HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

16 October 2013

CAYSTON 75 mg, powder and solvent for nebuliser solution

B/84 vials + 88 ampoules of solvent + 1 ALTERA nebuliser (CIP: 34009 375 151 1 5)

Applicant: GILEAD SCIENCES

INN	Aztreonam lysine
ATC code (2013)	J01DF01 (Antibacterials for systemic use, Monobactams)
Reason for the review	**Extension of indication**
List concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123-2)
Indications concerned	**"Therapy of chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis (CF) aged 6 to 17 years"**

Actual Benefit	**Substantial**
Improvement in Actual Benefit	**In the absence of data showing superiority by comparison with clinically relevant comparators (TOBI and COLIMYCINE), the Committee believes that CAYSTON does not provide <u>any improvement in actual benefit (IAB V, nonexistent)</u> in the "therapy of chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis (CF) aged 6 to 17 years".**
Therapeutic use	**CAYSTON, the only beta-lactam antibacterial for nebulised use, is a first-line treatment for chronic pulmonary infections due to *P. aeruginosa* in patients with cystic fibrosis aged 6 to 17 years as an alternative to other inhaled antibiotics as part of planned, routine treatment for chronic bronchial infection with *P. aeruginosa*. It is an additional means of treatment, particularly in patients previously treated with tobramycin by inhalation (TOBI). The need for 3 aerosols a day might limit children's compliance with treatment. Data supporting the durability of the observed short-term benefit in subsequent treatment cycles are limited and the risk of resistance emerging needs to be monitored.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation	Dated initiated (centralised procedure): 21 September 2009 Extension of indication: 23 July 2012
Prescribing and dispensing conditions / special status	List I Initial six-month hospital prescription Orphan medicinal product

ATC Classification	2013	
	J	Antiinfectives for systemic use
	J01	Antibacterials for systemic use
	J01D	Other beta-lactam antibacterials
	J01DF	Monobactam
	J01DF01	Aztreonam

02 BACKGROUND

Review of the application for inclusion of an extension of indication for the proprietary medicinal product CAYSTON 75 mg, powder and solvent for nebuliser solution, on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use.

CAYSTON was initially included, in the "therapy of chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis (CF) aged 18 years and older", on the lists for National Health Insurance and for hospital use, by orders of 15 March 2013 (Official Gazette of 22 March 2013).

The extension of indication concerns the "therapy of chronic pulmonary infections due to *Pseudomonas aeruginosa* **in patients with cystic fibrosis (CF) aged 6 to 17 years**".

03 THERAPEUTIC INDICATIONS

"CAYSTON is indicated for the therapy of chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis aged **6 years and older**.

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

04 DOSAGE

"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 indicated in children aged 6 years and older. In clinical studies with CAYSTON patients younger than 6 years of age were excluded. The safety and efficacy of CAYSTON in children younger than 6 years of age has not been established. The dosing in children aged 6 years and older is the same as for adults. Dosage is not based on weight or adjusted for age."

05 THERAPEUTIC NEED

Cystic fibrosis is a rare disease for which there is currently no curative treatment. The disease is characterised by episodes of pulmonary infection associated with inflammation, which lead to worsening respiratory function, respiratory failure and ultimately death.

Infection with and then colonisation by *P. aeruginosa* is a turning point in the course of the disease. Its incidence is 76% in patients aged 30 to 34 years, but is lower in children. This pathogen must be managed rapidly with appropriate antibiotic therapy. The almost systematic nature of this infection and the fact that *P. aeruginosa* is multi-drug-resistant mean there is interest in any new drug with potential activity on this pathogen, either in adults or children[1,2,3].

Overall management primarily involves preventing pulmonary infections, including those due to *P. aeruginosa*, a microbe frequently encountered in the environment. The antibiotic therapy recommended for *P. aeruginosa* may combine different routes of administration: inhaled, oral (PO) and intravenous (IV).[2,3]

As in adults, the proprietary medicinal product CAYSTON 75 mg, powder and solvent for nebuliser solution, could be a new treatment option as an alternative to the use of other antibiotics used by inhalation in patients with cystic fibrosis aged 6 to 17 years.

