HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

18 December 2013

TADIM 1 million international units (IU) of powder for nebuliser solution

Box30 vials (CIP: 34009 387 113 2 5)

Applicant: CENTRE SPECIALITES PHARMACEUTIQUES (CSP)

INN	Colistimethate sodium
ATC Code (2012):	J01XB01 (Antibacterials for systemic use, polymyxins)
Reason for the request	**Inclusion**
List concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123-2)
Indications concerned	**"TADIM is indicated for the treatment by inhalation of colonisation and infections of the lung due to susceptible *Pseudomonas aeruginosa* in patients with cystic fibrosis.** **Consideration should be given to official guidance on the appropriate use of antibacterial agents."**

Actual Benefit	*The Committee considers that the actual benefit of the proprietary medicinal product TADIM in the Marketing Authorisation indication is:* - *substantial within the context of its administration with a "conventional" nebuliser system requiring a pneumatic generator (Pari LC system).* - *insufficient within the context of its administration with the portable nebuliser system fitted with "AAD" and "VMT" (I neb AAD system) technologies or the Respironics Sidestream system with a Portaneb compressor.*
Improvement in Actual Benefit	TADIM does not provide an improvement in actual benefit (**IAB V, non-existent**) compared with COLIMYCIN 1 MIU nebuliser solution.
Therapeutic use	*Within the context of administering TADIM with a "conventional" nebuliser system requiring a pneumatic generator (Pari LC system):* When a colonisation or infection of the lungs due to *P. aeruginosa* in patients with cystic fibrosis justifies colistin treatment by inhalation, TADIM represents an alternative treatment option to the use of the colistin currently marketed in the form of a nebuliser solution (COLIMYCIN 1 MIU). *Within the context of administering TADIM with the portable nebuliser system fitted with "AAD" and "VMT" (I-neb AAD system) technologies or the Respironics Sidestream system with a Portaneb compressor:* In the absence of a clinical trial, the role of TADIM is difficult to define.
Recommendation	The Committee is concerned about the use of a portable device being preferred without any clinical evaluation because its availability free of charge and its convenience of use might make the patient more independent in managing his/her illness.

01 ADMINISTRATIVE AND REGULATORY INFORMATION

MA (mutual recognition procedure)	Date initiated: 14 June 2012 (Reference Member State: UK)
Prescribing and dispensing conditions / special status	List I Initial biannual hospital prescription

ATC Classification	2012	
	J	Antiinfectives for systemic use
	J01	Antibacterials for systemic use
	J01X	Other antibacterials
	J01XB	Polymyxins
	J01XB01	Colistin

02 BACKGROUND

Review of the application for inclusion of the proprietary medicinal product TADIM 1 MIU powder for nebuliser solution on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use.

TADIM is a colistimethate sodium-based (or colistin) proprietary medicinal product, with a composition identical to that of COLIMYCIN 1 MIU powder and solvent for nebuliser solution in terms of its quality and quantity.

TADIM can be inhaled either with a "conventional" nebuliser system requiring a pneumatic generator (Pari LC system), such as COLIMYCIN 1 MIU, or a portable nebuliser system, known as an "I neb AAD system", fitted with "AAD" (Adaptive Aerosol Delivery) and "VMT" (Vibrating Mesh Technology), or Respironics Sidestream with a Portaneb compressor.

03 THERAPEUTIC INDICATIONS

"TADIM is indicated for the treatment by inhalation of colonisation and infections of the lung due to susceptible *Pseudomonas aeruginosa* in patients with cystic fibrosis.

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

04 DOSAGE

"Sputum cultures should be obtained to confirm colonisation *with Pseudomonas aeruginosa </pt153* sensitive to colistimethate sodium prior to initiating treatment with TADIM.

The recommended dosages are as follows. They are to be adjusted according to clinical response:

- Children > 2 years of age and adults: 1 to 2 million IU two or three times daily.
- Children < 2 years: the safety of use and efficacy of TADIM have not been demonstrated in patients less than 2 years of age.

Dosage is determined by the severity and type of infection.

