HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

24 July 2013

COLOBREATHE 1,662,500 IU, inhalation powder, hard capsules

B/56, with Turbospin inhaler (CIP: 34009 268 847 2 7)

Applicant: FOREST LABORATORIES

INN	Colistimethate sodium (colistin)
ATC Code (2012)	J01XB01 (Antibacterials for systemic use, polymyxins)
Reason for the request	**Inclusion**
Lists concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123-2)
Indications concerned	**"COLOBREATHE is indicated for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis aged 6 years and older."**

Actual Benefit	**Moderate**
Improvement in Actual Benefit	**Taking account of the efficacy and safety data, and despite its ease of administration compared with nebuliser solutions, the Committee considers that COLOBREATHE does not provide an improvement in actual benefit (IAB V) in the management of chronic pulmonary infections due to *P. aeruginosa* in patients with cystic fibrosis aged 6 years and older.**
Therapeutic Use	**Taking account of the low level of evidence demonstrating that its efficacy is non-inferior to tobramycin (TOBI), the fact that its efficacy has not been compared with colistin nebuliser solution, and a safety profile that seems less good than the safety profiles of tobramycin and colistin nebuliser solution, COLOBREATHE should only be used as a second-line therapy in the management of chronic pulmonary infections due to *P. aeruginosa* in patients with cystic fibrosis aged 6 years and older, when no alternative treatments can be considered.**

1 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (centralised procedure)	Starting date: 13/02/2012
Prescribing and dispensing conditions / special status	List I Initial six-month hospital prescription

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

2 BACKGROUND

This is an application for inclusion of the proprietary medicinal product COLOBREATHE 1,662,500 IU inhalation powder, hard capsules on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use.

COLOBREATHE is a new presentation of colistimethate sodium (colistin) as an inhalation powder; colistin is also available as a nebuliser solution or an infusion.

3 THERAPEUTIC INDICATIONS

"COLOBREATHE is indicated for the management 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."

4 DOSAGE

"The first dose should be given under medical supervision. The efficacy of COLOBREATHE has been demonstrated in a study of 24 weeks' duration. Treatment may be continued for as long as the physician considers that the patient is obtaining clinical benefit.
Adults
One capsule to be inhaled twice daily. The dose interval should be as close as possible to 12 hours.
Paediatric population
Children of 6 years of age and older
The same dose recommendations as for adults apply to children of 6 years of age and older.
Children below 6 years of age
The safety and efficacy of COLOBREATHE in children under 6 years of age have not been established. No data are available.
Renal impairment
No dose adjustment is considered to be necessary.
Hepatic impairment
No dose adjustment is considered to be necessary."

5 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 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 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 frequently encountered microbe. The antibiotic therapy recommended for P. aeruginosa may combine different routes of administration: inhaled, oral (PO) 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.

COLOBREATHE is a new dosage form of colistin, administered as a dry powder via a portable inhaler, which could be a new treatment option as an alternative to the currently marketed nebuliser solution form of colistin (COLIMYCINE 1 MIU).

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). 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.

6 CLINICALLY RELEVANT COMPARATORS

The clinically relevant comparators are all the antibiotics which have an identical or similar spectrum of antimicrobial activity to COLOBREATHE and which are recommended in the treatment of pulmonary infections with *P. aeruginosa* in patients with cystic fibrosis.[1]

6.1 Inhaled antibiotics

NAME *Company*	INN	Dosage	Indication in MA	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	YES	19/12/2012	Substantial	N/A
TOBI 300 mg/5 ml nebuliser solution *NOVARTIS*	Tobramycin	300 mg twice daily	YES	20/07/2011	Substantial	N/A
TOBI PODHALER 28 mg inhalation powder, hard capsules *NOVARTIS*	Tobramycin	112 mg twice daily	YES	30/11/2011	Substantial	IAB V
CAYSTON 75 mg powder and solvent for nebuliser solution *GILEAD*	Aztreonam	75 mg 3 times/day	YES	15/12/2012	Substantial	IAB V

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 COLIMYCINE 1 MIU and TOBI.

6.2 Oral antibiotics

INN	Dosage	Number of doses/day	Indication in MA
Ciprofloxacin	40 mg/kg/day (child) 1 to 1.5 g/day (adult) Max. 1,500 mg/day (child and adult)	2	YES for age > 5 years
Azithromycin	250 to 500 mg/day	1	YES dosage > MA (adult) off-label (child)

6.3 Intravenous antibiotics

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

◗ Conclusion:

As COLOBREATHE is a new dosage form of colistimethate sodium (or colistin) administered as a dry powder via a portable inhaler, the most relevant comparator is the currently marketed form of colistin, a nebuliser solution (*COLIMYCINE 1 MIU).*

The other inhaled antibiotics are also clinically relevant comparators. However, it should be noted that TOBI PODHALER and CAYSTON have only been available for a short period of time.

7 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

7.1 Reimbursement in the main European countries

COLOBREATHE is already reimbursed or soon to be reimbursed in the main European countries, according to data supplied by the company.

