SUMMARY OF RISK MANAGEMENT PLAN FOR CAYSTON (AZTREONAM)

This is a summary of the risk management plan (RMP) for Cayston. The RMP details important risks of Cayston, how these risks can be minimized, and how more information will be obtained about Cayston's risks and uncertainties (missing information).

Cayston's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Cayston should be used.

This summary of the RMP for Cayston should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Cayston's RMP.

1. The Medicine and What is it Used for

Cayston is authorized for the suppressive therapy of chronic pulmonary infections due to Pseudomonas aeruginosa in patients with cystic fibrosis (CF) aged ≥ 6 years (see SmPC for the full indication). It contains aztreonam as the active substance and it is given by inhalation.

Further information about the evaluation of Cayston's benefits can be found in Cayston's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000996/human_med_000686.jsp&mid=WC0b01ac058001d124

2. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of Cayston, together with measures to minimize such risks and the proposed studies for learning more about Cayston's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the public (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

2A. List of important risks and missing information

Important risks are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of the medicinal product. Potential risks are concerns for which an association with the use of the medicinal product is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 1. List of Important Risks and Missing Information

Important Identified Risks	None
Important Potential Risks	Toxic epidermal necrolysis
	Development of resistance (with clinical sequelae) to aztreonam and other antibiotics
Missing Information	None

2B. Summary of Important Risks

Cayston has been assigned the legal status of a medicine subject to medical prescription in the European Union (EU), whereby therapy should be initiated by a doctor experienced in the management of Cystic Fibrosis (as described in section 4.2 of the SmPC).

Table 2. Summary of Important Risk(s) and Missing Information

Important Identified Risks	**None**
Important Potential Risks	**Toxic epidermal necrolysis**
Evidence for linking the risk to the medicine	Study reports for CP-AI-003, CP-AI-005, CP-AI-007, CP AI 006, GS US 205 0117, EA-US-205-0111, and GS US 205 0110.
Risk factors and risk groups	Risk factors for hypersensitivity reactions to AZLI may include: • Hypersensitivity to IV aztreonam • Hypersensitivity to β-lactam antibiotics • Increased age (because of corresponding increased cumulative antibiotic exposure {Wills 1998}) Animal and human data demonstrate a low risk of cross-reactivity between aztreonam and the β-lactams (penicillins, cephalosporins, and carbapenems) {Adkinson 1990}, {Jensen 1991}, although cross-reactivity may be expected based on the structural similarities between the classes. Aztreonam does not have a bicyclic core structure, unlike the β-lactams, and is considered to be only weakly immunogenic.

