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Committee for Medicinal Products for Human Use (CHMP)

Cayston

(aztreonam)

Procedure No.: EMEA/H/C/000996/P46/029

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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Glossary of abbreviations and definition of terms

AE	adverse event
ANCOVA	analysis of covariance
AUC_{ave}	mean time-adjusted area under the curve
AZLI	Aztreonam 75 mg powder and solvent for nebuliser solution (Cayston)
Bcc	*Burkholderia cepacia* complex
BMI	body mass index
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFQ-R RSS	Cystic Fibrosis Questionnaire-Revised Respiratory Symptoms Scale
CFU	colony-forming units
CI	confidence interval
EU	European Union
FEF_{25-75}	forced expiratory flow during the middle half of the forced vital capacity
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
IV	Intravenous
LSM	least-squares mean
MIC	minimum inhibitory concentration
MIC_{50}	minimum inhibitory concentration at which 50% of isolates are inhibited
MIC_{90}	minimum inhibitory concentration at which 90% of isolates are inhibited
MMRM	mixed-effect model repeated measures
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-sensitive *Staphylococcus aureus*
PA	*Pseudomonas aeruginosa*
PIP	Paediatric Investigation Plan
SAE	serious adverse event
SD	standard deviation
SE	standard error
TID	3 times daily
US	United States

1. Recommendation

Based on the review of the data on safety and efficacy, the Rapporteur considers that the article 46 paediatric data (EMEA/H/C/000996/art 46 evaluating the efficacy and safety of aztreonam lysine in the treatment of cystic fibrosis (CF) (paediatric and adult) patients infected with Burkholderia spp. did not contribute to new safety/efficacy information. Moreover Cayston 75 mg is not indicated for use in the treatment of Burkholderia-infection in CF patients, hence this study has no added value for te approved indication.

No clinical benefit could be observed in paediatric patients, and no new safety information other than already stated in the SmPC was observed. The Rapporteur is of the opinion that the data do not warrant any changes to the SmPC. The benefit-risk for Cayston 75 mg in the approved indication remains positive.

2. Introduction

2.1 Type of application and aspects on development

The present paediatric data is submitted by the MAH in accordance with article 46 of Regulation (EC) No 1901/2006. This study is not part of an agreed paediatric investigation plan (PIP).

The MAH submitted one 2-part study (GS-US-0205-0127) which is a double-blind, randomized, placebo-controlled study of 24 weeks of aztreonam lysine (AZLI) in patients with *Burkholderia* species infection (part 1), followed by an open label study (part 2) for 24 weeks. This study included 100 cystic fibrosis (CF) patients with *Burkholderia* infection of which only **17** were paediatric patients (6 AZLI treated, and 11 placebo).

The MAH did not propose any SmPC changes.

Cayston 75 mg (aztreonam lysine [AZLI]) is presently not approved for treatment of *Burkholderia* infection in CF patients.

2.2 About the product

The CHMP issued a final positive Opinion for granting a conditional MA to Cayston on 21 September 2009. The conditional marketing authorisation was renewed on 26 August 2010. On 5 September 2011 the conditional marketing authorisation was lifted in a marketing authorisation not subject to specific obligations. The MAH filled a variation to expand the currently approved indication (see below) for Cayston 75 mg with paediatric patients aged 6 and older. Approval of the variation is pending (see Final variation assessment report dated 13 April 2012).

Currently approved indication(s)

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.

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

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

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.

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).

2.3 Burkholderia infection in CF patients

Cystic fibrosis is characterized by progressive, obstructive pulmonary disease complicated by chronic airway infection. Common infectious organisms in patients with CF include *Staphylococcus aureus*, *Pseudomonas aeruginosa* (PA), *Burkholderia spp.*, *Achromobacter spp*., and *Stenotrophomonas maltophilia*. Acquisition of specific pathogens, including PA and *Burkholderia spp*., can significantly alter the clinical course of the patient with CF (Courtney, 2004; Treggiari, 2007). Infected patients experience progressive obstruction of the airways and loss of lung function that is due in large part to the inflammatory response to chronic bacterial infection. Loss of pulmonary function is the primary cause of death in patients with CF (Cystic Fibrosis foundation, 2006; anonymous, 2007).