Country	Reimbursement	Date reimbursement started	Indications reimbursed
Netherlands	YES	05/03/2012	All indications in the MA
Austria	YES	12/04/2012	All indications in the MA
Germany	YES	01/06/2012	All indications in the MA
United Kingdom	YES	09/08/2012	All indications in the MA
Belgium	YES	01/03/2013	All indications in the MA
Denmark	YES	Not recorded	All indications in the MA
Luxembourg	YES	Pending publication in Official Journal	All indications in the MA
Spain	Application for reimbursement under submission	Not applicable	Not applicable
Italy	Application for reimbursement under submission	Not applicable	Not applicable

7.2 Assessment in the United Kingdom by NICE (National Institute for Health and Clinical Excellence)

It should be noted that the use of COLOBREATHE (colistimethate sodium inhalation powder, hard capsules) and TOBI PODHALER (tobramycin inhalation powder, hard capsules) in the management of chronic pulmonary infections due to *P. aeruginosa* in patients with cystic fibrosis has been covered by guidelines produced in the UK by NICE (the National Institute for Health et Clinical Excellence) in March 2013:[4]

"Colistimethate sodium DPI is recommended as an option for treating chronic pulmonary infection caused by *P. aeruginosa* in people with cystic fibrosis only if they would clinically benefit from continued colistimethate sodium but do not tolerate it in its nebulised form and thus tobramycin therapy would otherwise be considered […]."

A summary of the NICE guidelines on the use of COLOBREATHE and TOBI PODHALER is provided in the appendix.

[4] NICE (National Institute for Health and Clinical Excellence). Colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis – NICE technology appraisal guidance 276. March 2013.

8 ANALYSIS OF AVAILABLE DATA

The company provided data relating to 5 studies from the clinical development plan for COLOBREATHE (colistimethate sodium), namely:

- 3 phase I or phase II studies (COLO/DPI/98/01, COLO/DPI/98/02 and PPL-252) primarily evaluating pharmacokinetic and pharmacodynamic properties and safety
- 1 phase II safety study (COLO/DPI/02/05),[5] comparing the safety of colistimethate sodium in the form of inhalation powder hard capsules to colistimethate sodium in the form of nebuliser solution
- 1 phase III efficacy study (COLO/DPI/02/06 or Freedom study),[6] comparing the efficacy of colistimethate sodium in the form of inhalation powder hard capsules to tobramycin in the form of nebuliser solution.

For efficacy, only data from the phase III efficacy study and the phase II safety study will be analysed.

For safety and adverse effects, all the studies submitted by the company will be analysed.

A literature search did not reveal any other studies relevant to the application for the inclusion of COLOBREATHE.

[5] Geddes D, Davies J, Conway S, Jaffe A. A Randomised, Open Label Cross-Over Study to Compare the Safety of a Dry Powder Formulation of Inhalated Colistimethate Sodium and Nebulised Colistimethate Sodium in Cystic Fibrosis Patients with *Pseudomonas aeruginosa* Lung Infection. [Unpublished.]

[6] Schuster A, Haliburn C, Döring G, *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.

8.1 Efficacy

Data are presented from the phase III efficacy study (COLO/DPI/02/06 or Freedom study) and the phase II safety study (COLO/DPI/02/05).

8.1.1 Phase III efficacy study (COLO/DPI/02/06 or Freedom study)

- **Study methodology**

Reference	**Phase III efficacy study (COLO/DPI/02/06 or Freedom study)** **Schuster A, Haliburn C, Döring G, Goldman MH, Freedom Study Group.** 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.
Type of study	Open-label, randomised, controlled, non-inferiority study.
Time and place of study	March 2004 to August 2007. Europe: Austria, Belgium, Denmark, France, Germany, Great Britain, Italy, Poland, Portugal, Russia, Spain and Ukraine.
Study objective	To evaluate the efficacy of colistimethate sodium 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 years and older with cystic fibrosis.
Selection criteria	Main inclusion criteria: - Male or female patients aged 6 years or older - Documented diagnosis of cystic fibrosis - Chronic pulmonary infection with *P. aeruginosa* - Willing to take inhaled antibiotics - FEV1 between 25% and 75% of predicted value - Patient has received a minimum of 2 cycles (ON/OFF) of tobramycin nebuliser solution (TOBI) just before randomisation (W0, visit 1) Main non-inclusion criteria: - Evidence of acute pulmonary exacerbation (W0, visit 1) - Previous known hypersensitivity or intolerance to β2-agonists or colistin - Pregnancy or breastfeeding - Taking antibiotics with activity against *P. aeruginosa* as treatment for an exacerbation or taking oral antibiotics for prophylactic reasons (W0, visit 1) - Respiratory tract infection with *Burkholderia cepacia* complex or allergic bronchopulmonary aspergillosis
Treatment	Colistimethate sodium (COLOBREATHE) group: One 1,662,500 IU capsule twice daily, every day for 24 weeks + usual treatment (excluding treatment for *P. aeruginosa*) Tobramycin (TOBI) control group: Inhalation of one 300 mg/5 ml ampoule twice daily for a cycle of 28 days, followed by a cycle of 28 days without administration, for a total of 24 weeks (i.e. three ON/OFF cycles) + usual treatment (excluding treatment for *P. aeruginosa*)
Primary endpoint	Primary endpoint: Relative change in FEV1 value as percentage of predicted value between week 24 and baseline value (change in FEV1% predicted). Non-inferiority hypothesis: The non-inferiority hypothesis was validated if the lower limit of the 95% confidence interval (95% CI) for the difference between the two treatment groups (colistimethate sodium versus tobramycin) was greater than -3.0% for the primary endpoint.