[1] Orphanet Encyclopaedia. Cystic fibrosis. April 2006. http://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=FR&Expert=586
[2] HAS (Haute Autorité de Santé). Cystic fibrosis – National Diagnosis and Treatment Protocol for a rare disease. Chronic Conditions Guide. November 2006.
[3] ANAES (National Agency for the Accreditation of Healthcare Organisations) and SFP (French Paediatric Society). Consensus Conference: Management of patients with cystic fibrosis (pulmonary disease and infection): Guidelines (long version). November 2002.

06 CLINICALLY RELEVANT COMPARATORS

The clinically relevant comparators are all the antibiotics which have an identical or similar spectrum of antimicrobial activity to CAYSTON and which are indicated and/or recommended in the treatment of pulmonary infections with *P. aeruginosa* in cystic fibrosis patients aged 6 to 17 years[3].

06.1 Inhaled antibiotics

NAME *Company*	INN	Dosage	Last TC opinion	AB	IAB
COLIMYCINE 1 MIU powder and solvent for nebuliser solution *SANOFI*	Colistin	1 to 6 MIU/day in 1 to 3 doses	19/12/2012	Substantial	Not applicable
COLOBREATHE 1,662,500 IU Inhalation powder, hard capsule *FOREST*	Colistin	1,662,500 IU 2 times/day	24/07/2013	Moderate	Level V
TOBI 300 mg/5 ml nebuliser solution *NOVARTIS*	Tobramycin	300 mg 2 times/day	20/07/2011	Substantial	Not applicable
TOBI PODHALER 28 mg Inhalation powder, hard capsule *NOVARTIS*	Tobramycin	112 mg 2 times/day	30/11/2011	Substantial	Level V

N.B.: COLOBREATHE and TOBI PODHALER were not yet on the market when the ANAES and SFP guidelines were drawn up, but they have a Marketing Authorisation indication in the treatment of pulmonary infections with *P. aeruginosa* in patients with cystic fibrosis aged 6-17 years, as do COLIMYCINE and TOBI.

06.2 Oral antibiotics

INN	Dosage	Number of doses/day	Population affected by the MA
Ciprofloxacin	40 mg/kg/day (child) 1 to 1.5 g/day (adult) Max. 1500 mg/day (child and adult)	2	adults and children > 5 years
Azithromycin	250 to 500 mg/day	1	adults (off-label in children)

06.3 Intravenous antibiotics

INN	Dosage	Number of doses/day	Population affected by the MA
Ticarcillin (± clavulanic acid)	250 mg/kg/day (child) 400 mg/kg/day (adult) Max. 15 g/day (adult) Max. 20 mg/kg/day clav. ac. (child) Max. 1200 mg/day clav. ac. (adult)	3 to 4	adults and children
Piperacillin (± tazobactam)	300 mg/kg/day (child) 200 mg/kg/day (adult) Max. 12 g/day (adult)	3 to 4	adults and children > 12 years
Ceftazidime	200 to 250 mg/kg/day Max. 12 g/day	3 or continuous infusion (with loading dose)	adults and children
Aztreonam	150 to 200 mg/kg/day Max. 12 g/day	3	adults (off-label in children)
Imipenem	75 to 100 mg/kg/day Max. 4 g/day	3	adults and children
Meropenem	120 to 160 mg/kg/day Max. 6 g/day	3 to 4	adults (off-label in children)
Tobramycin	8 to 10 mg/kg/day	1 to 3	adults and children
Amikacin	20 to 30 mg/kg/day Max. 20 mg/kg/day (adult) with total dose < 1.5 g	1 to 3	adults and children
Ciprofloxacin	30 mg/kg/day (child) 400 to 1200 mg/day (adult) Max. 1200 mg/day (child and adult)	2 to 3	adults and children > 5 years
Colistin	0.1 to 0.15 MIU/kg/day	2 to 3	adults and children

◗ Conclusion:
The most relevant comparators are other inhaled antibiotics: tobramycin (TOBI) and colistin (COLYMICINE).

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

CAYSTON is reimbursed in several European countries in the treatment of chronic pulmonary infections due to *P. aeruginosa* in cystic fibrosis patients aged 18 years and older (adult population).

Country	Date reimbursement started	Special conditions
Germany	2009 (adult population)	None
United Kingdom	2009 (adult population)	None
Spain	2010 (adult population)	None
Italy	2012 (adult population)	Reserved for hospital use
France	2013 (adult population)	None

No information is available about the reimbursement of CAYSTON in the paediatric population in these various countries.