Dosage may thus vary from 1 to 2 million IU depending on the patient's state of health.

Initial colonisation with *Pseudomonas aeruginosa* sensitive to colistimethate sodium may be treated with a 3-week course of 2 million IU twice daily in conjunction with other parenteral or oral antibiotics.

In the event of frequent and recurrent infections (less than three positive cultures of *Pseudomonas aeruginosa* sensitive to colistimethate sodium in a six month period), the dose may be increased up to a maximum of 2 million IU three times daily for up to 3 months, in conjunction with other parenteral or oral antibiotics.

Chronic colonisation (three or more positive cultures of *Pseudomonas aeruginosa* sensitive to colistimethate sodium in a six month period) may require long-term therapy with 1 to 2 million IU twice daily. Additional parenteral or oral antibiotics, may be necessary to treat acute exacerbations of pulmonary infection.

TADIM should be administered after physiotherapy or administration of other inhaled treatments. Other inhaled therapies may include agents to reduce the viscoelasticity of sputum and bronchodilators.

Mode of administration

TADIM is intended for administration by nebulisation using a suitable nebuliser.
The characteristics of the nebulisation of the product based on *in vitro* studies carried out with different nebuliser systems are detailed below:

Characteristic			Nebuliser system			
			Respironics I-neb AAD		Pari LC plus with a Pari TurboBoy S compressor	Respironics Sidestream with a Portaneb compressor
			With a 0.3 ml inhalation chamber (grey)	With a 0.5 ml inhalation chamber (lilac)		
(a)	**Distribution of size of droplets (µm)**	**Median size: d_{50}**	4.34	4.81	4.78	3.32
(b)	Total quantity of product released from the mouthpiece of the nebuliser (Million IU)		0.333	0.579	0.407	0.239
(c)	Fine particle fraction (% < 5 µm)		59.55	53.01	52.67	76.07
(d)	Total quantity of product supplied to the patient (Million IU < 5 µm)		0.198	0.307	0.214	0.182
(e)	Distribution time		3 minutes, 36 seconds	8 minutes, 29 seconds	7 minutes, 4 seconds	5 minutes, 18 seconds
(f)	Rate of distribution of product to the patient (Million IU/minute)		0.055	0.036	0.030	0.034

- Measured using 1 million IU of TADIM, with 1 ml (I-neb AAD) and 3 ml (Pari LC plus and Sidestream) of a mixture of water for injectable preparations and sodium chloride 0.9% (50:50) adjusted to the recommended volume for each nebuliser system.
- TurboBoy S set at a pressure of 1.2 bar and a flow rate of 4.5 l/min. Portaneb set at a pressure of 0.8 bar and a flow rate of 6 l/min
- (d) calculated from (b) /100 x (c)
- (f) = (d) / (e)

For special precautions concerning disposal and handling of the reconstituted solution, see section 6.6 of the SPC."

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. It is prevalent in 76% of patients aged 30 to 34 years. 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 substance 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 frequently encountered bacteria. The anti-pyocyanic antibiotic treatment recommended may combine different administration routes: inhaled, oral and intravenous (IV).[2,3]

Colistimethate sodium (or colistin) is a polypeptide antibiotic, available in inhaled and IV forms, which is one of the antibiotics currently recommended for the treatment of *P. aeruginosa* bronchopulmonary infections in patients with cystic fibrosis.[2,3]

Despite its toxicity and narrow spectrum, the role of this drug in the treatment of bronchopulmonary infections has become topical again, because of the emergence of multi-drug-resistant strains of *P. aeruginosa*. Colistimethate sodium (or colistin) usually has no cross-resistance with other antibiotics.

1 Encyclopédie Orphanet. Mucoviscidose. [April 2006]. http://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=FR&Expert=586

2 HAS (Haute Autorité de Santé). Mucoviscidose - Protocole national de diagnostic et de soins pour une maladie rare. Guide - Affection de longue durée. November 2006.