Secondary endpoints	Secondary endpoints included: - Change in resistance to *P. aeruginosa* antibiotics between W0 and W24 - Change in quality of life between W0 and W24 and ease of use of treatments - Time to use of other antibiotics for *P. aeruginosa* and duration of use - Safety
Sample size	A difference of 2% in favour of colistimethate sodium compared to tobramycin was hypothesised for the primary endpoint (change in FEV1% predicted). On the basis of this hypothesis, and supposing a standard deviation of 16%, a sample of 324 assessable patients was deemed necessary (i.e. 162 patients in each group) to demonstrate that colistimethate sodium is non-inferior to tobramycin with a power of 80% and a two-tailed test at the 5% level. The theoretical sample size was estimated as 360 patients, taking a 10% dropout rate into account.
Method for statistical analysis of the results	➢ ANCOVA analysis For the primary endpoint (change in FEV1% predicted), the two groups were compared using an analysis of covariance (ANCOVA) integrating the main effects of treatment, baseline value and pooled centres into the model. ➢ ANCOVA analysis after log transformation Based on the ANCOVA, a Shapiro-Wilk test was performed in order to test the hypothesis of normal distribution. In case of deviations from the normal distribution, the protocol provided for a log transformation to supplement the ANCOVA. ➢ Non-parametric analysis Based on the log transformation, the Shapiro-Wilk test was repeated to test the hypothesis of normal distribution. If deviations from the normal distribution were still present despite the log transformation, the study protocol provided for non-parametric analysis of the data to supplement the ANCOVA and log transformation. **No statistical analysis had priority over another in the statistical analysis plan.**

➢ Efficacy results

- **Number of subjects analysed**

A total of 380 patients were randomised (187 patients in the colistimethate sodium group versus 193 in the tobramycin group). 374 of these patients (183 versus 191) were included in the ITT analysis and 298 (141 versus 157) were included in the PP analysis. The analysis populations are presented in Table 1.

Table 1: Analysis populations

Subjects analysed*	Colistimethate sodium	Tobramycin	Total
Randomised patients, n (%)	187 (100.0)	193 (100.0)	380 (100.0)
ITT population, n (%)	183 (97.9)	191 (99.0)	374 (98.4)
PP population, n (%)	141 (75.4)	157 (81.3)	298 (78.4)

* - Randomised patients: population for the safety analysis
- Intention-to-treat (ITT) population: all randomised patients who were exposed to at least one dose of the medicines in the study and who had a chronic infection as confirmed by the laboratory
- Per-protocol population (PP): all randomised patients who were exposed to at least one dose of the medicines in the study and who adhered to the study protocol

On inclusion, the clinical and demographic characteristics of patients included were comparable in both treatment groups. The majority of patients were male (54.5%) with a mean age of 21 years (59% ≥ 18 years; 23% aged 13 to 17 years; 18% aged 6 to 12 years). The mean FEV1 was 51% (52% in the colistimethate sodium group versus 51% in the tobramycin group), with a median value of 52% (53% versus 50%).

86% of patients included (ITT population) (82.9% in the colistimethate sodium group versus 89.1% in the tobramycin group) completed the 24 weeks of treatment (end-of-study visit), and 14%

(17.1% versus 10.9%) stopped treatment early; the main reasons for stopping were the occurrence of adverse effects (9.6% versus 1.6%) and withdrawal of consent (4.8% versus 5.7%).

- **Results for the primary endpoint**

The results for the primary endpoint (change in FEV1% predicted) are presented for the PP and ITT populations using the last observation carried forward (LOCF) method.

ANCOVA analysis

The results of the ANCOVA analysis are presented in Table 2.

Table 2: Change in FEV1% predicted between inclusion (W0, visit 1) and the end-of-study visit (W24, visit 6) (PP and ITT analysis, LOCF). ANCOVA analysis.

PP population	Colistimethate sodium (N=141)	Tobramycin (N=157)	Difference (%)	95% CI for difference (%)
Mean (± SD)	-0.30 (± 10.31)	1.12 (± 11.12)	-	-
Adjusted mean	-1.02	0.47	-1.49	[-3.79; 0.81]
ITT population	Colistimethate sodium (N=183)	Tobramycin (N=190)	Difference (%)	95% CI for difference (%)
Mean (± SD)	-0.90 (± 10.02)	0.35 (± 10.76)	-	-
Adjusted mean	-1.28	-0.13	-1.16	[-3.15; 0.84]

In the PP analysis, as the lower limit of the 95% CI for the adjusted difference (-3.79%) was below the defined limit for the non-inferiority of colistimethate sodium to tobramycin (-3.0%), the non-inferiority hypothesis could not be validated.

Based on the ANCOVA, a Shapiro-Wilk test was performed in order to test the hypothesis of normal distribution. As there were deviations from the normal distribution, the ANCOVA analysis was supplemented with a log transformation.

ANCOVA analysis after log transformation

Based on this log transformation, the non-inferiority criterion of -3.0% on the lower limit of the 95% CI for the adjusted difference was equivalent to a lower limit of 0.940 for the adjusted ratio. The results are presented in Table 3.

Table 3: FEV1% predicted ratio between inclusion (W0, visit 1) and the end-of-study visit (W24, visit 6) (PP and ITT analysis, LOCF). ANCOVA analysis after log transformation.