08 SUMMARY OF PREVIOUS ASSESSMENTS

In its initial opinion on CAYSTON (adult population), the Committee's conclusions were as follows:

Date of opinion	15 February 2012 (inclusion on the list of medicines reimbursed by National Health Insurance and inclusion for hospital use)
Indication	"therapy of chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis aged 18 years and older"
AB	Substantial AB
IAB	IAB V

09 ANALYSIS OF THE NEW DATA AVAILABLE

The clinical dossier is based mainly on three phase III studies included in the clinical development programme of CAYSTON that have already been presented in the initial opinion of the Transparency Committee (Opinion of 15 February 2012) on the application for inclusion in adults:

- two comparative studies *versus* placebo
  - **study CP-AI-005**[4] assessing the efficacy and safety of CAYSTON in a dose of 75 mg, 2 or 3 times a day over a treatment cycle of 28 days in 211 patients (of which 46 children, i.e. 21.8% of the study population) previously treated with tobramycin solution by inhalation (TOBI) for 28 days.
  - **study CP-AI-007**[5] assessing the efficacy and safety of CAYSTON in a dose of 75 mg, 3 times a day over a treatment cycle of 28 days in 164 patients (of which 37 children, i.e. 22.6% of the study population).
- a comparative study *versus* tobramycin solution for inhalation (TOBI)
  - **study GS-US-205-0110**[6]: assessing the efficacy and safety of CAYSTON in a dose of 75 mg 3 times a day *versus* TOBI in a dose of 300 mg 2 times a day, over 3 cycles of 28 days' treatment in 268 patients (of which 59 children, i.e. 22.0% of the study population).

The extension of indication in paediatrics (patients aged 6 to 17 years) was obtained on the basis of an analysis (provided for in the protocol) of the results for the paediatric sub-population included in these studies.
Consequently, after a summary of the results obtained in the main analysis, the results of the sub-group analyses in paediatric patients (population corresponding to the extension of indication) will be given in detail here for information purposes.

09.1 Efficacy

Summary of the Transparency Committee's conclusions on these studies (TC Opinion of 15 February 2012)

"The clinical efficacy of CAYSTON (aztreonam lysine in nebuliser solution) was assessed mainly in 3 comparative studies, of which 2 double-blind *versus* placebo (studies CP-AI-005 and CP-AI-007) and one open *versus* inhaled tobramycin (study GS-US-205-0110).

In the two studies *versus* placebo, CAYSTON was administered in a single cycle of 28 days, in patients (mostly adults) with cystic fibrosis. The inclusion criteria were in particular FEV1 between 25% and 75% of predicted (at least 60% of patients had an FEV1 of greater than or equal to 50%) and chronic pulmonary infection with *P. aeruginosa* (*PA).*
In study CP-AI-005 the patients had received 28 days of inhaled tobramycin before inclusion, with no therapeutic window. The median time before it was necessary to administer other antibiotics (primary efficacy endpoint) was longer in the CAYSTON group (grouped data: 75 mg 2 and 3 times a day) than in the placebo group (92 *versus* 71 days; p=0.007).
In study CP-AI-007, CAYSTON (3 times a day, n=80) was superior to placebo (n=84) in terms of the improvement in respiratory symptoms (primary efficacy endpoint) assessed on day 28 by the patient on the CFQ-R scale (7.08 *versus* -2.63; difference 9.71 [4.31; 15.11]; p=0.0005).
In these two studies, the change on day 28 in pulmonary function and in the concentration of *PA* in the sputum was also in favour of CAYSTON.
All of these improvements fade within two weeks (day 42) after stopping treatment with CAYSTON.

In the study (GS-US-205-0110) *versus* inhaled tobramycin (TOBI 300 mg/5 ml, nebuliser solution)

[4] McCoy KS, Quittner AL, Oermann CM, *et al*. Inhaled aztreonam lysine for chronic airway Pseudomonas aeruginosa in cystic fibrosis. Am J Respir Crit Care Med. 2008;178(9):921-8.
[5] Retsch-Bogart GZ, Quittner AL, Gibson RL, *et al*. Efficacy and safety of inhaled aztreonam lysine for airway pseudomonas in cystic fibrosis. Chest. 2009;135(5):1223-32.
[6] Assael BM, Pressler T, Bilton D, *et al*. Inhaled aztreonam lysine vs. inhaled tobramycin in cystic fibrosis: A comparative efficacy trial. J Cyst Fibros. 2012 Sep 14. pii: S1569-1993(12)00136-1. [Epub ahead of print].