3 ANAES (National Health Accreditation and Assessment Agency) 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 TADIM, indicated and/or recommended in the treatment of pulmonary infections with *P. aeruginosa* in patients with cystic fibrosis.[3]

06.1 Inhaled antibiotics

NAME *Company*	INN	Dosage	Transparency Committee Opinion
COLIMYCIN 1 MIU powder and solvent for nebuliser solution *Applicant: SANOFI-AVENTIS FRANCE*	Colistin	1 to 6 MIU/day in 1 to 3 doses	Inclusion (hospital use 19/10/2005 hospital use and national health insurance 2/03/2005) AB: Substantial IAB: II Renewal of inclusion (19/12/2012) AB: Substantial
COLOBREATHE 1,662,500 IU inhalation powder hard capsules *FOREST LABORATORIES*	Colistin	1,662,500 IU 2 times/day	Inclusion (hospital use and national health insurance 24/07/2013) AB: Moderate IAB: V, non-existent
TOBI 300 mg/5 ml nebuliser solution *NOVARTIS PHARMA SAS*	Tobramycin	300 mg 2 times/day	Inclusion (hospital use and national health insurance 21/02/2001) AB: Substantial IAB: II Renewal of inclusion (20/07/2011) AB: Substantial
TOBI PODHALER 28 mg inhalation powder hard capsules *NOVARTIS PHARMA SAS*	Tobramycin	112 mg 2 times/day	Inclusion (hospital use and national health insurance 30/11/2011) AB: Substantial IAB: V, non-existent
CAYSTON 75 mg powder and solvent for nebuliser solution *GILEAD*	Aztreonam	75 mg 3 times/day	Inclusion (hospital use and national health insurance 15/12/2012) AB: Substantial IAB: V, non-existent

N.B.: COLOBREATHE, TOBI PODHALER and CAYSTON 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, as do COLIMYCIN and TOBI.

06.2 Oral antibiotics

INN	Dosage	Number of doses/day	Population affected by the MA
Ciprofloxacin	40 mg/kg/d (children) 1 to 1.5 g/d (adults) Max. 1,500 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/d (children) 400 mg/kg/d (adults) Max. 15 g/day (adult) Max. 20 mg/kg/d clav. ac. (children) Max. 1,200 mg/d clav. ac. (adults) (adults)	3 to 4	adults and children
Piperacillin (± tazobactam)	300 mg/kg/d (children) 200 mg/kg/d (adults) Max. 12 g/day (adult)	3 to 4	adults and children > 12 years
Ceftazidime	200 to 250 mg/kg/d Max. 12 g/day	3 or continuous infusion (with loading dose)	adults and children
Aztreonam	150 to 200 mg/kg/d Max. 12 g/day	3	adults (off-label in children)
Imipenem	75 to 100 mg/kg/d Max. 4 g/day	3	adults and children
Meropenem	120 to 160 mg/kg/d Max. 6 g/day	3 to 4	adults (off-label in children)
Tobramycin	8 to 10 mg/kg/d	1 to 3	adults and children
Amikacin	20 to 30 mg/kg/d Max. 20 mg/kg/d (adults) with total dose < 1.5 g	1 to 3	adults and children
Ciprofloxacin	30 mg/kg/d (children) 400 to 1,200 mg/d (adults) Max. 1,200 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:**

TADIM is a colistimethate sodium-based (or colistin) proprietary medicinal product and is able to be administered either via a "conventional" nebuliser system requiring a pneumatic generator, or a portable nebuliser system fitted with AAD and VMT (I-neb AAD system) technologies or the Respironics Sidestream system with a Portaneb compressor.

The most relevant comparators are the colistin presentations currently on the market in the form of nebuliser solutions (COLIMYCIN 1 MIU) and nebuliser powder for a portable inhaler (COLOBREATHE 1,662,500 IU). However, COLOBREATHE has not been available for long.

The other inhaled antibiotics are also clinically relevant comparators.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

TADIM (or PROMIXIN in some countries) was reimbursed after obtaining its Marketing Authorisation in 2003 in the United Kingdom (national procedure), then gradually in different European countries, following two mutual recognition procedures in 2004, then in 2010.