PP population	Colistimethate sodium (N=141)	Tobramycin (N=157)	Ratio	95% CI for ratio
Mean (± SD)	0.974 (± 0.204)	0.997 (± 0.196)	-	-
Adjusted mean	0.965	0.988	0.977	[0.935; 1.020]
ITT population	Colistimethate sodium (N=183)	Tobramycin (N=190)	Ratio	95% CI for ratio
Mean (± SD)	0.964 (± 0.199)	0.986 (± 0.190)	-	-
Adjusted mean	0.960	0.979	0.980	[0.943; 1.018]

In the PP analysis, as the lower limit of the 95% CI for the adjusted ratio (0.935) was below the defined limit for the non-inferiority of colistimethate sodium to tobramycin (0.940), the non-inferiority hypothesis could not be validated. This lower limit corresponds to a lower limit of -3.07% in the 95% CI for the adjusted difference.

Based on the ANCOVA performed after log transformation, a Shapiro-Wilk test was performed to test the hypothesis of normal distribution. As the hypothesis of normal distribution was still not satisfied, the ANCOVA and ANCOVA following log transformation were supplemented with a non-parametric analysis.

Non-parametric analysis

The results of the non-parametric analysis are presented in Table 4.

Table 4: Change in FEV1% predicted between inclusion (W0, visit 1) and the end-of-study visit (W24, visit 6) (PP and ITT analysis, LOCF). Non-parametric analysis.

PP population	Colistimethate sodium (N=141)	Tobramycin (N=157)	Difference (%)	95% CI for difference (%)
Median	-1.28	-0.61	-0.67* -0.65**	[-2.50; 1.16]* [-2.49; 1.29]**
ITT population	Colistimethate sodium (N=183)	Tobramycin (N=190)	Difference (%)	95% CI for difference (%)
Median	-1.43	-1.09	-0.56* -0.51**	[-2.16; 1.00]* [-2.07; 1.07]**

* Wilcoxon rank-sum test
** Van Elteren test

In the PP analysis, as the lower limit of the 95% CI for the difference between the groups (-2.50% or -2.49% depending on the test used) was greater than the defined limit for the non-inferiority of colistimethate sodium to tobramycin (-3.0%), the non-inferiority hypothesis could be validated. This result is confirmed in the ITT analysis.

- **Results for secondary endpoints**

Change in resistance to *P. aeruginosa* antibiotics at 24 weeks of treatment

In the patients included (ITT population), the percentage of drug-resistant isolates (defined by MIC greater than or equal to the measured critical concentration of 8 µg/ml for *P. aeruginosa)* changed from 0.0% to 0.05% for colistin in the colistimethate sodium group versus 15.7% to 18.8% for tobramycin in the tobramycin group. The results are presented in Table 5.

Table 5: Number and percentage of drug-resistant isolates between inclusion (W0, visit 1) and the end-of-study visit (W24, visit 6) (ITT population).

	Colistimethate sodium (N=183)		Tobramycin (N=191)	
	Number of isolates	Number of drug-resistant isolates (%)	Number of isolates	Number of drug-resistant isolates (%)
Tobramycin				
W0	246	37 (15.0%)	261	**41 (15.7%)**
W24	202	31 (15.3%)	213	**40 (18.8%)**

	Colistimethate sodium (N=183)		Tobramycin (N=191)	
	Number of isolates	Number of drug-resistant isolates (%)	Number of isolates	Number of drug-resistant isolates (%)
Colistin				
W0	246	**0 (0.0%)**	261	1 (0.4%)
W24	202	**1 (0.5%)**	213	1 (0.5%)

Change in quality of life at 24 weeks of treatment

Quality of life was evaluated using a cystic fibrosis-specific questionnaire (CFQ-R) at 24 weeks of treatment. No difference was observed between the two groups (colistimethate sodium and tobramycin) regarding quality of life.

Ease of use of study treatments

71.9% of the patients included (ITT population) (90.7% in the colistimethate sodium group versus 53.9% in the tobramycin group) felt that the treatments were “very easy” or “easy” to use.

Time to use of other antibiotics for *P. aeruginosa*

The mean time to use of other antibiotics for *P. aeruginosa* was 55.3 days (± 43.2) in the colistimethate sodium group versus 51.8 days (± 41.9) in the tobramycin group.

Duration of use of other antibiotics for *P. aeruginosa*

The mean duration of use of other antibiotics for *P. aeruginosa* was 13.6 days in the colistimethate sodium group versus 14.4 days in the tobramycin group.

