HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

15 February 2012

CAYSTON 75 mg, powder and solvent for nebuliser solution
B/84 glass vials - 88 ampoules with an Altera nebuliser (CIP code: 375 151-1)

Applicant: GILEAD SCIENCES

aztreonam lysine
ATC code: J01DF01

List I
Medicine for initial six-monthly hospital prescription only.
Renewal not restricted.

Date of Marketing Authorisation (centralised procedure): 21/09/2009
This is an orphan medicinal product (EU/3/04/204 decision of 21 June 2004).

Reason for request: Inclusion on the list of medicines refundable by National HealthInsurance and approved for hospital use.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

aztreonam lysine

1.2. Background

Aztreonam lysine is in the form of a nebuliser solution.

1.3. Indication

"CAYSTON (aztreonam lysine) is indicated for the suppressive therapy of chronic pulmonary infections due to Pseudomonas aeruginosa (PA) in patients with cystic fibrosis aged 18 years or older.
This indication is primarily based on two controlled studies versus placebo that evaluated CAYSTON over a single 28 day cycle. Data concerning the sustainability of benefits observed in the short-term for previous treatment cycles are limited. Consideration should be given to official guidance on the appropriate use of antibacterial agents".

1.4. Dosage

"[…] **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.
Controlled data on the efficacy of multiple cycles are not yet available.
Only the doctor may decide if additional cycles, i.e. more than the initial cycle of 28 days, are to be scheduled. If additional cycles are prescribed, a minimum of 28 days without treatment with CAYSTON is thus recommended.
Elderly population:
Clinical studies of CAYSTON did not include a sufficient number of patients aged 65 years and older to determine whether they respond differently to treatment than younger patients. If CAYSTON is to be prescribed to the elderly, then the posology is the same as for adults.
Paediatric population:
This medicinal product is not recommended for use in children below 18 years as there is limited safety and efficacy information.
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 eBase Controller or an eFlow rapid Control Unit."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

J : antiinfectives for systemic use
J01 : antibacterials for systemic use
J01D : other betalactam antibacterials
J01DF : monobactams
J01DF01 : aztreonam

2.2. Medicines in the same therapeutic category

2.2.1. Strictly comparator medicines

CAYSTON is the only nebulised antibiotic in the monobactam category.

2.2.2. Not-strictly comparator medicines in the same therapeutic category

There is another presentation for aztreonam, for parenteral use: AZACTAM 1 g powder/solution.

2.3. Medicines with a similar therapeutic aim

These are antibiotics with the same or neighbouring spectrum of antimicrobial activity, administered via IV, orally or nebulised, recommended[1] for the treatment of bronchopulmonary infections due to *Pseudomonas aeruginosa* (*PA)* associated with cystic fibrosis.

Main nebulised antibiotics used in the treatment of *PA* infection

Name	DC	Proposed dosage	Number of times taken / day
TOBI 300 mg/5 ml, nebuliser solution * (if aged > 6 years)	tobramycin	600 mg/day	2
COLOMYCIN 1 MIU, powder and solvent for nebuliser inhalation	Colistin	1 to 6 million units/day	1 to 3

NB: prior to these guidelines, TOBI PODHALER 28 mg, inhalation powder, hard capsules (new presentation for tobramycin for inhalation) obtained a Marketing Authorisation in the indication "treatment of chronic pulmonary infection due to Pseudomonas aeruginosa (PA) in patients with cystic fibrosis aged 6 years and older".

[1]French Paediatric Society, ANAES. Management of cystic fibrosis patients. Consensus conference; Nov 2002; Paris, France.

Main IV antibiotics used in the treatment of *PA* infection

Name	Proposed dosage in mg/kg per day	Number of times taken per day
Ticarcillin (± clavulanic acid)	250 (C) Max. 20/kg/day clav. acid (C) 400 (A) Max. 15 g/day ticarcilin (A) Max. 1,200 mg/day clav. acid (A)	3 to 4
Piperacillin (± tazobactam; Marketing Authorisation if aged >12 years)	300 (C) 200 (A) Max. 12 g/day (A)	3 to 4
Ceftazidime	200-250 Max. 12 g/day	3 or continuous infusion (loading dose)
Aztreonam (Marketing Authorisation for adults)	150-200 Max. 12 g/day	3
Imipenem	75 to 100 Max. 4 g/day	3
Meropenem (Marketing Authorisation for adults and children weighing at least 50 kg)	120 to 160 Max. 6 g/day	3 to 4
Tobramycin	8 to 10	1 to 3
Amikacin	20-30 Max. 20 mg/kg/day (A) Total dose < 1.5 g	1 to 3
Ciprofloxacin (Marketing Authorisation if aged > 5 years)	30 (C) 400 to 1,200 mg/day (A) Max. 1,200 mg/day (C) (A)	2 to 3
Colistin	0.1-0.15 million units/kg/day	2 to 3