07.1 Reimbursement in other countries

TADIM (or PROMIXIN in some countries) is currently reimbursed in the main European countries, according to data provided by the company.

Country	Reimbursement	Start of reimbursement	Indications reimbursed
United Kingdom	Yes	March 2003	MA indication
Norway	Yes	February 2005	MA indication
Denmark	Yes	September 2005	MA indication
Germany	Yes	January 2007	MA indication
Greece	Yes	March 2007	MA indication
Spain	Yes	August 2007	MA indication
Portugal	Yes	April 2010	MA indication
Italy	Yes	July 2010	MA indication
Sweden	Yes	June 2011	MA indication
Austria	Yes	October 2011	MA indication
Netherlands	Yes	February 2012	MA indication
Poland	Under assessment	Not applicable	Not applicable
Belgium	Not on the market	Not applicable	Not applicable
Luxembourg	Not on the market	Not applicable	Not applicable
Ireland	Not on the market	Not applicable	Not applicable

07.2 Assessment in the United Kingdom by the MHRA

Following the mutual recognition procedure (Reference Member State: United Kingdom), the MHRA (*Medicines and Healthcare Products Regulatory Agency*) has updated the *public assessment report* (PAR) for PROMIXIN. It should be noted that PROMIXIN 1 MIU, which obtained a Marketing Authorisation in 2003 in the United Kingdom (national procedure), is a generic name for COLIMYCIN 1 MIU.

Within the context of this mutual recognition procedure, no new preclinical or clinical study has been carried out which has been deemed acceptable taking account of the generic character of the product approved for over 10 years and the well-established use of the active substance with an acceptable safety profile and recognised efficacy. Moreover, as PROMIXIN 1 MIU has the same composition as the brand drug COLIMYCIN 1 MIU in terms of quality and quantity, it was not deemed necessary to study the bioequivalence between these two proprietary medicinal products. The mutual recognition procedure is therefore based on bibliographical data and the well-established use of the product in several countries.

08 ANALYSIS OF AVAILABLE DATA

The company has provided a bibliographical record comprising publications of clinical trials on the efficacy and safety of inhaled colistin, as well as data relating to the use of colistin with the I-neb AAD nebuliser in the Marketing Authorisation indication of TADIM.

08.1 Efficacy

8.1.1 Efficacy data for inhaled colistin (non-specific study of the proprietary medicinal product TADIM)

- A study[4] comparing the efficacy of colistin in the form of inhalation powder hard capsules (COLOBREATHE®) *versus* tobramycin in the form of nebuliser solution (TOBI®) in the treatment of chronic pulmonary infections with *Pseudomonas aeruginosa* in adults and children aged 6+ with cystic fibrosis. This study had already been analysed by the Transparency Committee when the proprietary medicinal product COLOBREATHE[5] was assessed and cannot be considered relevant within the context of this assessment given the difference in pharmaceutical form and dosage between the proprietary medicinal product TADIM and the proprietary medicinal product COLOBREATHE.
- A study[6] comparing the efficacy and safety of inhaled tobramycin versus inhaled colistin, in combination with ciprofloxacin in *P. aeroginosa* eradication in subjects with cystic fibrosis with chronic colonisation by *P. aeruginosa.* This study did not show any difference between the two groups in terms of *P. aeroginosa* eradication. It cannot be considered relevant within the context of this assessment as the comparator chosen, tobramycin, has no Marketing Authorisation in France in this indication.
- A study[7] comparing the efficacy and safety of tobramycin 300 mg x 2/d aerosols (administered with a Pari LC Plus® nebuliser coupled with the CR50 Medic Aid® compressor) with that of colistin 1 MU x 2/d (administered with a Ventstream Medic-Aid® nebuliser coupled with the CR50 Medic Aid® compressor) in subjects with stable cystic fibrosis with a chronic *PA* infection. This study had already been analysed by the Transparency Committee when the proprietary medicinal product COLIMYCIN 1 MIU in the form of a nebuliser solution was assessed. <ph850/[8] For the record, the Transparency Committee's conclusion on this study was as follows: *"The open-label Hodson study, which compared colistin and tobramycin by inhalation in the treatment of chronic infections of the lung due to Pseudomonas aeruginosa over a period of 4 weeks, showed a decrease in bacterial inoculum in the bronchial sputum in the two treatment groups. The mean relative change in the FEV1 observed under tobramycin (6.7%) was greater than that observed under colistin (0.37%). It should be noted that these results are short-term results and that colimycin was administered at a low dose. The administration of inhaled colistin did not bring out any Pseudomonas aeruginosa resistance*." The data in the 5-month extension of this study[9] are in favour of inhaled tobramycin.