8.1.2 Phase II safety study (COLO/DPI/02/05)

- **Study methodology**

Reference	**Phase II safety study (COLO/DPI/02/05)** **Geddes D, Davies J, Conway S, Jaffe A.** A Randomised, Open Label Cross-Over Study to Compare the Safety of a Dry Powder Formulation of Inhalated Colistimethate Sodium and Nebulised Colistimethate Sodium in Cystic Fibrosis Patients with *Pseudomonas aeruginosa* Lung Infection. [Unpublished.]
Type of study	Open-label, randomised crossover study.
Time and place of study	August 2003 to May 2005. Great Britain.
Study objective	To evaluate the safety of colistimethate sodium in the form of inhalation powder hard capsules (COLOBREATHE) versus colistimethate sodium in the form of nebuliser solution (COLIMYCINE 1 MIU) in the treatment of chronic pulmonary infections with *Pseudomonas aeruginosa* in patients aged 8 years and older with cystic fibrosis.
Selection criteria	Main inclusion criteria: - Male or female patients aged 8 years or older - Documented diagnosis of cystic fibrosis - Chronic pulmonary infection with *P. aeruginosa* - Stable respiratory function in the 28 days prior to the first administration of a study treatment - Has already been treated with colistimethate sodium in the form of nebuliser solution (COLIMYCINE 1 MIU), showed no signs of intolerance and did not need to stop treatment - FEV1% predicted greater than or equal to 25% Main non-inclusion criteria: - Evidence of acute pulmonary exacerbation in the 28 days prior to first administration of the study treatments - Previous known hypersensitivity or intolerance to salbutamol or colistin - Pregnancy or breastfeeding - Taking antibiotics with activity against *P. aeruginosa* to treat an exacerbation or taking other antibiotics under certain conditions - Respiratory tract infection with *Burkholderia cepacia* complex or allergic bronchopulmonary aspergillosis
Products studied	Treatment A: colistin inhalation powder hard capsules (COLOBREATHE): One 125 mg capsule (1,662,500 IU) twice daily, every day for 4 weeks Treatment B: colistin nebuliser solution (COLIMYCINE 1 MIU): Inhalation of 1 MIU twice daily for 4 weeks Crossover: Patients received: - either treatment A then treatment B (sequence 1); - or treatment B then treatment A (sequence 2). A 72-hour washout period was necessary between the two treatments.
Primary endpoint	The primary endpoint was safety at 4 weeks of treatment.
Secondary endpoints	- Change in respiratory function (including change in FEV1% predicted) - Change in laboratory markers and quality of life
Method for statistical analysis of the results	Only the change in FEV1% predicted was subject to statistical analysis, in order to demonstrate that there was no significant pulmonary intolerance, i.e. that there was no reduction in FEV1% predicted in patients treated with colistimethate sodium inhalation powder hard capsules compared with the FEV1% predicted of patients treated with colistimethate sodium nebuliser solution (paired two-tailed t-test, α risk of type I error = 0.05).

➢ Efficacy results

- **Number of subjects analysed**

The study included 16 patients randomised into two groups (with a 1:1 ratio):
- Sequence 1 (treatment A then treatment B): 8 patients, with 4 < 14 years and 4 ≥ 14 years
- Sequence 2 (treatment B then treatment A): 8 patients, with 4 < 14 years and 4 ≥ 14 years

- **Duration of follow-up**

Patients were followed up for a period of 9 weeks, comprising:
- a washout period (72 h) before the first administration of a study treatment
- the first treatment sequence period (4 weeks)
- a washout period (72 h) between the two treatment sequence periods
- the second treatment sequence period (4 weeks)

- **Efficacy results**

Statistical analysis did not demonstrate any significant change in FEV1% predicted between the start and end of each 4-week treatment period, whatever the treatment sequence (statistical data not provided by the company).

8.2 Safety & adverse effects

The safety data presented are from the phase III efficacy study (Freedom study), the phase II safety study (COLO/DPI/02/05), the three other phase I or II studies, and the first periodic safety update report (PSUR). Data cited under the heading “Undesirable effects” in the SPC for COLOBREATHE are also presented.

8.2.1 Safety data from the phase III study (Freedom study)

Safety was evaluated in all randomised patients (the safety population), namely 380 patients. The percentage of patients who reported at least one adverse event was 93.6% in the colistimethate sodium group versus 89.1% in the tobramycin group. The percentage of patients who reported at least one adverse event classed as “severe” was higher in the colistimethate sodium group than in the tobramycin group (25.7% versus 6.7%). In addition, treatment was stopped due to an adverse event more frequently in the colistimethate sodium group than in the tobramycin group (11.8% versus 2.6%).

The most commonly reported adverse events were cough (15.7% in the colistimethate sodium group versus 10.3% in the tobramycin group), dysgeusia (10.7% versus 5.2%), throat irritation (7.6% versus 5.3%), dyspnoea (6.6% versus 8.2%) and respiratory tract infections (6.4% versus 7.1%).

Two deaths occurred in the tobramycin group following a respiratory tract infection, and five serious adverse events were considered to be related to the study treatments, comprising three in the colistimethate sodium group: convulsions (1), asthma (1) and haemoptysis (1) versus two in the tobramycin group: haemoptysis (2).

8.2.2 Safety data from the phase II study (COLO/DPI/02/05)

Safety was evaluated for all randomised patients who received at least one dose of one of the two treatments in this study: colistimethate sodium in the form of inhalation powder hard capsules (COLOBREATHE group) or in the form of nebuliser solution (COLIMYCINE 1 MIU group).

	Colistimethate sodium inhalation powder hard capsules (COLOBREATHE) (N=16)		Colistimethate sodium nebuliser solution (COLIMYCINE 1 MIU) (N=15)	
	No. patients	No. AEs	No. patients	No. AEs
Adverse events (AEs)	16	106	9	55
Treatment-related AEs	16	87	5	34
Treatment stopped due to an AE	2	9	0	0
Severity of AEs				
Mild	NR	77	NR	40
Moderate	NR	23	NR	14
Severe	NR	6	NR	1

The most commonly reported adverse events were dysgeusia (87.5% of patients), cough (81.3%) and throat irritation (81.3%) in the COLOBREATHE group versus cough (46.7% of patients) and wheezing (33.3%) in the COLIMYCINE 1 MIU group.

No deaths and no serious adverse events occurred during the study.

8.2.3 Other phase I or phase II studies

In the three other phase I or phase II studies, which included a total of 22 patients with cystic fibrosis and 12 healthy subjects, the most commonly reported adverse events were also cough, dysgeusia and throat irritation, both in patients with cystic fibrosis and in healthy subjects.