	Pre-existing hypersensitivity to β-lactams, as determined by retrospective clinical review of medical history case report forms, was reported for 20% of patients (75/375) in the Phase 3 placebo-controlled registration studies (CP-AI-005 and CP-AI-007), 24% of patients (65/274) in Study CP-AI-006, and 19% of patients (30/157) in Study GS-US-205-0117. Among patients treated with AZLI in the Phase 3 placebo-controlled, registration studies, occurrence of the following AEs were statistically significant ($p < 0.05$; Fisher's exact test) between patients with pre-existing hypersensitivity to β-lactams vs. patients without pre-existing hypersensitivity, respectively: cough (80% vs. 53%), dizziness (8% vs. 1%), dyspnea (23% vs. 7%), herpes simplex (5% vs. 0%), nausea (13% vs. 2%), non-cardiac chest pain (10% vs. 2%), pyrexia (26% vs. 9%), rash (8% vs. 1%), and stomatitis (8% vs. 0%). Formal analyses of the safety profile of AZLI in patients with or without a history of allergy to β-lactam antibiotics were also conducted following the completion of open-label Study CP-AI-006. Few drug-related AEs that may reflect allergic reactions were reported. No drug-related AEs of bronchospasm or hypersensitivity were reported. The incidence of drug-related rash in Study CP-AI-006 was higher in the subgroup of patients with pre-existing allergies to β-lactams than in those without (3.1% vs. 0.5%). However, the incidences of arthralgia (1.5% vs. 3.8%) and wheezing (0% vs. 3.3%) were higher in the subgroup of patients without pre-existing allergies to β-lactams. The incidence of pyrexia was similar among patients with a history of allergy to β-lactams and those without (1.5% vs. 1.4%) in Study CP-AI-006. The incidences of AEs (identified in CP-AI-006) that occurred among AZLI-treated patients with pre-existing hypersensitivity to β-lactams vs. patients without pre-existing hypersensitivity in Study GS-US-205-0117 were: cough (73% vs. 39%), dizziness (7% vs. 7%), nausea (0% vs. 3%), pyrexia (13% vs. 7%), arthralgia (7% vs. 2%), and wheezing (7% vs. 7%). Data from these analyses must be interpreted with caution, as assignment to the allergy subgroups is based solely on the patients' self-reported medical histories. In addition, the risk of allergy increases with increased exposure to β-lactams and increased exposure may reflect a greater severity of underlying CF disease. Furthermore, some symptoms of allergic reactions may overlap with those of pulmonary exacerbations. Thus, any differences in AE incidence rates between CF patients with or without a history of allergy to β-lactam antibiotics may reflect differences in the severity of underlying CF disease in the 2 groups rather than a difference in the safety profile of AZLI. There have been isolated case reports of immediate hypersensitivity to aztreonam in patients with a history of hypersensitivity to penicillin {de la Fuente Prieto 1993}, {Hantson 1991}, {Soto Alvarez 1990}. As aztreonam shares a common R-group side chain with ceftazidime, a proportion of patients with ceftazidime allergy would be expected to cross-react. In a retrospective study by Burrows et al., 4 out of 51 patients (8%) exposed to both aztreonam and ceftazidime were allergic to both antibiotics {Burrows 2007}. Cooper reported a single case report of fixed drug eruption due to aztreonam and ceftazidime cross-reactivity in a CF patient {Cooper 2010}. In an open clinical trial, IV aztreonam was administered repeatedly to 15 CF patients (mean age 20 years [range 11 to 33 years]; 60% females) who had no previous exposure or hypersensitivity to aztreonam (demonstrated by negative skin-prick test and lack of reaction to an IV test dose) {Jensen 1991}. However, the patients did have a history of severe hypersensitivity reactions (including anaphylactic shock, generalized urticaria, and drug-associated fever) to 1 or more β-lactam antibiotics. A total of 56 14-day courses of aztreonam were administered. No type 1 hypersensitivity reactions (IgE-mediated hypersensitivity) occurred although a low and transient increase in levels of hepatic enzymes was observed

	during therapy in 4 patients. Two of these 4 patients developed hypersensitivity reactions after repeated courses of aztreonam and discontinued aztreonam. The first patient developed drug-associated fever at the end of his third course and on rechallenge with aztreonam, this patient developed a fever (39 ºC) within 48 hours, along with a severe headache and transient rash. The second patient developed drug-associated fever at the end of her fourth course; however, she did not receive the drug again, as no further anti-pseudomonal treatment was required. A similar multicenter trial was conducted in 19 CF patients (mean age 22.5 years [range 5 to 39]; 53% females) with well documented allergies to penicillin and/or cephalosporin antibiotics {Moss 1991}. All patients had a history of at least 1 systemic immediate hypersensitivity reaction to a β-lactam antibiotic. All patients had received several courses of β-lactam antibiotics before experiencing an allergic reaction. Six patients had prior exposure to aztreonam. Eighteen of the 19 patients had negative skin tests with aztreonam and were treated with IV aztreonam for 10 to 21 days, along with tobramycin and other therapy as clinically indicated. Seventeen patients tolerated aztreonam well; the other patient, who had an allergy to ticarcillin, developed bronchospasm and was withdrawn from treatment. Two patients who were successfully treated with aztreonam during the study developed systemic allergic reactions to subsequent courses; 1 of the patients had an allergy to piperacillin, the other an allergy to ceftazidime.
Risk Minimization Measure(s)	Routine risk minimization measures: SmPC Section 4.4, and 4.8 Additional risk minimization measures: None
Important Potential Risk	**Development of resistance (with clinical sequelae) to aztreonam and other antibiotics**
Evidence for linking the risk to the medicine	Study reports for CP-AI-003, CP-AI-005, CP-AI-007, CP AI 006, GS US 205 0117, EA-US-205-0111, GS US 205 0110, GS-US-205-0160 and GX-US-205-0128.
Risk factors and risk groups	Antibiotic monotherapy Prolonged, multiple courses of antibiotic therapy
Risk Minimization Measure(s)	Routine risk minimization measures: SmPC Section 4.4, and 5.1 Additional risk minimization measures: None
Missing Information	None

2C. Post-authorization Development Plan

2C.1 Studies which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Cayston.

2C.2 Other Studies in Post-Authorization Development Plan

There are no other studies required for Cayston.