A = Adult
C= Child

Main oral antibiotics used to treat *PA* infection

Name	Proposed dosage	Number of times taken / day
Ciprofloxacin (Marketing Authorisation if aged > 5 years)	40 mg/kg/day (C) 1 to 1.5 g/day (A) Max. 1,500 mg/day (C) (A)	2
Azithromycin (No Marketing Authorisation for children)	250 to 500 mg/day	1

3 ANALYSIS OF AVAILABLE DATA

The clinical file is primarily based on three controlled, randomised, multicentre phase III studies:

Two studies evaluating CAYSTON versus placebo with a treatment cycle of 28 days for patients with cystic fibrosis and a chronic pulmonary infection due to *PA*:

- study CP-AI-005[2] evaluating the efficacy and tolerance of CAYSTON (75 mg 2 or 3 times per day) on 211 patients (165 adults and 46 children) pre-treated for 28 days with TOBI.
- study CP-AI-007[3] evaluating the efficacy and tolerance of CAYSTON at a dose of 75 mg 3 times per day on 164 patients (127 adults and 37 children).

One non-controlled, follow-up study to 18 months, on 274 patients, followed studies CP-AI-005 and CP-AI-007 with the primary objective being to evaluate the tolerance of repeated exposure to CAYSTON. The secondary objectives included assessment of the efficacy of the medicinal product. However, given the non-comparative nature of this study, no conclusion could be drawn regarding sustained long-term efficacy. In addition, only tolerance and tolerance data were taken into account.

A comparative study versus nebulised tobramycin (TOBI):

- study GS-US-205-0110: evaluating the efficacy and tolerance of CAYSTON (75 mg 3 times/day) versus TOBI (300 mg 2 times/day) over 3 cycles of 28 days of treatment in adult and paediatric patients (268 patients: 59 children at least 6 years old and 209 adults) with cystic fibrosis and a pulmonary infection due to *Pseudomonas aeruginosa* (*PA*).

3.1. Efficacy *versus* placebo

Study CP-AI-005

- Objective

The objective was to evaluate the efficacy and tolerance of CAYSTON, administered over 28 days, in the treatment of chronic pulmonary infections due to *PA* in patients with cystic fibrosis having had treatment over 28 days with TOBI.

- Methodology

Main inclusion criteria:

- stabilised pulmonary infection with recent sputum cultures positive for *PA*,
- above 6 years old,
- forced expiratory volume in 1 second (FEV1) during the eligibility assessment appointment ranging between 25% and 75% of the theoretical value.

Main non-inclusion criteria:

- previous history of infection with sputum cultures positive for *B. cepacia* during the last two years,
- previous history of daily continuous oxygen support higher than 2 l/min over night,
- chest x-ray showing significant acute anomalies during the eligibility assessment appointment or in the previous 90 days,
- women who are pregnant, breastfeeding or not using an effective method of contraception.

[2] McCoy *et al.* Inhaled aztreonam lysine for chronic airway Pseudomonas aeruginosa in cystic fibrosis. American Journal of Respiratory and Critical Care Medicine 2008; 178: 921-8.
[3] Retsch-Bogart *et al*. Efficacy and safety of inhaled aztreonam lysine for airway Pseudomonas in cystic fibrosis. Chest 2009; 135: 1223-32.

Treatment:

Patients were randomised (Day-28 before inclusion) and received treatment with TOBI for 28 days. On Day 0 (start of inclusion) patients started, double-blind according to the randomisation group, a 28 day treatment (a course) with CAYSTON (75 mg 2 or 3 times per day) or the placebo (2 or 3 times per day).

Primary efficacy endpoint:
Interval before needing to administer other antibiotics via nebuliser or IV for the *PA* infection, due to the appearance of predefined symptoms, such as the reduction in tolerance to exercise, an increase in coughing, an increase in sputum and a decrease in appetite.

Secondary efficacy endpoints:
• difference in FEV1
• difference in concentration of *PA* in sputum expressed as $\log_{10}$ of CFU (Colony Forming Units)/g (number of colonies per gram of sputum),
• improvement in respiratory symptoms evaluated by the patient using the CFQ-R (Cystic Fibrosis Questionnaire-Revised) scale which is graduated from 0 to 100 points.

Note: for each efficacy endpoint, an analysis comparing all patients who received CAYSTON 75 mg (either 2 or 3 times per day) with all the patients who received the placebo (2 or 3 times per day) was initially carried out. If this comparison between the two groups showed a difference, then analyses comparing each of the CAYSTON 75 mg groups, 2 and 3 times per day, with all the patients who received the placebo (2 or 3 times per day) were carried out.

