The format of this leaflet was defined by the Ministry of Health and its content was checked and approved by the Ministry of Health in March 2014 and updated according to the guidelines of the Ministry of Health in November 2019.

Cayston®

1. NAME OF THE MEDICINAL PRODUCT

Cayston®.

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.

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 $\geq$ 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 ($\geq$ 1/10), common ($\geq$ 1/100 to < 1/10) and uncommon ($\geq$ 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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il
Additionally, adverse events can be reported directly to the registration holder by email to DrugSafety.Israel@gilead.com.

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 aztreonam experienced 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.

Aztreonam 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 aztreonam 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 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 aztreonam as 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.

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 aztreonam 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 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.

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 aztreonam dose 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 aztreonam demonstrated 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
Lysine monohydrate

Solvent
Water for injection
Sodium chloride

6.2 Incompatibilities

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

6.3 Shelf life

The expiry date of Cayston and solvent are indicated on the packaging materials.

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:

- Pack containing one 28-day pack of Cayston plus one Altera Nebuliser Handset

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. MANUFACTURER

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

8. REGISTRATION HOLDER

Gilead Sciences Israel Ltd.
4 HaHarash Street,
Hod Hasharon Business Park,
Hod Hasharon,
4524075
Israel

Reference: EU label from April 2019.

Date of leaflet update	Sections updated	Reference for update	Comments
February 2019	4.4 Special warnings and precautions for use 4.8 Undesirable effects 5.1 Pharmacodynamic properties 5.2 Pharmacokinetic properties 6.3 Shelf life	EU label from May 2018	
November 2019	6.5 Nature and contents of container 6.6 Special precautions for disposal and other handling	EU label from April 2019	

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