8.2.4 Periodic safety update report (PSUR)

The first PSUR for COLOBREATHE covered the period from 13 February 2012 to 17 August 2012. A few minor events were reported from a pharmacokinetics study requested by the EMA (European Medicines Agency). This study was carried out to observe the systemic absorption of COLOBREATHE in patients with cystic fibrosis. In the 14 patients included, 9 mild or moderate adverse events were reported: bronchial obstruction (2), chest pain (2), cough (2), complication associated with use of the inhaler (1), wheezing (1) and new bacterial colonisation (1).

8.2.5 "Undesirable effects" section of the SPC

"Summary of the safety profile
The safety of COLOBREATHE has been assessed in a total of 237 subjects (225 cystic fibrosis patients and 12 healthy volunteers). Of these, 187 patients aged 6 years and above were exposed to COLOBREATHE one capsule twice daily in a 24-week, phase 3 comparative study. There were 32 patients aged 6-12 years, 41 patients aged 13-17 years and 114 patients aged 18 years and older. The most commonly reported adverse reactions as a percent of all COLOBREATHE-treated patients were: unpleasant taste (62%), cough (59.4%), throat irritation (43.9%), dyspnoea (16.6%) and dysphonia (10.7%). Inhalation may induce coughing or bronchospasm which may be controlled by pre-treatment with inhaled $beta_2$ agonists.

Sore throat or mouth has been reported with nebulised colistimethate sodium and may occur with COLOBREATHE. This may be related to *Candida albicans* infection or hypersensitivity. Skin rash may also indicate hypersensitivity and if this occurs treatment should be withdrawn.

Tabulated list of adverse reactions
In the 24-week clinical study, the following adverse reactions were observed across all ages.
Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare <1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	Very Common	Common	Uncommon
Immune system disorders			Drug hypersensitivity
Metabolism and nutrition disorders			Weight fluctuation, decreased appetite
Psychiatric disorders			Anxiety
Nervous system disorders		Balance disorder, headache	Convulsions, somnolence
Ear and labyrinth disorders		Tinnitus	Ear congestion
Respiratory, thoracic and mediastinal disorders	Dyspnoea, cough, dysphonia, throat irritation	Haemoptysis, bronchospasm, asthma, wheezing, chest discomfort, lower respiratory tract infection, productive cough, lung crackles	Chest pain, dyspnoea exacerbated, pharyngolaryngeal pain, epistaxis, sputum purulent, abnormal chest sound, increased upper airway secretion
Gastrointestinal disorders	Dysgeusia	Vomiting, nausea	Diarrhoea, toothache, salivary hypersecretion, flatulence
Musculoskeletal and connective tissue disorders		Arthralgia	
Renal and urinary disorders			Proteinuria
General disorders and administration site conditions		Pyrexia, asthenia, fatigue	Thirst
Investigations		Forced expiratory volume decreased	
Injury, poisoning and procedural complications			Medication error

Paediatric population

In the 24-week clinical study, where COLOBREATHE was administered twice daily to adults and children aged 6-17, the adverse reactions identified in the paediatric population were similar to those for the overall population. The most commonly reported adverse reactions as a percent of COLOBREATHE-treated patients were: cough (55%), unpleasant taste (51%), throat irritation (34%), dyspnoea (10%) and dysphonia (10%).”

8.3 Summary & discussion

A phase III non-inferiority (delta threshold = 3%) study (COLO/DPI/02/06 or Freedom study) compared the efficacy and safety of colistimethate sodium in the form of inhalation powder hard capsules (COLOBREATHE) with the efficacy and safety of tobramycin in the form of nebuliser solution (TOBI) in the treatment of chronic pulmonary infection with *P. aeruginosa* in adults and children aged 6 years and older with cystic fibrosis (N = 380 patients, 187 in the colistimethate sodium group versus 193 in the tobramycin group). Patients were pre-treated with inhaled tobramycin (no patients were naïve to all treatments) and patients with a severe infection (acute pulmonary exacerbation) were excluded.

The treatment duration was 24 weeks. Patients in the colistimethate sodium group received continuous treatment for the 24 weeks, at the dose of one 1,662,500 IU capsule twice daily, and patients in the tobramycin group received intermittent treatment with a 28-day cycle followed by a cycle of 28 days without administration (i.e. three 8-week ON/OFF cycles lasting for a total period of 24 weeks), at the dose of one inhalation of 300 mg/ 5ml twice daily.

The primary efficacy endpoint was relative change in FEV1 value as a percentage of the predicted value between week 24 and the baseline value (change in FEV1% predicted). The non-inferiority hypothesis was validated if the lower limit of the 95% confidence interval (95% CI) for the difference between the two treatment groups (colistimethate sodium versus tobramycin) was greater than -3.0% for the primary endpoint.

Several statistical analyses (provided for in the protocol) were performed on the primary endpoint (analysis of covariance [ANCOVA], ANCOVA analysis after log transformation, and non-parametric analysis), and these analyses were not prioritised.

The non-inferiority hypothesis was only validated in the non-parametric analysis, with a 95% CI lower limit for the difference between the two groups that was greater than the non-inferiority limit (-3.0%) both in the PP population (-2.50% or -2.49% depending on the test used) and the ITT population (-2.16% or -2.07% depending on the test used). However, the fact that multiple statistical analyses were performed (ANCOVA, then ANCOVA following log transformation, then non-parametric analysis) without any statistical analysis being given priority over another limits the level of evidence for the demonstration of non-inferiority.