- Results

Two hundred and eleven patients were randomised.
The mean age of the patients was 26 years (78% were 18 years or older).
At Day-28, (before treatment with TOBI) the mean FEV1 value was 55%; at Day 0 (after treatment with TOBI and before CAYSTON/placebo) the FEV1 was 57%.
Patients received at least three courses (mean of 5.3) of TOBI during the 12 months prior to inclusion. An antibiotic nebuliser solution of colistin was also used for certain patients. Patients were generally co-treated, especially with antibiotics (73%, of whom 70% with azithromycin) and medicinal products for obstructive respiratory conditions (99%).

Results for the primary efficacy endpoint:
The median interval before needing to administer other antibiotics was longer in the CAYSTON group (75 mg, 2 and 3 times per day) than in the placebo group (Table 1). However, a significant difference was only observed in the CAYSTON group administered twice daily (p=0.002), and not in the group receiving CAYSTON according to the dosage recommended in the Marketing Authorisation (75 mg, 3 times per day).

Table 1: Results for the primary efficacy endpoint (study CP-AI-005)

	Placebo (n=76)	CAYSTON 2/day (n=69)	CAYSTON 3/day (n=66)	CAYSTON total (n=135)	Difference (p)
Median interval (day) before needing to administer other antibiotics (IV or nebulised)	71	NE	87	92	21 (0.007)
% patients who had treatment with antibiotics (IV/nebulised)*	56.6	36.2	43.9	40.0	
% of patients who had treatment with antibiotics (oral/IV/nebulised)*	60.5	47.8	59.1	53.3	

Difference (p): difference calculated between the CAYSTON group (grouped data: 75 mg 2 and 3 times per day) and the placebo group.
* Descriptive analyses
NE: not able to evaluate

Results for the secondary efficacy endpoints:
At Day 28, an improvement in FEV1, in respiratory symptoms (measured on the CFQ-R scale) and in log10 CFU values for *P. aeruginosa* in the sputum was observed in the CAYSTON group compared with the placebo group.
However, this improvement reduced in the two weeks (Day 42) following stopping treatment with CAYSTON for pulmonary function and the concentration of *PA* in the sputum.

Table 2: Results for the secondary efficacy endpoints (study CP-AI-005)

	Placebo (n=76)	CAYSTON 2/day (n=69)	CAYSTON 3/day (n=66)	CAYSTON total (n=135)	Difference* 95% CI (p)
Mean FEV1 value (% of the theoretical value)					
Day 0	54%	56%	55%	56%	
Mean variation in FEV1 compared with Day 0 (%)					
Day 28	-2.4	3.8	4.0	3.9	6.3 [2.5; 10.1] (0.001)
Day 42	-5.0	1.6	0.1	0.9	5.8 [2.0; 9.7] (0.003)
Concentration of *PA* in the sputum: adjusted mean** variation in $\log_{10}$ of CFU (%)					
Day 28	0.23	-0.49	-0.37	-0.43	-0.66 [-1.13; -0.19] (0.006)
Day 42	0.17	0.46	0.02	0.24	0.07 [-0.43; 0.57] NS
Mean (adjusted***) variation in respiratory symptoms using the CFQ-R scale					
Day 14	-2.06	2.86	4.10	3.47	5.53 [1.35; 9.70] (0.010)
Day 28	-0.66	5.10	3.56	4.34	5.01 [0.81; 9.21] (0.020)

* Difference 95% CI (p): difference calculated between the CAYSTON group (grouped data: 75 mg 2 and 3 times per day) and the placebo group.
** Analysis using ANCOVA with treatment conditions and highest MIC at inclusion as covariates.
*** Analysis using ANCOVA with score on inclusion as covariate.

- Discussion

Patients included in this study were pre-treated for 28 days with TOBI before receiving CAYSTON or the placebo, depending on the randomisation group. According to the Marketing Authorisation for TOBI, after 28 days of treatment, the patient must have a break for the next 28 days. In addition, effects observed should be interpreted as the results from treatment with TOBI followed by CAYSTON. Furthermore, assessment of the efficacy over a single 28 day cycle limits the transferability of results to "real life" situations.

Study CP-AI-007

- Objective

The aim of this study was to evaluate the efficacy and tolerance of one 28 day cycle of treatment of CAYSTON (75 mg, 3 times per day) versus placebo, in the treatment of chronic pulmonary infections due to Pseudomonas *aeruginosa* (*PA*) in patients with cystic fibrosis.

- Methodology

The main inclusion and non-inclusion criteria were identical to those for study CP-AI-005.

Treatment:
Patients were randomised to receive double-blind CAYSTON (75 mg, 3 times per day) or the placebo (3 times per day).