CAYSTON was administered for 3 cycles of 28 days over a period of 24 weeks, in 268 patients (59 children ≥ 6 years and 209 adults) with cystic fibrosis. The inclusion criteria were in particular FEV1 ≤ 75% of predicted (mean FEV1 52% on inclusion) and a sputum culture or a throat swab positive for *PA* within 3 months before inclusion. The patients had previously been treated with inhaled tobramycin within 12 months before their inclusion, of which 85% for more than 84 days.
The improvement in FEV1 (primary efficacy endpoint) over 3 courses was on average greater in the patients treated with CAYSTON than in those treated with TOBI: 2.05% vs -0.6%; difference 2.7; p= 0.0023. The changes in FEV1 observed in the inhaled tobramycin group are small compared with those usually observed with TOBI and could be explained by the fact that all the patients in the study had previously been exposed to TOBI (of which 85% for more than 84 days). In the subgroup of patients previously treated with inhaled tobramycin for less than 84 days in the previous 12 months, the difference between CAYSTON and TOBI is not significant. The impact of these results is limited by the open design of the study and by the questionable clinical relevance of the difference between the 2 groups.

The available safety data did not reveal any major problem about safety of use. However, these data are limited and cannot dispel concerns about the risk of long-term resistance."

Efficacy data in the paediatric subpopulation

A total of 142 paediatric patients aged 6 to 17 years with an FEV1 of ≤ 75% of predicted received CAYSTON in the 3 phase III clinical studies. In these studies, the results in the paediatric subpopulation were of the same order as those described in the adult population. The main results of the subgroup analysis of these studies are given below for information purposes.

Comparative studies of CAYSTON *versus* placebo

Study	**CP-AI-005**[4]
Primary efficacy endpoint:	Median time to use of IV or inhaled antibiotics
Total population (n=211)	CAYSTON = 92 days *versus* placebo = 71 day; p=0.007
Subpopulation 6-12 years (n=10)	**CAYSTON = 92 days *versus* placebo = not evaluable**
Subpopulation 13-17 years (n=36)	**CAYSTON = not evaluable *versus* placebo = 71 days**

Study	**CP-AI-007**[5]
Primary efficacy endpoint:	Change in the score for respiratory symptoms (CFQ-R score)
Total population (n=164)	CAYSTON = +7.08 *versus* placebo = -2.63; p=0.0005
Subpopulation 6-17 years (n=37)	**CAYSTON = +12.73 *versus* placebo = -6.19; p=0.0006**

Comparative study of CAYSTON *versus* inhaled tobramycin (TOBI)

Study	**GS-US-205-0110**[6]
Non-inferiority criterion	Change in FEV1 over 1 cycle of treatment (PP population)
Total population (n=268)	CAYSTON = +8.60% *versus* TOBI = +0.75% Difference = 7.86% / 95% CI =[-3.84; 11.88] (non-inferiority achieved)

Subpopulation 6-17 years (n=59)	**CAYSTON = +9.08% *versus* TOBI = +2.80% Difference = 6.28% / 95% CI =[-1.20 ; +13.76] (non-inferiority achieved)**
Superiority criterion	Change in FEV1 over 3 cycles of treatment (ITT population)
Total population (n=268)	CAYSTON = +2.05% *versus* TOBI = -0.66% Difference = 2.70%; p=0.002
Subpopulation 6-17 years (n=59)	**CAYSTON = +2.23% *versus* TOBI = +0.10% Difference = 2.14 (NS)**

09.2 Safety/Adverse effects

The safety data are based firstly on the three phase III studies presented in section "9.1 Efficacy" (**CP-AI-005, CP-AI-007** and **GS-US-205-0110**) and secondly on the following three studies:

- a phase II, placebo-controlled study:
  - **study CP-AI-003**[7] assessing the efficacy and safety of CAYSTON in a dose of 75 mg, twice a day or a dose of 225 mg twice a day, over a treatment cycle of 14 days in 105 patients (of which 21 children treated with CAYSTON, i.e. 20.0% of the study population).
- a non-comparative phase III study:
  - **study CP-AI-006**[8] assessing the efficacy and safety of CAYSTON in a dose of 75 mg, twice a day or 3 times a day, over treatment cycles of 28 days (up to 9 cycles of treatment, with a therapeutic window of 28 days between each cycle) in 274 patients (of which 55 children treated with CAYSTON, i.e. 20.0% of the study population).
- a phase III, placebo-controlled study:
  - **study GS-US-205-0117**[9] assessing the efficacy and safety of CAYSTON in a dose of 75 mg, 3 times a day over a treatment cycle of 28 days in 157 patients (of which 89 children treated with CAYSTON, i.e. 56.7% of the study population).