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[4] Schuster A, et al. Safety, efficacy and convenience of colistimethate sodium dry powder for inhalation (Colobreathe DPI) in patients with cystic fibrosis: a randomised study. Thorax. 2013; 68(4): 344-50.

[5] See Transparency Committee opinion of 24 July 2013 on the proprietary medicinal product COLOBREATHE Available at: http://www.has-sante.fr/portail/jcms/c_1638060/fr/colobreathe?xtmc=&xtcr=1

[6] Taccetti G, et al. Early antibiotic treatment for *Pseudomonas aeruginosa* eradication in patients with cystic fibrosis: a randomised multicentre study comparing two different protocols. Thorax. 2012; 67(10): 853-9.

[7] Hodson M, et al. A randomised clinical trial of nebulised tobramycin or colistin in cystic fibrosis. Eur Respir J. 2002; 20(3): 658-64.

[8] See Transparency Committee opinion of 19 October 2005 on the proprietary medicinal product COLIMYCIN 1 MIU. Available at: http://www.has-sante.fr/portail/jcms/c_400700/fr/colimycine-1-mui-poudre-et-solvant-pour-inhalation-par-nebuliseur-flacon-ampoule-de-3-ml-boite-de-1?xtmc=&xtcr=4

[9] Adeboyeku D, et al. Open follow-up study of tobramycin nebuliser solution and colistin in patients with cystic fibrosis. J Cyst Fibros. 2006; 5(4): 261-3.

8.1.2 Usage data for colistin with the I-neb AAD system

The company presented the following data:

- 1 Cochrane Review[10] which evaluated the use of different nebuliser systems available in patients with cystic fibrosis;
- 1 observational, retrospective, non-comparative[11] study which evaluated patient compliance with TADIM treatment inhaled with the I-neb AAD system in 28 patients;
- 1 experimental, before and after, open-label[12] study which evaluated patient satisfaction as regards tobramycin treatment inhaled with a "conventional" nebuliser system, then TADIM treatment inhaled with the I-neb AAD system in 25 patients.

As the studies which evaluated patient compliance and satisfaction showed significant weaknesses in their methods (non-comparative studies and low numbers), only the data from the Cochrane Review will be detailed in this opinion.

Cochrane Review
The aim of this systemic review was to evaluate the efficacy, safety, cost and impact (disease burden, compliance, quality of life) of using different nebuliser systems in patients with cystic fibrosis.

The studies included in this review had to be controlled, randomised or quasi-randomised, with sufficient evidence of similarities to the characteristics of the groups at baseline; the patients had to have cystic fibrosis, with or without exacerbation. The treatments studied could be: tobramycin, colistin, dornase alfa, hypertonic saline or other aerosol treatments (single dose treatment, acute short-term treatment or long-term maintenance treatment) and nebuliser systems compared had to be "conventional", "ultrasonic", "AAD", "VMT" and "AAD-VMT" systems.
With regard to inhaled colistin, two studies (Byrne et al[13]; Dodd et al[14]) compared a "conventional" system with an "AAD" system alone, known as a "Halolite AAD system" (device without VMT technology) of a previous generation to that of the I neb AAD system (device with AAD and VMT technologies).

