Risk Management Plan (RMP) in the EU

for

Colistimethate sodium (Colobreathe®)

RMP version to be assessed as part of this application	
RMP version number	10.0
Data lock point for this RMP	30.06.2024
Date of final sign off	05.07.2024
Rationale for submitting the updated RMP	Removal of risks and additional risk minimization measures following PRAC recommendation after PSUSA procedure N° EMEA/H/C/PSUSA/00009112/202302
Summary of significant changes in this RMP	Revised list of safety concerns and discontinuation of additional risk minimization measures.

QPPV Name: Katja Pecjak

QPPV signature:

Other RMP versions under evaluation	
RMP Version number	Not applicable.
Submitted on	Not applicable.
Procedure number	Not applicable.

Details of the currently approved RMP	
Version number	9.0
Approved with procedure	EMEA/H/C/001225
Date of approval (opinion date)	12 February 2020

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List of Abbreviations

ADR	Adverse Drug Reaction

AE	Adverse Event
ARMM	Additional Risk Minimisation Measure
ATC	Anatomical Therapeutic Chemical
CF	Cystic Fibrosis
CFLD	Cystic Fibrosis-associated Liver Disease
CFPE	Cystic Fibrosis Pulmonary Exacerbations
CFRD	Cystic Fibrosis Related Diabetes
CI	Confidence Interval
CSR	Case Safety Report
CTD	Common Technical Document
DIOS	Distal Intestinal Obstruction Syndrome
DPI	Dry Powder Inhaler
DVD	Digital Versatile Disc
e.g.	example given
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FEV1	Forced Expiratory Volume in 1 Second
HCP	Healthcare Professional
HLT	High Level Term
i.e.	Id est (eng. that means)
INN	International Non-proprietary Name
IU	International Unit
LRTI	Lower Respiratory Tract Infection
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
MDT	MultiDisciplinary Teams
NEC	Not Elsewhere Classified
PASS	Post Authorisation Safety Studies
PEG	Polyethylene Glycol
PIL	Patient Information Leaflet

PSUR	Periodic Safety Update Report
PT	Preferred Term
SAE	Serious Adverse Event
SMQ	Standardised MedDRA Query
SPC, SmPC	Summary Of Product Characteristics
TBD	To Be Determined
TOBI	Tobramycin Inhalation Powder
UK	United Kingdom

Part I: Product(s) Overview

Table 1: Part I.I Product(s) Overview

Active substance(s) **(INN or common name)**	Colistimethate sodium
Pharmacotherapeutic group(s) (ATC Code)	Antibacterials for systemic use, other antibacterials. ATC code: J01XB01
Marketing Authorisation Applicant	Essential Pharma Ltd. Vision Exchange Building, Triq it-Territorjals, Zone 1, Central Business District, Birkirkara, CBD 1070, Malta
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	COLOBREATHE® 1,662,500 IU inhalation powder, hard capsules
Marketing authorisation procedure	Centralized procedure
Brief description of the product	Chemical class: Cyclic polypeptide antibiotics
	Summary of mode of action: Colistimethate sodium is a cyclic polypeptide antibiotic in the polymyxin group with activity against a range of Gram-negative organisms including Pseudomonas aeruginosa. Polymyxins are cationic agents which work by a physicochemical action, damaging the cell membrane, and are specific for aerobic Gram negative bacteria that have a hydrophobic outer membrane.
	Important information about its composition: None.
Hyperlink to the Product Information	Please refer to CTD Module 1.3.1.
Indication(s) in the EEA	Current: Colobreathe® is indicated for the management of chronic pulmonary infections due *to Pseudomonas aeruginosa* in patients with cystic fibrosis (CF) aged 6 years and older.
	Proposed: Not applicable.
Dosage in the EEA	Current: Adults and children of 6 years of age and older; one capsule to be inhaled twice daily. The dose interval should be as close as possible to 12 hours.

	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. Colobreathe® is approved for inhalation use only. Colobreathe® capsules are to be used only with the Turbospin inhaler.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Colistimethate sodium 1,662,500 IU inhalation powder, hard capsules
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety Specification

Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

Indication

The management of chronic pulmonary infections due to *Pseudomonas aeruginosa* (*P. aeruginosa*) in patients with cystic fibrosis (CF) aged 6 years and older.

Incidence:

The incidence of chronic infection with *Pseudomonas aeruginosa* in cystic fibrosis patients increases with age. By 18 years of age, approximately 80% of cystic fibrosis patients harbor *Pseudomonas aeruginosa*. (Mitchell RS et al (2007) Robbins Basic Pathology. Saunders/Elsevier. ISBN 1-4160-2973-7) Colobreathe® was removed from the community register of Orphan Medicinal Products on 12th October 2011.

Prevalence:

Cystic fibrosis (CF) is a congenital, recessively inherited disorder, which affects one of 2,000 newborns in Caucasian populations. In Europe, approximately 35,000 children and young adults have CF. (Hoiby N. Recent advances in the treatment of *Pseudomonas aeruginosa* infection in cystic fibrosis. BMC Med 2011;9:32 On line doi: 10.1186/1741-7015-9-32).