Data from clinical studies

In the three comparative phase II and III studies *versus* placebo (**CP-AI-003**, **CP-AI-005** and **CP-AI-007**), the incidence of adverse events (AEs) was comparable between the paediatric and adult populations; the commonest AEs were: cough (59% of paediatric patients *versus* 49% of the adult patients), productive cough (25% *versus* 27%), nasal congestion (18% *versus* 14%), fever (18% *versus* 8%) and oropharyngeal pain (16% *versus* 11%). In the other phase III studies (**GS-US-205-0110**, **CP-AI-006** and **GS-US-205-0117**), the incidence of AEs was also comparable between the paediatric and adult populations.
In the three comparative phase II and III studies *versus* placebo (**CP-AI-003**, **CP-AI-005** and **CP-AI-007**), the frequency of serious AEs (SAEs) was 11% (paediatric population) *versus* 7% (adult population); most of the SAEs were pulmonary exacerbations. In another comparative phase III study *versus* tobramycin in nebuliser solution (TOBI) (**GS-US-205-0110**), the frequency of SAEs was 43% (paediatric population) *versus* 28% (adult population) in the CAYSTON group and 26% (paediatric population) *versus* 36% (adult population) in the TOBI group. Most of the SAEs were respiratory, thoracic and mediastinal disorders. In a phase III study (**CP-AI-006**), the frequency of SAEs was 51% (paediatric population) *versus* 38% (adult population).

In one phase III study (**CP-AI-006**), fever was more commonly observed in the paediatric than in the adult patients (55% *versus* 43%).

[7] Gibson RL, Retsch-Bogart G, Montgomery B, *et al*. Aztreonam for Inhalation (AI) in Patients With Cystic Fibrosis & P. Aeruginosa Infection. [Not published].
[8] Oermann CM, Retsch-Bogart GZ, Quittner AL, *et al*. An 18-month study of the safety and efficacy of repeated courses of inhaled aztreonam lysine in cystic fibrosis. Pediatr Pulmonol. 2010;45(11):1121-34.
[9] Wainwright CE, Quittner AL, Geller DE, *et al*. Aztreonam for inhalation solution (AZLI) in patients with cystic fibrosis, mild lung impairment, and P. aeruginosa. J Cyst Fibros. 2011;10(4):234-42.

In one phase III study (**GS-US-205-0110**), haemoptysis was more commonly observed in the patients aged 13 to 17 years in the CAYSTON group than in the TOBI group (21.4% [5 patients] *versus* 3.2% [1 patient]).

In all the phase III studies (**CP-AI-005**, **CP-AI-006**, **CP-AI-007**, **GS-US-205-0110** and **GS-US-205-0117**), the development of resistance to aztreonam was observed in all the population (adults and children): a transient reduction in the susceptibility of strains of *P. aeruginosa* to aztreonam (increase in MIC_{50} and/or MIC_{90} up to 4 times the values observed on inclusion) which was generally reversible 2 weeks after stopping treatment.

Summary of the safety profile in the paediatric population (according to the SPC)

As regards the safety population:
"A total of 137 paediatric patients aged 6 to 17 years with FEV1 ≤ 75% predicted received CAYSTON in phase 2 and phase 3 clinical studies (6-12 years, n = 35; 13-17 years, n = 102)."
(Note: the data from phase III clinical studies were not all included in the SPC).

As regards fever:
"In the phase 2 and phase 3 placebo-controlled studies of CAYSTON, pyrexia was observed with a higher incidence rate in paediatric patients aged 6 to 17 years (18%) compared to adults (8%)."

As regards 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."

As regards resistance to aztreonam (not specific to the paediatric population) :
"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. However, decreased *P. aeruginosa* susceptibility was not predictive of clinical efficacy of CAYSTON during the study."

09.3 Summary & discussion

The efficacy data in the paediatric population are taken from a subgroup analysis of children included in the 3 phase III clinical studies in the CAYSTON clinical development programme that have already been presented in the Transparency Committee's initial Opinion (Opinion of 15 February 2012) on inclusion for adult use.

