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Committee for Medicinal Products for Human Use (CHMP)

Cayston

(Aztreonam lysine)

Procedure No: EMEA/H/C/000996/P46/032

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. INTRODUCTION

On 28 May 2013, the MAH submitted a completed paediatric study for Cayston 75 mg in accordance with article 46 of Regulation (EC) No 1901/2006.

2. SCIENTIFIC DISCUSSION

2.1. Information on the development program

The commercially available formulation of Cayston was used in the study.

2.2. Clinical aspects

Study EA-US-205-0122 was an expanded access program conducted in Canada. The primary objective of this program was to provide expanded access to Cayston to Canadian patients with cystic fibrosis (CF) and chronic *Pseudomonas aeruginosa* (PA) infection who had limited treatment options and were at risk for disease progression. Although Study EA-US-205-0122 was not part of the agreed Cayston Paediatric Investigation Plan (EMEA-000827-PIP01-09-M01), it did include three paediatric patients.

The MAH did not propose any SmPC changes.

Description

Study EA-US-205-0122 was an expanded access program conducted in Canada. This was an open-label program with no formal hypothesis testing planned. Only safety data were collected.

Methods

Objectives

The primary objective of this study was as follows: To provide expanded access to CAYSTON to Canadian patients with CF and chronic PA infection who have limited treatment options and are at risk for disease progression prior to commercial availability and establishment of reimbursement programs through Provincial Ministries of Health.

Study design

This was an open-label, expanded access program of Cayston for patients with CF and PA airway infection who had limited treatment options and were at high risk for disease progression. Subjects who met the inclusion/exclusion criteria were enrolled in the study and received Cayston 75 mg TID in 56-day cycles of therapy (28 days on Cayston followed by 28 days off) until 1 of the following events occurred: voluntary withdrawal from study, the investigator requested withdrawal for subject benefit, death, New Drug Submission approval by Health Canada and reimbursement programs were available through Provincial Ministries of Health, or until study termination by Gilead.

Study population /Sample size

Forty-five patients - who had forced expiratory volume in 1 second predicted (FEV_1 %) being <50%, aged ≥6 years with CF and chronic PA infection who were at high risk for disease progression were included in the expanded program (table 1). This program included four adults patients from the open label study CP-AI-006. The other 41 patients were not enrolled in any Cayston trial before.

Table 1. Overview of Study EA-US-205-0122

Study (Module 5 Reference)	Design	Geographic Location	Study Population	Treatment	Subjects Treated	Duration
EA-US-205-0122 (m5.3.5.2)	Open-label, multicenter, expanded access program for Canadian subjects with CF and *PA* airway infection.	5 sites in Canada	Subjects ≥ 6 years of age with CF and chronic *PA* airway infection who had limited treatment options and were at risk for disease progression.	AZLI 75 mg 3 times daily	Total: 45 subjects 0 subjects aged 6 to 12 years 3 subjects aged 13 to 17 years 42 subjects aged ≥ 18 years	Up to 17 treatment cycles of 28 days, each followed by a 28-day off-treatment period

Treatment
Patients who met the inclusion/exclusion criteria could receive Cayston 75 mg 3 times daily in 56-day cycles of therapy (28 days on Cayston followed by 28 days off) until 1 of the following events occurred: voluntary withdrawal from study, the investigator requested withdrawal for patient benefit, death, new drug submission approval by Health Canada and reimbursement programs were available through Provincial Ministries of Health, or the study was terminated the MAH.

2.3 Results
Only three paediatric patients (one patient aged 13 years (F, Asian) and two patients aged 17 years (M,F, Caucasian)), receiving at least 1 dose of Cayston, were enrolled of which two completed the program. The remaining 42 patients in the study were between the ages of 18 and 65 years. Overall, thirty-four patients (75.6%) completed the study.

Of the 3 paediatric patients one patient - eligible for lung transplant - had a FEV_1 % predicted of 28%. The two other patients had a FEV_1 % predicted of 110% and 47% respectively. All three patients were treatment compliant.