- Presentation of two studies relating to inhaled colistin included in the review

Byrne et al study[13]
This was an experimental crossover study, carried out in two parts: in the first part, the patients received a single dose of treatment with each of the two nebuliser systems in the study in a randomised order and with at least 1 week's interval; in the second part, after a period without treatment (*washout)* of 7 days, the patients received the treatment with one of the two nebuliser systems in the study for 7 days, then after another *washout* period of 7 days, they received the treatment with another nebuliser system for 7 days.
The co-primary endpoints were the duration of treatment administration (nebulisation time) and the lung deposition of the radiolabelled colistin.

[10] Daniels T, et al. Nebuliser systems for drug delivery in cystic fibrosis. Cochrane Database Syst Rev. 2013; 4: CD007639.
[11] McNamara P, et al. Open adherence monitoring using routine data download from an adaptive aerosol delivery nebuliser in children with cystic fibrosis. J Cyst Fibros. 2009; 8(4): 258-63.
[12] Quintana-Gallego E, et al. [Nebulized colistin versus tobramycin in the treatment of chronic Pseudomonas colonization in cystic fibrosis patients]. Med Clin (Barc). 2013 Jan 28. [Epub ahead of print]. [Article in Spanish].
[13] Byrne N, et al. Comparison of lung deposition of colomycin using the HaloLite and the Pari LC Plus nebulisers in patients with cystic fibrosis. Arch Dis Child. 2003; 88(8): 715-8.
[14] Dodd M, et al. Interaction between bronchodilators and nebuliser device in Cystic Fibrosis patients taking Colistin using a halolite adaptive aerosol delivery (AAD) system compared to a high output conventional nebuliser system. J Cyst Fibros. 2002; 1 (Suppl 1): S106. [Abstract P121 in *Abstracts of the 25th European Cystic Fibrosis Conference. Genoa, Italy, June 20-23, 2002*. *J Cyst Fibros. 2002; 1 (Suppl 1): S1-S187*].

Respiratory function (relative change of FEV1, expressed as a percentage of the theoretical value, or $FEV_{1\%}$) was studied among the secondary endpoints.
The study included a cohort of 15 child and adult patients, aged 7 to 23 (average age = 14.1).
In terms of the co-primary endpoints: nebulising time was shorter with the "AAD" system (298 minutes) than with the "conventional" system (382.5 minutes), i.e. a mean difference = 84.50 minutes; 95% CI = [41.62; 127.38]; however, the lung deposition of radiolabelled colistin was greater with the "conventional" system than with the "AAD" system (mean difference = 6.04 MBq; 95%CI = [4.29; 7.79]).
In terms of the secondary endpoints: change of $FEV_{1\%}$ was not different between the two groups.

Dodd et al study[14]
This was a study carried out in parallel and multicentre groups (Australia, Canada, USA and Europe). The patients received treatment with one of the two nebuliser systems in the study ("conventional" system versus AAD system alone, known as a "Halolite AAD" system) for 26 weeks.
The primary efficacy endpoint was respiratory function (relative change of FEV1 expressed as a percentage of the theoretical value, or $FEV_{1\%}$, at 28 days and at 26 weeks of treatment).
Patient satisfaction and safety were studied among the secondary endpoints.
A total of 259 child and adult patients (median age = 17) were included.
In terms of the primary efficacy endpoint: the change of $FEV_{1\%}$ was greater with the "AAD" system than with the "conventional" system at 28 days of treatment (mean difference = -10.50%; 95% CI = [-17.77; -3.23]), but not at 26 weeks of treatment (mean difference = -4.20%; 95% CI = [-14.93; 6.53]).
In terms of the secondary endpoints: patient satisfaction was in favour of the "AAD" system over the "conventional" system (RR = 0.45; $CI_{95\%}$ = 0.35; 0.57]), although chest compression was reported more frequently under the "AAD" system than with the "conventional" system.