Primary efficacy endpoint: changes in respiratory symptoms evaluated by the patient using the CFQ-R scale, compared with Day 0.

Secondary efficacy endpoints:
• change in FEV1 compared with Day 0,
• change in concentration of *PA* in the sputum, expressed as $\log_{10}$ of CFU/g (number of colonies per gram of sputum) compared with Day 0,
• treatment with other anti-*P. aeruginosa* antibiotics via IV or nebulised.

- Results

A total of 164 patients (127 adults and 37 children) were included.
The mean age of the patients was 30 years (77% were 18 years or older). At Day 0, the mean FEV1 value was 55%.
The mean number of doses of TOBI received in the 12 months prior to inclusion was 1.8 (± 2.2). Patients were also pre-treated with antibiotics (10%) and medicinal products for obstructive respiratory conditions (93%), which they continued to take during the study. Thirty four percent of patients started a new antibiotic treatment (other than CAYSTON) during the study (15% of whom had tobramycin).

Primary efficacy endpoint:
An improvement in respiratory symptoms was observed in the group of patients treated with CAYSTON (3 times per day) *versus* placebo (Table 3).

Table 3: Results for primary efficacy endpoint (study CP-AI-007)

Mean (adjusted*) CFQ-R scores for respiratory symptoms	Placebo (n=84)	CAYSTON (n=80)	Difference 95% CI (p)
Initial values on Day 0	60.88	60.45	
Changes on Day 14	-0.98	7.01	7.98 [3.50; 12.47] (0.001)
Changes on Day 28	-2.63	7.08	9.71 [4.31; 15.11] (0.001)
Changes on Day 42	-5.71	0.62	6.33 [1.22; 11.43] (0.015)

* Analysis using ANCOVA with severity of the disease and relevant scores at inclusion as covariates.

Results for the secondary efficacy endpoints:
The results observed at Day 28, for the changes in FEV1 and in differences in concentration of *PA* in the sputum, were also in favour of CAYSTON (Table 4). However, as with study CP-AI-005, these effects were reduced in the two weeks following stopping treatment with CAYSTON (Table 4).

The percentage of patients who received another antibiotic treatment regimen, either via IV or nebulised, did not differ between the two groups.

Table 4: Results for the secondary efficacy endpoints (study CP-AI-007)

	Placebo (n=84)	CAYSTON (n=80)	Difference 95% CI (p)
Mean adjusted* variation in FEV1 compared with Day 0 (%)			
Day 28	-2.4	7.9	10.3 [6.3; 14.3] (< 0.0001)
Day 42	-2.6	3.1	5.7 [2.1; 9.4] (0.002)
Mean adjusted** variation (%): log_{10} CFU of *PA* in the sputum:			
Day 28	0.069	-1.384	-1.453 [-2.12; -0.79] (< 0.0001)
Day 42	-0.010	-0.078	-0.069 [-0.67; 0.54] NS
Patients who had treatment with another antibiotic (%)			
IV/nebulised	22.6	15.0	(0.2364)
oral	25.0	11.3	(0.0267)
oral/IV/nebulised	35.7	17.5	(0.0131)

** Analysis using ANCOVA with treatment conditions, FEV1 at inclusion and the severity of the disease as covariants.
*** Analysis using ANCOVA with severity of the disease as covariant.

- Discussion

The assessment was based on a single 28 day cycle; the transferability of results to "real life" situations remains low.

3.2. Efficacy *versus* comparator active ingredient (TOBI 300 mg/5 ml, nebuliser solution)

Study GS-US-205-0110

- Objective

The aim was to compare the efficacy and tolerance of CAYSTON versus TOBI (nebulised tobramycin) in the treatment of pulmonary infections due to *PA* in 268 adult and paediatric patients, aged at least 6 years, with cystic fibrosis.

- Methodology

The study had two phases:
- one randomised 3 cycle phase carried out as an open-label study (performed in Europe and the USA)
- one 3 cycle extension phase carried out as an open-label study (performed only in Europe).
The results from this extension phase are not yet available.

Main inclusion criteria:
- Patients aged 6 years or over;
- Patients with cystic fibrosis and with a sputum culture or a throat swab positive for *PA* in the 3 months prior to inclusion;
- Patients who received treatment with antibiotic aerosols and did not show any signs of intolerance to this type of medication;
- FEV1 ≤ 75% of the value predetermined at appointment 1;
- Chest x-ray at appointment 1 (or MRI in the 180 days prior to appointment 1) with absence of significant acute anomalies.