For the secondary endpoints (change in resistance to antibiotics for *P. aeruginosa* at 24 weeks of treatment, change in quality of life at 24 weeks of treatment, time to use of other antibiotics for *P. aeruginosa* and duration of use of these antibiotics), analysis of the data did not reveal any difference between the two groups in the study. Only ease of use seemed to favour colistimethate sodium in the form of inhalation powder hard capsules.

In terms of safety, colistimethate sodium in the form of inhalation powder hard capsules seemed to induce more adverse events than tobramycin in the form of nebuliser solution. In fact, the percentage of patients who reported at least one adverse event classed as “severe” was higher in the colistimethate sodium group than in the tobramycin group (25.7% versus 6.7%). In addition, treatment was stopped due to an adverse event more frequently in the colistimethate sodium group than in the tobramycin group (11.8% versus 2.6%). The most commonly reported adverse events were cough (15.7% in the colistimethate sodium group versus 10.3% in the tobramycin group), dysgeusia (10.7% versus 5.2%), throat irritation (7.6% versus 5.3%), dyspnoea (6.6% versus 8.2%) and respiratory tract infections (6.4% versus 7.1%).

There are no phase III clinical trials comparing COLOBREATHE with the currently marketed form of colistin, a nebuliser solution (COLIMYCINE 1 MIU), which is the main treatment alternative; COLOBREATHE is a new dosage form of colistimethate sodium (or colistin) administered as a dry powder via a portable inhaler. In a phase II safety study (COLO/DPI/02/05) with a crossover design conducted in 16 patients (age ≥ 8 years) pre-treated with COLIMYCINE 1 MIU and with a stable infection for at least 28 days with no signs of intolerance to colistin, COLOBREATHE seemed to cause more adverse events than COLIMYCINE 1 MIU. The most commonly reported adverse events were dysgeusia (87.5% of patients), cough (81.3%) and throat irritation (81.3%) in the COLOBREATHE group versus cough (46.7% of patients) and wheezing (33.3%) in the COLIMYCINE 1 MIU group.

8.4 Planned studies

As part of its Marketing Authorisation, COLOBREATHE is subject to a risk management plan (RMP) with post-marketing follow-up.

RMP subject		Proposed action
Identified major risks	Cough	Signals will be closely monitored in a post-authorisation study and through post-marketing surveillance and will each be the subject of a special report in future PSURs.
	Dysgeusia	
	Dyspnoea	
	Lower respiratory tract infection	
	Throat irritation	
	Productive cough	
	Chest pain	
	Wheezing	
	Bronchospasm	
	Exacerbation of myasthenia gravis	
Potential major risks	Off-label use	Signals will be closely monitored through post-marketing surveillance and will be the subject of an independent report in future PSURs.
	Oropharyngeal infection with *Candida albicans* or other yeasts	
	Accidental inhalation of particles from the capsule	Signals will be monitored through post-marketing surveillance and will be the subject of an independent report in future PSURs. Educational materials will be used to minimise the likelihood of this type of risk.
	Accidental ingestion of the capsule	
	Increased sensitivity to colistimethate due to the inhaled route of administration	Signals will be closely monitored through post-marketing surveillance and will be the subject of an independent report in future PSURs.
	Nephrotoxicity	
	Hepatotoxicity	
	Neurotoxicity	
	Medication error	Signals will be monitored through post-marketing surveillance and will be the subject of an independent report in future PSURs. Educational materials will be used to minimise the likelihood of this type of risk.
	Harm to fetus	Signals will be closely monitored through post-marketing surveillance and will be the subject of an independent report in future PSURs.

This RMP includes the following additional studies requested by the EMA:

- A study that aims to investigate systemic absorption of COLOBREATHE after it is administered in patients with cystic fibrosis who have a chronic pulmonary infection with *P. aeruginosa*
- An observational registry (PASS study) for post-marketing surveillance (phase IV study) with follow-up for 24 months, which aims to evaluate the safety of long-term exposure to COLOBREATHE in comparison with nebulised colistin in patients with cystic fibrosis
- A single-blind phase IV comparative study that aims to evaluate the efficacy and safety of COLOBREATHE in the management of initial colonisation in patients with cystic fibrosis.

9 THERAPEUTIC USE

Patients with cystic fibrosis should be managed in line with the guidelines issued in 2002 by ANAES and the SFP.[1]

Treatment 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 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. A combination of oral (ciprofloxacin) and inhaled (colistin) antibiotics has also been suggested.

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 antibiogram and 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.

◗ Conclusion

The available data suggest that COLOBREATHE is non-inferior to tobramycin nebuliser solution (TOBI) in terms of efficacy, but the level of evidence is not optimal.

COLOBREATHE is a treatment option that can be used as an alternative to the currently marketed form of colistin, a nebuliser solution (COLIMYCINE 1 MIU). No studies have compared the efficacy of COLOBREATHE with COLIMYCINE 1 MIU.

The safety profile of COLOBREATHE does not seem to be as good as the safety of TOBI or COLIMYCINE 1 MIU nebuliser solutions.

Taking account of the low level of evidence demonstrating that its efficacy is non-inferior to tobramycin (TOBI), the fact that its efficacy has not been compared with colistin nebuliser solution, and a safety profile that seems less good as the safety profiles of tobramycin and colistin nebuliser solution, COLOBREATHE should only be used as a second-line therapy in the management of chronic pulmonary infections due to *P. aeruginosa* in patients with cystic fibrosis aged 6 years and older, when no alternative treatments can be considered.