- Discussion among the authors of the review

The authors of the Cochrane Review (Daniels et al.[10]) discuss the following points in particular:

- No study evaluating the combined "AAD" and "VMT" technologies (integrated into the I-neb AAD system) was identified. The systems combining these two technologies are relatively recent and although there are observational studies on dosage or lung deposition, no randomised clinical study (neither experimental crossover design, nor parallel group design) could be included in this review;
- the level of evidence is significant with regard to some of the key points: there is variability in the administration of nebulised medicines depending on the nebuliser system used; the "AAD" and "VMT" systems significantly reduce the nebulising time; the "AAD" systems maintain or improve the lung deposition compared with the "conventional" systems; the deposition is variable with the "VMT" systems depending on the measuring method and the "VMT" system used;
- the level of evidence is lower with regard to the following points: there was a preference among patients for the "VMT" and "AAD" systems over the "conventional" systems; compliance with treatment could be improved by using the "AAD" systems; some "VMT" systems could be the cause of an increasing number of failures to respond to treatment or relapses.

➢ Conclusion put forward by the authors of the review

The authors of the Cochrane Review have come to the particular conclusion that at present:

- There is only limited evidence allowing the preferential use of new nebuliser technologies ("AAD" and "VMT" systems) over "conventional" nebuliser systems;
- Additional research is necessary to clearly establish the benefits of these new technologies, particularly regarding the combined "AAD" and "VMT" technologies (integrated into the I-neb AAD system) for which no randomised clinical study has been identified;
- Data available regarding the impact of different nebuliser systems on the patient-centred issues (disease burden, quality of life, satisfaction, compliance) are particularly limited.

08.2 Safety/Adverse effects

The company provided the last PSUR (periodic safety update report) covering the period of 20 June 2010 to 31 December 2010. Over this period, the total exposure to treatment was estimated to be 1,935 patient-years on the basis of the data from 12 countries. The analysis of these data did not reveal any new signal.

08.3 Summary & discussion

TADIM is a colistimethate sodium-based (or colistin) proprietary medicinal product, with a composition identical to that of COLIMYCIN 1 MIU in terms of its quality and quantity. It can be administered either using a "conventional" nebuliser system requiring a pneumatic generator, such as COLIMYCIN 1 MIU, or a portable nebuliser system fitted with AAD and VMT (I-neb AAD system) technologies or the Respironics Sidestream system with a Portaneb compressor.
Use of colistimethate sodium (or colistin) by inhalation with a "conventional" nebuliser system requiring a pneumatic generator in the treatment of infection due to *Pseudomonas aeroginosa* is well-established with a satisfactory safety and efficacy profile.
However, no clinical study has evaluated the efficacy and safety of colistimethate sodium (or colistin) within the context of its use with portable nebuliser systems fitted with AAD and VMT (I-neb AAD system) technologies or the Respironics Sidestream system with a Portaneb compressor.

08.4 Planned studies

Given its status as a generic drug in the United Kingdom (Reference Member State in the mutual recognition procedure), TADIM is not subject to an RMP (risk management plan).
Efficacy data on clinical criteria with the new portable nebuliser system fitted with AAD and VMT technologies (I-neb AAD system) are missing.

09 THERAPEUTIC USE

The treatment of patients with cystic fibrosis is based on recommendations made in 2002 by ANAES and SFP.[3]

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

The treatment for initial colonisation due to *P. aeruginosa* requires the combination of antibiotics taken intravenously (anti-pyocyanic beta-lactam antibiotics + aminoglycoside), followed or not by an antibiotic treatment by inhalation. The *oral* ciprofloxacin and colistin aerosol combination is also offered.

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

The benefit of inhaled antibiotic treatment in a programmed systematic treatment for chronic lung infection due to *P. aeruginosa* is demonstrated. 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, even if 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. The use of an oral antibiotic (ciprofloxacin) in the inter-treatment interval may be considered.

Role of TADIM in the therapeutic strategy:

Within the context of administering TADIM with a "conventional" nebuliser system requiring a pneumatic generator (Pari LC system):
When a colonisation or infection of the lungs due to *P. aeruginosa* in patients with cystic fibrosis justifies colistin treatment by inhalation, TADIM represents an alternative treatment option to the use of the colistin currently marketed in the form of a nebuliser solution (COLIMYCIN 1 MIU).