Main non-inclusion criteria:
- Previous history of sputum positive for *B. cepacia* during the last two years;
- Requiring daily oxygen support continually or higher than 2 l/min overnight;
- Use of oral corticosteroids at doses exceeding the equivalent of 10 mg of prednisone per day or 20 mg of prednisone every two days;

- Chronic treatment with azithromycin in the 28 days prior to appointment 1;
- Treatment with anti-*PA* antibiotics (regardless of the method of administration) in the 14 days prior to appointment 2 (randomisation).

Treatment:
Patients were randomised to receive three courses of treatment of 28 days with CAYSTON 75 mg 3 times/day (N=136) or TOBI 300 mg 2 times/day (N=132) with a break in treatment of 28 days between each course.
Patients were not able to receive any other anti-pseudomonas antibiotics during the breaks in treatment, except if the clinical study investigator judged it necessary, and in such cases the reason must be documented.

Primary efficacy endpoints:
• Change in FEV1 with one course of treatment between inclusion and Day 28 (non-inferiority analysis carried out as ITT);
• Change in FEV1 with three courses of treatment, between inclusion and the end of each of the three courses (Day 28, 42 and 56) (superiority analysis).
It should be noted that initially only a non inferiority analysis at 28 days was performed, but a superiority analysis of three courses of treatment was added through an amendment to the protocol.

➢ Results

A total of 268 patients were included in the study (CAYSTON: 136 patients; TOBI: 132 patients), 124 (91%) patients finished treatment in the CAYSTON group and 111 (84%) patients in the TOBI group.
The mean age of patients included was 26 years (78% were 18 years or older).
Everyone had been treated with TOBI during the 12 months prior to their inclusion, 85% of whom for more than 84 days.
At inclusion, the mean FEV1 was 52% of the theoretical value in each of the two groups.

Primary efficacy endpoints (Tables 5 and 6):
- An improvement in FEV1 at Day 28 for patients treated with CAYSTON was non-inferior to that observed for those treated with TOBI: 8.60% vs. 0.75%; difference of -7.86; 95% CI [-11.88; -3.84] (PP population);
- An improvement with three courses in FEV1 for patients treated with CAYSTON was superior to that observed for patients treated with TOBI: 2.05% vs. -0.66%; difference -2.70%; p= 0.0023 (ITT population).

Table 5: Results for the primary efficacy endpoints of study GS-US-205-0110 (PP population)

Endpoints	CAYSTON 75 mg 3 times/day (PP n=136)	TOBI 300 mg 2 times/day (PP n=132)	Difference TOBI – CAYSTON 95% CI
Variation in FEV1 between Day 0 and Day 28	8.60%	0.75%	-7.86 95% CI [-11.88; -3.84] p=0.0001 (analysis of non-inferiority)
Mean variation in FEV1 between Day 0 and Day 28, Day 42, Day 56	2.05%	-0.58%	-2.62 CI 95% [-4.39;-0.85] p=0.0038 (analysis of superiority)

Table 6: Results for primary efficacy endpoints for study GS-US-205-0110 (ITT Population)

Endpoints	CAYSTON 75 mg 3 times/day (ITT n=136)	TOBI 300 mg 2 times/day (ITT n=132)	Difference TOBI – CAYSTON 95% CI p
Mean FEV1 value at Day 0 (% of the theoretical value)	52	52	-
Variation in FEV1 between Day 0 and Day 28	8.35%	0.55%	-7.80 95% CI [-11.73; -3.86] p= 0.0001 (analysis of non-inferiority)
Mean variation in FEV1 between Day 0 and Day 28, Day 42, Day 56	2.05%	-0.66%	-2.70 95% CI [-4.43; -0.98] p= 0.0023 (analysis of superiority)

Continued improvement in FEV1 was observed for cycles of treatment by CAYSTON and TOBI.

Secondary and tertiary endpoints:

- For patients who received tobramycin for at least 84 days during the last 12 months, the improvement in FEV1 at Day 28 in patients treated with CAYSTON was non-inferior to those observed for patients treated with TOBI: 10.04% vs. 0.54%, difference -9.50% 95% CI [-13.86%; -5.14%]; p<0.0001
- The improvement in FEV1 over three courses of treatment was superior for patients treated with CAYSTON compared with those treated with TOBI: 3.26% vs. -0.21%, difference -3.47; p=0.0002 for patients who received tobramycin for at least 84 days during the last 12 months;
- The improvement at Day 28 for respiratory symptoms evaluated using the CFQ-R scale was superior for patients treated with CAYSTON compared with those treated with TOBI: 8.20 vs. 2.59; difference -5.61; p=0.0048;
- The improvement over three cycles of treatment for respiratory symptoms evaluated using the CFQ-R scale for patients treated with CAYSTON compared with those treated with TOBI was: 6.30 vs. 2.17; difference -4.13; p=0.0189;
- There was no statistically significant difference in the reductions in concentration of PA in the sputum between patients treated with CAYSTON and those treated with TOBI over the three cycles observed.
- a lower percentage of patients receiving another antibiotic treatment via IV and/or nebulised in the CAYSTON group was observed: 38.2% vs. 57.6% (p=0.002).
- a lower number of hospital admissions for respiratory events in the CAYSTON group was observed: 40 vs. 58 (p=0.044).