10 TRANSPARENCY COMMITTEE CONCLUSIONS

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

10.1 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 deterioration in respiratory function.

◗ The efficacy/adverse effects ratio of COLOBREATHE is considered to be modest, taking into account the low level of evidence demonstrating its efficacy and a safety profile that seems less good as the safety profile for tobramycin or colistin nebuliser solution.

◗ There are treatment alternatives to COLOBREATHE (other inhaled antibiotics).

◗ 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.
In the context of improving the overall management of these patients, no additional impact is expected from COLOBREATHE in comparison with other inhaled antibiotic treatments, in terms of reducing the morbidity and mortality specifically attributable to the control of chronic pulmonary infections.
Consequently, in view of the data available, COLOBREATHE does not provide any public health benefit.

◗ COLOBREATHE should only be used as a second-line therapy in the control of chronic pulmonary infections due to *P. aeruginosa* in patients with cystic fibrosis aged 6 years and older, when alternative treatments cannot be considered.

Taking account of these points, the Committee considers that the actual benefit of the proprietary medicinal product COLOBREATHE 1,662,500 IU inhalation powder, hard capsules is moderate in the control of chronic pulmonary infections due to *P. aeruginosa* in patients with cystic fibrosis aged 6 years and older.

The Committee recommends inclusion of COLOBREATHE 1,662,500 IU inhalation powder, hard capsules 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 dosage in the Marketing Authorisation.

◗ **Proposed reimbursement rate: 30%**

10.2 Improvement in actual benefit

Taking account of the efficacy and safety data, and despite its ease of administration compared with nebuliser solutions, the Committee considers that COLOBREATHE provides no improvement in actual benefit (IAB V, non-existent) in the management of chronic pulmonary infections due to *P. aeruginosa* in patients with cystic fibrosis aged 6 years and older.

10.3 Target population

The target population of COLOBREATHE consists of patients with cystic fibrosis aged 6 years and older 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).[7]
In 2010, the number of patients aged 6 years and older recorded in the registry was around 4,700. Because the 2010 registry, like the 2009 registry, represents 90% of the French population with cystic fibrosis, it is estimated that there are around 5,200 patients aged 6 years and older with cystic fibrosis in France. The number of centres participating in the registry has not actually changed between 2009 and 2010.
P. aeruginosa was present in 42.9% of patients who had sputum culture and cytology in 2010. It is therefore estimated that about 2,300 patients aged 6 years and older with cystic fibrosis have a pulmonary infection with *P. aeruginosa*.
Among patients colonised by *P. aeruginosa*, chronic colonisation is observed in about 23.5% of the total number of patients with cystic fibrosis. If only patients aged 6 years and older are considered, the proportion of patients with a chronic *P. aeruginosa* infection is 27.2%. It is therefore estimated that about 1,400 patients aged 6 years and older with cystic fibrosis have a chronic pulmonary infection with *P. aeruginosa*.
In practice, among patients aged 6 years and older with cystic fibrosis who have a chronic pulmonary infection with *P. aeruginosa*, the number of patients likely to receive COLOBREATHE will be much more limited because of the relatively low percentage of patients eligible for this treatment (clinical forms with pathogens sensitive to colistin, and where alternative treatments cannot be considered).

Taking account of these points, the target population of COLOBREATHE is estimated to be less than 1,400 patients.

11 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ **Packaging:** The packaging is not appropriate for the prescription conditions in terms of indication, dosage and treatment duration. The Committee wishes to reiterate that, in accordance with its deliberations of 20 July 2005, standardisation of pack size to 30 days is recommended for treatments lasting one month.

[7] Vaincre la Mucoviscidose and INED. Registre Français de la Mucoviscidose – Bilan des données 2010. March 2012.

12 APPENDIX

Summary of NICE guidelines on the use of COLOBREATHE and TOBI PODHALER[4]

Colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis

NICE technology appraisal guidance 276

1 Guidance

NOTE FOR IMPLEMENTATION: NICE has been made aware that colistimethate sodium dry powder for inhalation is not available at the time of publication of this guidance. We are investigating the consequences for the funding direction for this part of the guidance. The guidance and implementation requirements for tobramycin dry powder for inhalation stand as indicated in section 5 of the document.

1.1 Tobramycin dry powder for inhalation (DPI) is recommended as an option for treating chronic pulmonary infection caused by *Pseudomonas aeruginosa* in people with cystic fibrosis only if:

- nebulised tobramycin is considered an appropriate treatment, that is, when colistimethate sodium is contraindicated, is not tolerated or has not produced an adequate clinical response **and**
- the manufacturer provides tobramycin DPI with the discount agreed as part of the patient access scheme to primary, secondary and tertiary care in the NHS.

1.2 Colistimethate sodium DPI is recommended as an option for treating chronic pulmonary infection caused by *P. aeruginosa* in people with cystic fibrosis only if:

- they would clinically benefit from continued colistimethate sodium but do not tolerate it in its nebulised form and thus tobramycin therapy would otherwise be considered **and**
- the manufacturer provides colistimethate sodium DPI with the discount agreed as part of the patient access scheme to primary, secondary and tertiary care in the NHS.

1.3 People currently using tobramycin DPI or colistimethate sodium DPI that is not recommended according to 1.1 or 1.2 should be able to continue treatment until they and their clinician consider it appropriate to stop. For children and young people this decision should be made jointly by the clinician, the child or young person and their parents or carers.