Overall thirteen patients who were eligible for lung transplant had a mean (SD) FEV_1 % predicted at baseline of 30.69%, with all but one of the patients having baseline FEV_1 ≤50% predicted: 11 patients with a baseline FEV_1 ≤40% predicted and 1 patient with baseline FEV_1 >40% and ≤50% predicted.

For those patients who were not eligible for lung transplant, the mean (SD) FEV_1 % predicted at baseline was 46.22%, with the majority of patients having baseline FEV_1 ≤50% predicted: 13 patients with baseline FEV_1 ≤40% predicted and 10 patients with baseline FEV_1 >40% and ≤50% predicted.

Efficacy results
Not applicable as no efficacy data was collected.

Safety results
Of the 3 paediatric patients enrolled in the study, two experienced SAEs. One patient, age 17 years (F) at study entry, experienced 3 episodes of cystic fibrosis exacerbation and 1 patient, age 13 years (F) at study entry, experienced 5 episodes of lung disorder (including 4 episodes of pulmonary exacerbation and 1 episode of end-stage lung disease resulting in death). All reported adverse events were already listed in the SmPC. The third paediatric patient (17 years, M) did not experience SAE.

In the overall population treatment-emergent serious adverse events (SAEs) were experienced by 25 patients (55.6%). Percentages of patients experiencing SAEs overall and those experiencing respiratory SAEs were similar during each treatment cycle but varied over time. The variability seen at different treatment cycles may be due to the small number of patients enrolled in this study and the reduced patient numbers at each successive cycle.

Two adult patients experienced SAEs assessed as Cayston related (one patient experienced chest discomfort and dizziness, and one patient experienced chest discomfort). The patients experienced the adverse event during treatment cycle 1 and discontinued treatment. The patient experiencing dizziness improved without treatment over 1 hour. The event was considered drug related by the investigator.

As dizziness is a newly observed adverse event it needs to be closely monitored in future periodic safety update reports (PSURs).

Haemoptysis has not been reported within this study.

In the adult population one additional patient died, five patients discontinued Cayston due to SAEs and six patients interrupted Cayston due to SAEs. For overview refer to table 2. Overall the reported events are already listed in the SmPC.

Table 2: EA-US-205-0122: Frequent Treatment-Emergent SAEs and the Duration-Adjusted Rates Reported for ≥ 2 Patients (Safety Analysis Set, n = 45).

System Organ Class Event (Preferred Term)	Number of Subjects[a] n (%)	Duration-Adjusted Event Rate[b]
Any Treatment-Emergent SAE	25 (55.6)	0.080
General Disorders and Administration Site Conditions	2 (4.4)	0.002
Chest discomfort	2 (4.4)	0.002
Infections and Infestations	3 (6.7)	0.004
Infection	2 (4.4)	0.002
Respiratory, Thoracic, and Mediastinal Disorders	22 (48.9)	0.067
Lung Disorder[c]	13 (28.9)	0.038
Infective pulmonary exacerbation of cystic fibrosis	7 (15.6)	0.015
Lung infection pseudomonal	3 (6.7)	0.004
Pneumonia	2 (4.4)	0.002
Surgical and Medical Procedures	2 (4.4)	0.002
Lung transplant	2 (4.4)	0.002

Subjects are counted once only for each SOC and PT.

a Denominator for the percentages is the number of subjects in the safety analysis set.

b Rate is based on number of events and is adjusted for duration on study, which is defined as total number of days on study divided by 28.

c Included events of end-stage lung disease and pulmonary exacerbation

3. OVERALL CONCLUSION AND RECOMMENDATION

In conclusion the safety data resulting from this study do not warrant any SmPC changes at this moment, all reported side effects are already listed in the SmPC except for the adverse event “dizziness”. The Rapporteur is of the opinion that “dizziness” should be closely monitored in future PSURs. The article 46 paediatric submission is considered fulfilled.

The benefit/risk for the current approved indication remains positive.