Sub-group analyses also showed:

An insignificant difference between CAYSTON and TOBI for patients pre-treated with nebulised tobramycin for less than 84 days during the 12 months prior to the study:

- variation in FEV1 between Day 0 and Day 28 of 2.45% in the CAYSTON group (N=21, ITT) and 4.65% in the TOBI group (N=19, ITT); p=0.6046 (superiority analysis)
- mean variation in FEV1 between Day 0 and appointments 4 (Day 28), 6 (Day 42) and 8 (Day 56) of -1.33% in the CAYSTON group (N=21, ITT) and 0.51% in the TOBI group (N=19, ITT); p=0.4820.

Microbiology results:

Increases in MIC_{90} of *PA* compared with inclusion were observed at weeks 4, 12, 16, 20 and 24 in the CAYSTON group, although no changes were observed in the TOBI group.

The number of patients for whom the MIC for *PA* of aztreonam and tobramycin was higher than the critical concentration determined (8 µg/ml for aztreonam and 4 µg/ml for tobramycin) increased in the CAYSTON group between inclusion and week 24 (from 34% to 49%), although a decrease was observed for the TOBI group (from 35% to 32%) (Table 7).

Table 7: Variations in resistance to CAYSTON and TOBI between inclusion and week 24

	Cayston Group N = 136		TOBI Group N = 132	
	n		n	
Patients with MIC >8 µg/ml for PA isolates to aztreonam;[a] n (%)				
Inclusion (Week 0)	115	39 (33.9)	110	38 (34.5)
End of Study (Week 24)	114	56 (49.1)	96	31 (32.3)
Patients with MIC >4 µg/ml for PA isolates to tobramycin:[a] n (%)				
Inclusion (Week 0)	115	41 (35.7)	110	37 (33.6)
End of Study (Week 24)	114	43 (37.7)	96	35 (36.5)

[a]Parenteral breakpoint is 8 µg/mL for aztreonam and 4 µg/mL for tobramycin.

The presence of Methicillin-resistant *Staphylococcus aureus* (MRSA) in at least three successive swabs in patients not initially infected was observed for 3% of patients treated with CAYSTON, although this was not observed for the TOBI group.

- Discussion

The open-label nature of this study limits the usefulness of the results.
In this study, the variations in FEV1 observed in the comparator group (TOBI, nebulised tobramycin) are small compared with those normally observed in published studies with TOBI[4,5,6] which could be explained by the patients' previous exposure to TOBI (85% of whom for more than 84 days); sub-group analyses showed an insignificant difference between CAYSTON and TOBI for patients pre-treated with nebulised tobramycin for less than 84 days during the 12 months prior to the study. For this reason, the amount of effect observed in this study should be interpreted as the result from a treatment with TOBI followed by CAYSTON.

3.3. Adverse Effects

The tolerance of CAYSTON was evaluated in three phase III studies carried out on 344 patients, mainly adults (77%) with a chronic infection due to *P. aeruginosa*. During the two controlled phase III studies versus placebo, patients received CAYSTON 75 mg 2 times (69 patients) or 3 times (146 patients) per day for 28 days. During the open-label follow-up phase III study, 274 patients with cystic fibrosis received up to nine cycles of treatments lasting 28 days with CAYSTON 75 mg 2 or 3 times per day.
The most common adverse effects reported were:
Very common (≥ 1/10):

- wheezing, cough, pharyngolaryngeal pain, nasal congestion
- fever

Common (≥ 1/100, < 1/10):

- non-allergic bronchospasm, chest discomfort, rhinorrhoea
- skin eruptions

[4] Ramsey BW et al. Efficacy and safety of chronic intermittent administration of inhaled tobramycin in patients with cystic fibrosis. N Engl J Med 1999; 340: 23-30.
[5] Hodson ME et al. A randomised study of nebulised tobramycin or colistin in cystic fibrosis. Resp. J. 20 (3) 658-64, 2002.
[6]Michael W. Konstan *et al*. Safety, efficacy and convenience of tobramycin inhalation powder in cystic fibrosis patients: The EAGER study. Journal of Cystic Fibrosis 2011; 10(1): 54-61.