Although PA is the best characterized bacterial pathogen associated with CF pulmonary disease (Gibson, 2003; Davis, 1996; Pamukcu, 1995), *Burkholderia spp*. are recognized as causing significant change in the clinical course of patients with CF. The prevalence of infection with Burkholderia was 3% in 2007 (Cystic fibrosis foundation, 2010) with significant treatment centre and regional differences. Chronic airway infection with PA occurs in more than 69% of European CF patients by age 20. Approximately 50% of CF patients with *Burkholderia* have co-infection with PA.

Significant morbidity and mortality are associated with (Isles, 1984; Goss, 2004; Thomassen, 1985) *Burkholderia spp*., and epidemic strains are recognized that are more virulent. The most virulent strains are associated with ~40% loss of FEV_1 per year or a 2 year mortality rate of > 50%. Morbidity associated with *Burkholderia spp*. infection includes more days of feeling poorly, more frequent and difficult-to-treat exacerbations, significant weight loss, and accelerated loss of lung function.

There are no evidence-based effective antibiotic therapies available for the management of chronic *Burkholderia spp*. infection in CF patients, and these patients historically have been excluded from clinical trials of inhaled antibiotics. Patients typically receive a combination of systemic, oral, and/or inhaled antibiotics frequently or even continuously for control of their symptoms. Eradication of *Burkholderia* from the CF lung has not been successful (Waters, 2012) and antibiotic treatment is mainly suppressive.

Since patients with *Burkholderia* infection frequently have rapid life-threatening loss of lung function, they are often considered for lung transplantation. However, *Burkholderia* infection is associated with worse outcomes, and many transplant centres exclude or limit transplantation in these patients (Murray, 2008).

Burkholderia spp., gram negative bacteria, are usually susceptible to aztreonam (Kucher's handbook). Eucast only has 22 observations and MICs to aztreonam vary between 0.25 and 256 µg/ml. No cut off values have been validated. Based on this it is expected that AZLI is active against *Burkholderia*.

3. Scientific Discussion

In accordance with the pediatric article 46 regulation, the MAH submitted one final efficacy and safety study in CF patients infected with *Burkholderia*, aged 6 years and older, treated continuously for up to 12 months with Cayston 75 mg (Study GS-US-205-0127). Part 1 of the study (randomized phase) consisted of double-blind, randomized, placebo-controlled treatment for 24 weeks, and Part 2 (extension phase) consisted of open-label AZLI treatment for 24 weeks. All subjects received standard of care, including non-study antibiotics, as determined by the treating physician while participating in the study. Safety and efficacy were analysed through Week 24 for the randomized phase of the study and through Week 48 for the extension phase.

Of the 100 patients enrolled, only **17 were paediatric patients** (6 patients aged 6 to 12 years and 11 patients aged 13 to 17 years). In each paediatric patients group only 3 patients (6 in total) were treated with AZLI. Based on these small patient numbers no conclusions can be drawn.

3.1 Efficacy results in paediatric patients

The MAH only presented paediatric subgroup analysis for the primary endpoint FEV_1 % predicted in both randomised and extension phase. No significant clinical effect was observed for the primary endpoint in either paediatric subgroup (table 1 and 2). In the randomised phase the difference in least-squares mean (LSM) between AZLI *versus* placebo in patients ≥ 6 to ≤12 years was 5.17 (-25.08, 25.43) [p=0.624] and in patients >12 to <18 years 19.61 (-1.27, 40.48) [p=0.062]. Adjusted mean (SE) AUC_{ave} of relative change from extension phase baseline in FEV_1 % predicted at the end of the extension phase for subjects aged ≥ 6 to ≤ 12 years was 4.51 (4.13) for AZLI/AZLI-treated subjects and -3.01 (4.13) for placebo/AZLI-treated subjects. For subjects aged > 12 to < 18 years, the change from extension phase baseline in AUC_{ave} of relative change in FEV_1 % predicted was 7.49 (8.83) for AZLI/AZLI-treated subjects and 1.50 (5.28) for placebo/AZLI-treated subjects at the end of the extension phase.