These 3 comparative studies, 2 *versus* placebo and one open *versus* inhaled tobramycin (TOBI) included 142 patients aged 6 to 17 years with a FEV1 of between 25% and 75% predicted, 83 of whom received CAYSTON. The results observed in this paediatric subgroup were of the same order as those described in the adult population in terms of:

- median time before administration of other antibiotics required longer with CAYSTON than with placebo;
- increase in FEV1 larger with CAYSTON than with placebo; the change in FEV1 over 3 cycles of treatment was not statistically different between CAYSTON and TOBI in the 59 children included;
- improvement in respiratory symptoms (CFQ-R scores) larger with CAYSTON than with placebo;

- reduction in the sputum density of *P. aeruginosa*.

All of these improvements fade within 2 weeks after stopping treatment with CAYSTON.

The safety data in the paediatric population are taken from 5 phase III studies and one phase II study. No major problem with safety of use emerged. Fever was observed more commonly in children treated with CAYSTON than in adults treated with CAYSTON. Haemoptysis was observed more commonly in children treated with CAYSTON than in those treated with inhaled tobramycin (TOBI). The data on resistance to aztreonam are common to the adult and paediatric populations.

These data suggest that the efficacy and safety profiles for CAYSTON observed in the paediatric population are comparable to those observed in the overall population. However, these data are very limited and doubts remain, in particular as regards the persistence of the treatment's efficacy and the long-term risk of *P. aeruginosa* developing resistance to aztreonam.

010 THERAPEUTIC USE

The management of patients with cystic fibrosis is based on the guidelines issued in 2002 by ANAES and the SFP[3].

Treatment to manage chronic pulmonary infections in cystic fibrosis is part of the overall management of the disease. Bacterial colonisation occurs very early in the natural history of the condition. The first pathogens implicated are *Haemophilus influenzae* and *Staphylococcus aureus*. Infection with *P. aeruginosa* is a turning point in the course of the respiratory disease. By the time they are adults, around 70% of patients will have chronic colonisation with this microbe.

Treatment for initial colonisation with *P. aeruginosa* requires a combination of IV bactericidal antibiotics (a beta-lactam antibiotic with activity against *P. aeruginosa* + an aminoglycoside), which may or may not be followed by an inhaled antibiotic treatment. The combination of oral ciprofloxacin and colistin aerosols is also offered.

For chronic infection with *P. aeruginosa*, it is important to treat exacerbations, most often with dual therapy combining two IV antibiotics (beta-lactam agent with activity against *P. aeruginosa* + aminoglycoside). Antibiotics are chosen on the basis of the most recent antibiotic sensitivity test and the response to previous treatments. For multi-drug-resistant strains, triple therapy combining two IV antibiotics (a beta-lactam agent with activity against *P. aeruginosa* + an aminoglycoside) and an oral antibiotic (ciprofloxacin) may be used. IV colistin remains an option in this situation.

Inhaled antibiotic therapy has been proven to be beneficial as planned, routine treatment for chronic pulmonary infection with *P. aeruginosa*. It has the advantage of delivering antibiotics directly to the endobronchial site of infection, while reducing their systemic absorption and thus their toxicity. Inhaled tobramycin or colistin are indicated. In practice, tobramycin is the most frequently used inhaled antibiotic for this indication.

Any signs of clinical aggravation or worsening respiratory function, however minimal, must result in a course of IV antibiotic treatment. Routine three-monthly IV treatments have their place where there is difficulty adhering to inhaled treatment or in some patients who are better stabilised by repeated IV treatments. Use of an oral antibiotic (ciprofloxacin) may also be considered in between treatments.

Therapeutic use of CAYSTON:
CAYSTON, the only beta lactam for nebulised use, is a first-line treatment for chronic pulmonary infections due to *P. aeruginosa* in patients with cystic fibrosis aged 6 to 17 years as an alternative to other inhaled antibiotics as part of a planned, routine treatment for chronic bronchial infection with *P. aeruginosa*. It is an additional means of treatment, particularly in patients previously treated with tobramycin by inhalation (TOBI). The need for 3 aerosols a day might limit children's compliance with treatment. Data supporting the durability of the observed short-term benefit in subsequent treatment cycles are limited and the risk of resistance emerging needs to be monitored.