Tolerance data from the GS-US-205-0110 study (not taken into consideration in the current SPC) are as follows:

Patients were exposed to treatment for an average of 82.4 days in the CAYSTON group (N=136) and 78.4 days in the TOBI group (N=132).
The percentage of patients with adverse events considered as being linked to treatment by the clinical study investigator was higher (p=0.0388) in the CAYSTON group (31/136 or 22.8%, with 70 adverse effects) than in the TOBI group (17/132 or 12.9%, with 45 adverse effects). The majority of adverse effects were of a "respiratory, chest or mediastinum issue" nature (cough, productive cough, oropharyngeal pain, dyspnoea, wheezing, haemoptysis, blockage of the respiratory tract and dysphonia) (CAYSTON: 19 patients vs. TOBI: 14 patients).
Three patients from the CAYSTON group (2.2%) reported serious adverse effects linked to the study medication (wheezing in two patients; productive cough, dyspnoea, haemoptysis and discoloration of sputum in one patient).
No serious adverse effects linked to the study medication were reported in the TOBI group.

Nine patients treated with CAYSTON (6.6%) and one patient treated with TOBI (0.8%) stopped the study medication mainly due to respiratory adverse effects (including a productive cough, haemoptysis and dyspnoea).

Long-term resistance

During the follow-up study to 18 months, where 166/274 patients received nine cycles of treatment, the MIC_{50} and MIC_{90} of *PA* was only modified transiently (± 2 changes in dilution); there is always a theoretical risk that patients treated with CAYSTON may develop long-term resistance towards aztreonam or other betalactams.

3.4. Conclusion

The clinical efficacy of CAYSTON (aztreonam lysine nebuliser solution) was evaluated primarily through three comparative studies, two of which were double-blind, versus placebo (studies CP-AI-005 and CP-AI-007) and one open-label versus nebulised tobramycin (study GS-US-205-0110).

In the two studies versus placebo, CAYSTON was administered over a single cycle of 28 days, to patients (mainly adults) with cystic fibrosis. The inclusion criteria were primarily an FEV1 of between 25% and 75% of the theoretical value (at least 60% of patients had an FEV1 greater than or equal to 50%) and a chronic pulmonary infection due to *P. aeruginosa* (*PA).*
In study CP-AI-005, patients received 28 days of nebulised tobramycin before inclusion, without a break from treatment. The median interval before needing to administer other antibiotics (primary efficacy endpoint) was longer in the CAYSTON group (grouped data: 75 mg 2 and 3 times per day) than in the placebo group (71 versus 92 days, p=0.007).
In study CP-AI-007, CAYSTON (3 times per day, N=80) was superior to the placebo (N=84) in terms of improvements in respiratory symptoms (primary efficacy endpoint) evaluated at Day 28 by the patient using the CFQ-R scale (7.08 versus -2.63; difference 9.71 [4.31; 15.11]).
In both of these studies, changes at Day 28 in pulmonary function and concentration of *PA* in the sputum were also in favour of CAYSTON.
All of these improvements reduced in the two weeks (Day 42) following stopping treatment with CAYSTON.

In the study (GS-US-205-0110) versus nebulised tobramycin (TOBI 300 mg/5 ml, nebulisation solution) CAYSTON was administered in three cycles of 28 days over a period of 24 weeks, to 268 patients (59 children ≥ 6 years and 209 adults) with cystic fibrosis. The inclusion criteria were primarily FEV1 ≤ 75% of the theoretical value (mean FEV1 52% at inclusion) and a sputum culture or a throat swab positive for *PA* in the 3 months prior to inclusion. Patients were pre-treated with nebulised tobramycin during the 12 months prior to their inclusion, 85% of whom for more than 84 days.
Improvement in FEV1 (primary endpoint) over three courses was, on average, more significant for patients treated with CAYSTON than for those treated with TOBI: 2.05% vs. -0.6%; difference 2.7;

p=0.0023. Variations in FEV1 observed in the nebulised tobramycin group were small compared with those normally observed for TOBI, and may be explained by the previous exposure of all patients in the study to TOBI (85% of whom for more than 84 days). In the sub-group of patients pre-treated with nebulised tobramycin for less than 84 days during the 12 months prior to the study, the difference was not significant between CAYSTON and TOBI. The usefulness of these results is limited by the open-label nature of the study and by the questionable clinical relevance in difference between the two groups.

Tolerance data available did not highlight any major tolerance concerns. However, this data is limited and does not answer the uncertainties relating to the risk of long-term resistance.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Chronic infections due to *Pseudomonas aeruginosa* contribute to the development of progressive respiratory failure, a main cause of morbidity and morality in patients with cystic fibrosis.

The aim of treatment with antibiotics is to reduce the bacterial inoculum, lengthen the time between relapses and slow down the impairment of respiratory function.

The efficacy/adverse effects ratio for this proprietary medicinal product is high.