Data regarding secondary endpoints (use of systemic antibiotics, time to systemic or inhaled antibiotics for respiratory events and total number of hospitalizations, and AUC_{ava} CFQ-RSS) were all

based on the overall population (n=100). No significant differences were observed in the overall population. However, there were some observations of e.g. less required antibiotics use in respiratory events, and the time to use of inhaled or i.v. antibiotics in the AZLI group seemed to be delayed.

Numbers are too small to allow any conclusion.

Table 1: GS-US-205-0127 Randomized Phase: AUC_{ave} of Relative Change from Baseline in FEV1 % Predicted by Age Group at Week 24 (Full Analysis Set).

Subgroup	Statistics	AZLI	Placebo
≥ 6 to ≤ 12 years	N	3	3
	n	3	3
	Adjusted Mean (SE)	-0.95 (6.20)	-6.12 (6.20)
	Difference in LSM (95% CI)	5.17 (-25.08, 35.43)	
	p-value	0.624	
	Rank-Based ANCOVA p-value	0.502	
	Wilcoxon Rank Test p-value	1.000	
>12 to <18 years	N	3	8
	n	3	8
	Adjusted Mean (SE)	17.47 (7.13)	-2.13 (3.69)
	Difference in LSM (95% CI)	19.61 (-1.27, 40.48)	
	p-value	0.062	
	Rank-Based ANCOVA p-value	0.181	
	Wilcoxon Rank Test p-value	0.262	
< 18 years	N	6	11
	n	6	11
	Adjusted Mean (SE)	2.98 (4.52)	-0.34 (3.26)
	Difference in LSM (95% CI)	3.32 (-9.08, 15.72)	
	p-value	0.575	
	Rank-Based ANCOVA p-value	0.377	
	Wilcoxon Rank Test p-value	0.340	
≥ 18 years	N	42	41
	n	41	41
	Adjusted Mean (SE)	-0.13 (1.65)	-0.99 (1.65)
	Difference in LSM (95% CI)	0.85 (-3.92, 5.62)	
	p-value	0.723	
	Rank-Based ANCOVA p-value	0.627	
	Wilcoxon Rank Test p-value	0.831	

P-value for treatment difference was based on an ANCOVA model with baseline value as a covariate.

AUC_{ave} was the calculated area under the curve corrected for baseline and adjusted by the number of days on study through Week 24.

Table 2 GS-US-205-0127 Extension Phase: AUC_{ave} of Relative Change in FEV_1 % Predicted from Week 24 (Extension Phase Baseline) through Week 48 by Age Group (Full Analysis Set)

Subgroup	Statistics	AZLI / AZLI (N = 39)	Placebo / AZLI (N = 45)
≥ 6 to ≤ 12 years	N	3	3
	N	3	3
	LSMean (SE)	-4.51 (4.13)	-3.01 (4.13)
	Difference in LSMean Estimate (95% CI)	-1.50 (-20.17, 17.17)	
>12 to <18 years	N	3	8
	N	3	7
	LSMean (SE)	-7.49 (8.83)	1.50 (5.28)
	Difference in LSMean Estimate (95% CI)	-8.99 (-35.47, 17.48)	
< 18 years	N	6	10
	N	6	10
	LSMean (SE)	-5.48 (4.64)	-0.16 (3.56)
	Difference in LSMean Estimate (95% CI)	-5.32 (-18.18, 7.54)	
≥ 18 years	N	33	35
	N	33	34
	LSMean (SE)	-0.96 (1.67)	3.17 (1.64)
	Difference in LSMean Estimate (95% CI)	-4.13 (-9.01, 0.76)	

LSMeans and CIs were calculated based on an ANCOVA model with baseline value as a covariate.
AUC_{ave} was the calculated area under the curve corrected for extension phase baseline (Week 24) and adjusted by the number of days on study from Week 24 through Week 48.
All subjects received AZLI during the extension period.