011 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

011.1 Actual benefit

◗ Chronic infections with *P. aeruginosa* contribute to the development of progressive respiratory failure, the main cause of morbidity and mortality in patients with cystic fibrosis.

◗ Antibiotic therapy is a treatment that aims to reduce bacterial inoculum, make exacerbations less frequent and slow the pace of worsening respiratory function.

◗ The efficacy/adverse effects ratio of CAYSTON is substantial in patients with cystic fibrosis aged 6 years and older.

◗ There are treatment alternatives to CAYSTON in patients aged 6 years and older (other inhaled antibiotics).

◗ CAYSTON is a first-line therapy in patients aged 6 years and older.

◗ Public health benefit:

In terms of public health, while cystic fibrosis is a serious disease which is at present incurable, the burden of this disease is moderate because of its low prevalence. In the indication concerned, the burden is low because of the even smaller number of patients.
Improvement of the management of this disease is a public health need that is an established priority (National Rare Diseases Plan 2005-2008).
Within the context of improving the overall management of these patients, in the light of the data available and the current uncertainty about the emergence of long-term resistance to this beta-lactam, the medicinal product CAYSTON is not expected to have any additional impact in terms of reducing morbidity and mortality specifically attributable to the control of chronic pulmonary infections by comparison with other inhaled antibiotic treatments.
Consequently, in view of the available data, it is not expected that the proprietary medicinal product CAYSTON will benefit public health.

Taking account of these points, the Committee considers that the actual benefit of CAYSTON is substantial in the "therapy of chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis aged 6 to 17 years" and at the dosage in the Marketing Authorisation.

The Committee recommends inclusion of the medicinal product CAYSTON 75 mg, powder and solvent for nebuliser solution, on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the "therapy of chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis aged 6 to 17 years" and at the dosage in the Marketing Authorisation.

◗ **Reimbursement rate: 65%**

011.2 Improvement in actual benefit (IAB)

In the absence of data showing superiority by comparison with clinically relevant comparators (TOBI and COLIMYCINE), the Committee believes that CAYSTON does not provide any improvement in actual benefit (IAB V, nonexistent) in the "therapy of chronic pulmonary infections due to Pseudomonas aeruginosa in patients with cystic fibrosis (CF) aged 6 to 17 years".

011.3 Target population

The additional target population of CAYSTON consists of patients with cystic fibrosis aged 6 to 17 years who have a chronic pulmonary infection with *P. aeruginosa*.

This target population is estimated from the 2010 data report from the French cystic fibrosis registry, published in March 2012 by the organisation Vaincre la Mucoviscidose [Beat Cystic Fibrosis] and the French National Institute for Demographic Studies (INED)[10].

In 2010, the number of patients with cystic fibrosis under 18 years of age who were listed in the registry was 3040, of which about 2/3 aged 6 to 17 years, i.e. about 2050 patients. Given that the 2010 registry represents, like the 2009 registry, about 90% of the population with cystic fibrosis in France, the number of patients with cystic fibrosis aged 6 to 17 years in France is therefore estimated to be about 2300 patients. The number of centres participating in the registry did not actually change between 2009 and 2010.

P. aeruginosa is present in 42.9% of the total population of patients with cystic fibrosis who underwent a cytobacteriological sputum test in 2010. If only patients with cystic fibrosis aged 5 to 19 years are considered, the proportion of patients with *P. aeruginosa* infection is 37.7%. The number of patients with cystic fibrosis aged 6 to 17 years with a *P. aeruginosa* pulmonary infection is therefore estimated to be about 900.

Chronic colonisation is observed in 54.9% of the total population of patients with cystic fibrosis who are colonised by *P. aeruginosa*. If only patients with cystic fibrosis aged 5 to 19 years are considered, the proportion of patients colonised with *P. aeruginosa* who have a chronic infection is 37.0%. The number of patients with cystic fibrosis aged 6 to 17 years with a chronic *P. aeruginosa* pulmonary infection is therefore estimated to be about 350.

Taking account of these points, the additional target population for CAYSTON is estimated to be at most 350 patients with cystic fibrosis aged 6 to 17 years.

012 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ **Packaging:** Appropriate for the prescription conditions according to the indication, dosage and treatment duration.

[10] Vaincre la Mucoviscidose and INED. French Cystic Fibrosis Registry – 2010 data report. March 2012.