of the other ingredients of Cayston.

Take special care with Cayston

Your doctor needs to know:

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

Cayston is not for use in children under the age of 18.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding

It is important to tell your doctor if you are breast-feeding, if you are pregnant or planning to become pregnant, or when you think you are pregnant. Your doctor will help you decide what is best for you and your child.

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.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

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

3. HOW TO TAKE CAYSTON

Always take Cayston exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

- **Take Cayston 3 times a day for the 28-day treatment course.** 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 Altera Control Unit 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 therapies to treat cystic fibrosis, the recommended order is as follows:

1. bronchodilator
 2. dornase alfa (a medicine that helps to dissolve the thick mucous produced in the lungs)
 3. chest physiotherapy
 4. any other inhaled medicines
- and finally:
5. 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
- One plastic ampoule of solvent (0.17% w/v sodium chloride)
- An Altera Nebuliser Handset containing an Altera Aerosol Head connected to an Altera Control Unit (678G) or an eFlow rapid Control Unit (178G)

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).

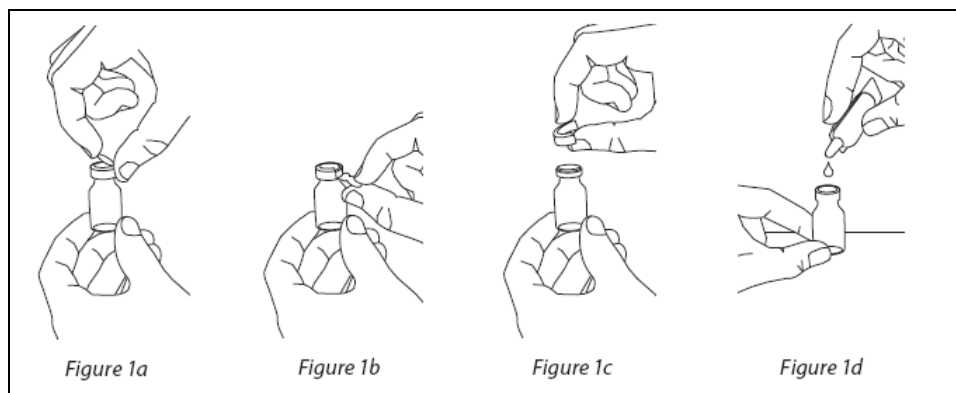
Check that your nebuliser works properly before starting your treatment with Cayston. Read the manufacturer's instructions for use provided with your Altera Nebuliser System carefully.

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. **Open the amber 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.
4. **Open the ampoule of solvent** by twisting off the tip. Squeeze out the contents completely into the vial (Figure 1d). 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.



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 2a). 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 2b).

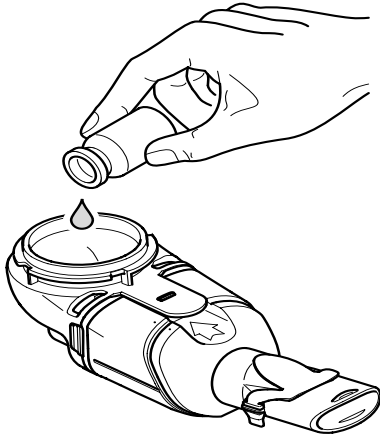


Figure 2a

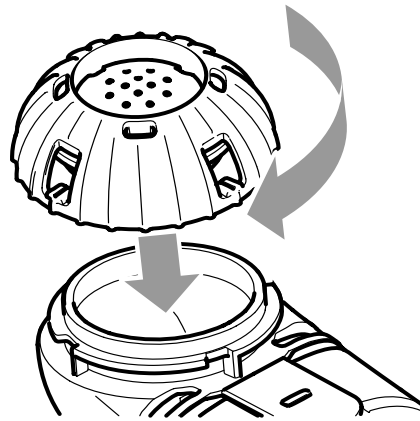


Figure 2b

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 3).

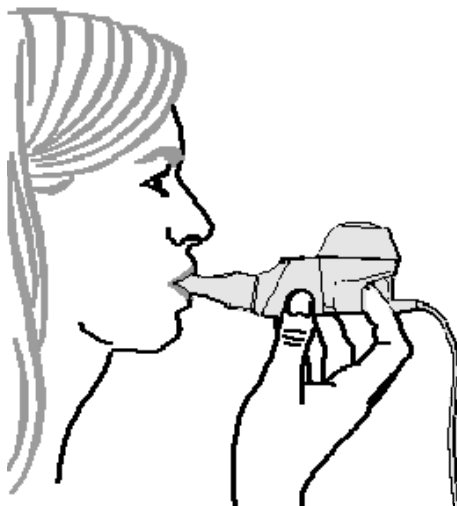


Figure 3

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 want to 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 product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Cayston 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.

The frequency of possible side effects listed below is defined using the following convention:

very common (affects more than 1 user in 10)

common (affects 1 to 10 users in 100)

uncommon (affects 1 to 10 users in 1,000)

rare (affects 1 to 10 users in 10,000)

very rare (affects less than 1 user in 10,000)

not known (frequency cannot be estimated from the available data).

Very common side effects

- Cough
- Wheezing
- Sore throat
- Blocked nose
- High temperature

Common side effects

- Difficulty breathing
- Runny nose
- Rash
- Chest discomfort

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.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CAYSTON

Keep out of the reach and sight of children.

Do not use Cayston 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 Cayston 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 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.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Cayston and the solvent contain

- The powder vial contains 75 mg aztreonam (which is the active substance) as lysine.
- The solvent ampoule contains water for injections and sodium chloride.

What Cayston looks like and contents of the pack

Cayston is a sterile, white to off-white, lyophilised powder.

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

The 1 ml solvent is contained in a plastic ampoule.

Each carton of Cayston contains a 28-day supply. This consists of:

- 84 vials of Cayston
- 88 ampoules of 1 ml solvent. The four extra solvent ampoules are in case of spillage.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

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Manufacturer:

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This leaflet was last approved in {MM/YYYY}.

This medicine has been given “conditional approval”.

This means that there is more evidence to come about this medicine.

The European Medicines Agency (EMA) will review new information on the medicine every year and this leaflet will be updated as necessary.

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