3.2 Microbiology results

Burkholderia spp. in sputum

No separate data with respect to the paediatric patients was presented by the MAH. Interpretation of the individual paediatric data is difficult as in most cases there is no quantitative data on the CFU/g sputum on *Burkholderia* available other than "*present*". In the exceptional case where exact data is presented, it is noticed that reduction of *Burkholderia spp*. CFU/g sputum is intermittently.

From the overall population data on a small number of subjects in the AZLI treatment group (15 subjects [31%]) and placebo treatment group (20 subjects [38%]) was presented. In the randomized phase the average adjusted mean (SE) change from baseline in $\log_{10}$ *Burkholderia spp*. CFU/g sputum at Week 24 was not significantly different between patients treated with AZLI (1.41 [0.58]) and patients treated with placebo (0.48 [0.50]) (treatment difference: 0.93, p-value: 0.232). However, an increase was observed among AZLI-treated patients across the 6 months of treatment.

In week 48 (extension phase) the $\log_{10}$ *Burkholderia spp*. CFU/g sputum returned to baseline values in the AZLI/AZLI treated patients (adjusted mean 0.04 (SE 0.78). However as the observation is only based on 13 patients no conclusion is allowed.

Overall, it can be concluded that *Burkholderia* is not eradicated from the paediatric patients. In the overall population *Burkholderia* disappeared equally in the AZLI *and* placebo treated patients. This lack of eradication might result in aztreonam-resistant isolates after partly suppressive therapy.

Furthermore it can be questioned whether the used dosage of 75 mg AZLI TID was well chosen. The MAH did not perform a pharmacokinetic study performed in *Burkholderia* infected CF patients. As these patients have a worse clinical picture, e.g. fast declining lung function, it is uncertain whether AZLI concentrations reached effective levels within these patients.

MIC-values

All paediatric patients were infected with different *Burkholderia* species. (*B. cenocepacia (4/17)* and *B. multivorans (10/17)).* Although the MAH did not present the paediatric data separately, it was noticed that in the individual paediatric patient data MIC values increased 2 to 4-fold from baseline to week 24. In the overall study population the same trend is shown. In the AZLI group MIC_{50} for *Burkholderia* increased 2-fold (from 1024 µg/ml at baseline to 2048 µg/ml at week 24) and MIC_{90} increased 4-fold (from 512 µg/ml at baseline to 2048 µg/ml at week 24). In the extension phase a 2-fold reduction was observed in the AZLI/AZLI group for both MIC's. In the placebo/AZLI group both MIC's remained unchanged over the treatment course (48 weeks), being 128 and 1024 µg/ml respectively. This indicates that *Burkholderia*'s susceptibility to aztreonam persistently decreased over time (48 weeks).

3.3 Safety results

Based on the submitted data no new safety information which is not already stated in the SmPC for Cayston was identified. No pediatric deaths occurred during the overall study**.**

4. Rapporteur's Overall Conclusion and Recommendation

The MAH submitted an efficacy and safety study in CF patients infected with *Burkholderia spp*, aged 6 years and older (GS-US-205-0127) in accordance to the article 46 regulation. Cayston 75 mg (aztreonam lysine [AZLI]) is presently not indicated for the treatment of *Burkholderia* in CF patients. The study only included 17 paediatric patients from a total of 100 patients. Of these 17 patients only 6 were treated with AZLI. Due to this small numbers no firm conclusions with regard to the paediatric population can be drawn.

Overall, *Burkholderia* is not eradicated in AZLI treated patients, and MIC-values are increasing over time indicating that *Burkholderia* resistance to AZLI is a potential risk with long term treatment. One can not exclude that this is due to inadequate dosing. There is no pharmacokinetic study in *Burkholderia* infected CF patients. It is thus uncertain whether AZLI concentrations reached effective levels within these patients.

No new safety information has become available from the present submitted study. All reported side effects are already listed in the SmPC.

Hence the Rapporteur is of the opinion that the data do not warrant or support any SmPC changes. The benefit-risk for the current approved indication remains positive.

5. Request for supplementary information

None

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