There are treatment alternatives.

Public health benefit

In terms of public health, while cystic fibrosis is at present a serious incurable disease, the burden of this disease is moderate because of its low prevalence. In the indication concerned, the burden is low because of the small number of patients.

The improvement in the management of this disease is a public health need that is an established priority (Rare Diseases Plan, 2005-2008).

Within the scope of improving the management of these patients, given the data available and the current uncertainties regarding the development of long-term resistance to this betalactam, it is not expected that CAYSTON will provide an additional benefit in the reduction in morbidity and mortality specifically relating to the control of chronic pulmonary infections compared with other nebulised antibiotic treatments.

Consequently, on the basis of the available data, it is not expected that CAYSTON will benefit public health.

The Actual Benefit of this proprietary medicinal product is substantial.

4.2. Improvement in actual benefit (IAB)

Despite representing a useful alternative treatment, in the absence of data demonstrating a clinically relevant superiority compared with other comparators (TOBI and COLOMYCIN), the Committee considers that CAYSTON does not provide an improvement in actual benefit (IAB V) in the management of chronic pulmonary infections due to Pseudomonas aeruginosa in patients with cystic fibrosis aged 18 years or older.

4.3. Therapeutic use[7]

The management of bronchopulmonary infections in cystic fibrosis is integral in the overall management of the disease.

Bacterial colonisation occurs very early in the natural progression of the disease. The initial germs involved are *Haemophilus influenzae* and *Staphylococcus aureus*.

Infection due to *Pseudomonas aeruginosa* (*PA*) is a developmental change in this respiratory disease. As adults, approximately 70% of patients will have a chronic colonisation of this germ.

[7] French Paediatric Society, ANAES. Management of cystic fibrosis patients. Consensus conference; Nov. 2002; Paris, France.

The treatment of a first-time colonisation of PA requires association of bactericidal antibiotics via IV (betalactam + aminoside), followed, or not, by treatment with nebulised antibiotics. Combining oral ciprofloxacin and aerosol colistin is also a proposed treatment.

For chronic infection by PA, it is often necessary to treat relapses with dual therapy combining a betalactam anti-pyocyanic with an IV aminoside. The choice of antibiotics is based on the last antibiotic sensitivity test and responses to previous treatments.
In cases of multi-resistant strains, triple therapy combining oral ciprofloxacin with dual therapy may be used. Colistin via IV is still a possible choice in this situation.

The benefit of nebulised antibiotic therapy in the scheduled systematic treatment of bronchial infection due to P. aeruginosa is shown. Its advantage is the direct delivery of antibiotics to the endobronchial infection site and to reduce their systemic absorption and thus their toxicity. Tobramycin or nebulised colistin are used.

Signs, no matter how small, of a worsening in health or respiratory function will result in treatment with IV antibiotics.
Systematic quarterly courses of IV antibiotics are to be used in cases where nebulised treatment is difficult or for some patients who are better stabilised using repeated IV courses. Treatment with oral ciprofloxacin as a middle course may be used.

Therapeutic use of CAYSTON
CAYSTON is a first-line treatment for chronic pulmonary infections due to Pseudomonas aeruginosa, as an alternative to other nebulised antibiotics.
CAYSTON falls within the scope of a scheduled systematic treatment of chronic bronchial infection due to Pseudomonas aeruginosa. It is a useful alternative means of treatment, especially for patients pre-treated with TOBI based on the results from a comparative study versus TOBI.

Data establishing the sustainability observed in the short-term, on previous treatment cycles, are limited.

4.4. Target population

The target population for CAYSTON is defined as adult patients with cystic fibrosis and a chronic pulmonary infection due to *PA.*
Estimation of the target population is based on 2009 data from the French cystic fibrosis register.[8]
In 2009, the number of adults 18 years or older included on the register was 2,579. Considering that the register represents 90% of the population with cystic fibrosis in France, it is estimated that approximately 2,900 adults aged 18 years and older have cystic fibrosis in France.
PA may be present in 44.8% of patients who had a sputum cytology exam in 2009. It is therefore estimated that approximately 1,300 patients aged 18 years or older with cystic fibrosis have a pulmonary infection due to PA.
Among the patients colonised by *PA*, a chronic colonisation is observed in 56.5% of cases. By applying this percentage to the adult population, this would represent approximately 700 patients.
On this basis, the target population may be estimated at approximately 700 patients per year.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services at the dosages in the Marketing Authorisation.

4.5.1. Packaging: Appropriate for the prescription conditions.

4.5.2. Reimbursement rate: 65%

[8] Beat Cystic Fibrosis, National Institute for demographic studies. French register for cystic fibrosis. Summary of data 2009. INED, 2011.