Within the context of administering TADIM with the portable nebuliser system fitted with "AAD" and "VMT" (I-neb AAD system) technologies or the Respironics Sidestream system with a Portaneb compressor:
In the absence of a clinical trial, the role of TADIM is difficult to define.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

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

010.1 Actual benefit

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

◗ Antibiotic treatment is a treatment aiming to decrease the bacterial inoculum, space out the exacerbations and slow down deterioration of respiratory function.

◗ The efficacy/adverse effects ratio is high within the context of administering TADIM with a "conventional" nebuliser system requiring a pneumatic generator (Pari LC system). However, in the absence of a clinical trial, the efficacy/adverse effects ratio is poorly established within the context of administering TADIM with the portable nebuliser system fitted with "AAD" and "VMT" (I neb AAD system) technologies and the Respironics Sidestream system with a Portaneb compressor.

◗ There are treatment alternatives to this proprietary medicinal product.

◗ This medicinal product is a first-line therapy.

◗ 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.
As part of the improvement in the overall treatment of these patients, TADIM is not expected to have any additional impact in terms of reducing the morbidity and mortality specifically attributable to infections of the lung compared with other inhaled antibiotic treatments.
Consequently, in light of the available data, TADIM has no public health benefit.

Taking account of these points, the Committee considers that the actual benefit of TADIM in the Marketing Authorisation indications is:

- **Substantial within the context of administering TADIM with a "conventional" nebuliser system requiring a pneumatic generator (Pari LC system).**
- **Insufficient within the context of administering TADIM with the portable nebuliser system fitted with "AAD" and "VMT" (I-neb AAD system) technologies or the Respironics Sidestream system with a Portaneb compressor.**

The Committee:

- **recommends inclusion of TADIM on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indications and at the dosages in the Marketing Authorisation and when the medicine is administered using a "conventional" nebuliser system requiring a pneumatic generator.**
- **does not recommend inclusion of TADIM on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indications and at the dosages in the Marketing Authorisation and when the medicine is administered *with the portable nebuliser system fitted with "AAD" and "VMT" (I-neb AAD system) technologies or the Respironics Sidestream system with a Portaneb compressor.***

◗ Proposed reimbursement rate: 100%

010.2 Improvement in actual benefit (IAB)

TADIM does not provide an improvement in actual benefit (IAB V, non-existent) compared with COLIMYCIN 1 MIU nebuliser solution.

010.3 Target population

The target population of TADIM is made up of patients with cystic fibrosis aged 2+ years with *P. aeruginosa* colonisation or infection of the lung.

Estimation of this target population is carried out from the 2011 data sheet from the French Cystic Fibrosis Registry published in February 2013 by the organisation Vaincre la Mucoviscidose and the INED (French National Institute for Demographic Studies).[15]

In 2011, the number of patients recorded in the registry was about 6,046 patients, including 5,720 patients aged 2 and older.

A positive sample of *P. aeruginosa* was observed in 42.6% of patients with cystic fibrosis who had at least one cytobacteriological examination of sputum (CBES). In patients aged 2+, *P. aeruginosa* would be present in 43.7% of patients. The number of patients aged 2+ with cystic fibrosis who have an infection of the lungs due to *Pseudomonas aeruginosa* is therefore estimated to be about 2,500 patients.

Chronic colonisation was observed in 53.2% of patients (including 54.3% in patients aged 2+) with cystic fibrosis colonised by *P. aeruginosa*. The number of patients aged 2+ with cystic fibrosis who had a chronic infection of the lungs due to *P. aeruginosa* is therefore estimated to be about 1,350 patients.

Taking account of these points, the target population of TADIM is estimated to be at most between 1,350 and 2,500 patients with cystic fibrosis aged 2+.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee is concerned about the use of a portable device being preferred without any clinical evaluation because its availability free of charge and its convenience of use might make the patient more independent in managing his/her illness.

◗ Packaging

Appropriate for the prescription conditions as regards indication, dosage and treatment duration.

[15] Vaincre la Mucoviscidose and INED. Registre Français de la Mucoviscidose – Bilan des données 2011. February 2013.