The latest figures in June 2010 (last orphan designation maintenance report) state prevalence as 0.45 per 10,000 persons.

Demographics of the population in the authorised indication and risk factors for the disease:

The demographic profile for CF patients with *P. aeruginosa* infection mirrors that of CF patients in general.

Risk factors for initial *P. aeruginosa* infection are not well understood. The ongoing EPIC observational study showed that cystic fibrosis genotype functional class had an important effect on age at initial *P. aeruginosa* acquisition (Rosenfeld M, EPIC Study Group, 2012). A positive culture immediately after treatment of first isolate was a strong risk factor for development of chronic infection (Hansen CR, 2008). Persistent *P. aeruginosa* isolates were more often cytotoxic, but it was not possible to predict the risk of persistence based on bacterial characteristics for each individual patients. Unknown factors such as host-pathogen and pathogen-pathogen interactions needed further examination (Hansen CR, 2008).

The main existing treatment options:

The recommended treatment options for patients with chronic *P. aeruginosa* infection include three approved inhaled aerosol antibiotics, tobramycin, aztreonam and colistin. The best strategy includes an intermittent one month-on one month-off regime for inhaled tobramycin or aztreonam and continuous administration for inhaled colistin. Administering another inhaled antibiotic in the off month cycle or administering continuously inhaled antibiotic is also practiced and may benefit those patients with unstable disease (Döring, 2012). Currently the optimal antibiotic treatment regimen is not established for eradication of *P. aeruginosa* because a number of treatment regimens have showed similar effectiveness including tobramycin inhalation solution,

combination of oral ciprofloxacin and inhaled colistin and intravenous therapy (Döring, 2012). The combination of inhaled colistin for 3 weeks–3 months of treatment plus oral ciprofloxacin has been used successfully (Høiby N, 2005). In children with CF and new *P. aeruginosa* infection, inhalation of tobramycin inhalation solution (28 days) or inhaled colistin plus oral ciprofloxacin (3 months) resulted in similar eradication success at the end of treatment (80 and 90% respectively) and similar clinical evolution during the first two years of follow-up (Proesmans M., 2013).

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

P. aeruginosa respiratory infection in CF patients is associated with poor survival due to the ensuing lung damage. It is not possible to accurately predict the decline in lung function. Various cohort studies have previously demonstrated a lung function decline in adult patients of approximately 3% to 5% Forced expiratory volume in 1 second (FEV1) predicted per annum (Walters S., 2000) The use of inhaled anti-pseudomonal therapy is one approach that has been used to slow or prevent this decline in lung function, by controlling or eradicating the infection.

Important co-morbidities:

Table 2: Important co-morbidities found in the target population

Disease	Incidence	Prevalence	Mortality
Cystic fibrosis related diabetes (CFRD)	CFRD occurs in 10-15% of all CF patients (CF Trust)	The prevalence of Cystic Fibrosis Related Diabetes (CFRD) increases with the age of the patient but is more common and develops at an earlier age in CF patients who are pancreatic insufficient. The median age of diagnosis has been reported as 18 -21 years but as length of survival of CF patients increases this may change. Analysis of reports suggests that 70-90% of CF patients surviving to age 40 will have CFRD and 50% of CF patients aged 30 have CFRD (Lanng et al., 2001).	A medical chart review study conducted on 664 patients determined that overall mortality for patients with CFRD was 1.8 per 100 person-years, compared with 0.5 in patients with CF without diabetes (P = 0.0002); The authors noted that neither rate changed significantly from mortality reported for 2003–2008(Lewis et al., 2015).

Disease	Incidence	Prevalence	Mortality
Vitamin deficiency	Malabsorption of fat soluble vitamins (A, D, E and K) is likely in most patients with CF, particularly those who are pancreatic insufficient. Biochemical evidence of fat soluble vitamin deficiency has been found by two months of age in untreated screened infants with CF (Sokol et al, 1989; Feranchak et al, 1999).	See incidence statement	This has not been demonstrably associated with increased mortality.
Meconium Ileus	16-20% in infants (Irish M, 2011).	See incidence statement	Survival rates for infants with both complicated and simple meconium ileus are in the order of 85-100%. In a 32 year study, there were 8 (9%) deaths due to meconium ileus, with 5 of these patients having complicated meconium ileus and 3 having simple meconium ileus (Escobar et al., 2005)
Exocrine Pancreatic Disease	Exocrine pancreatic insufficiency, causing an inability to properly digest food, occurs in the majority (85% to 90%) of patients with CF (Heubi J, 2007). It is mainly associated with "severe" CFTR mutations, where both alleles are completely non-functional (eg. ΔF508/ΔF508). It occurs in very few patients with one "severe" and one "mild" CFTR mutation where there still is a little CFTR activity, or where there are two "mild" CFTR mutations (Kristidis et al., 1992)	See incidence statement	Malnutrition, an outcome of exocrine pancreatic disease, was once thought to be an inevitable consequence of cystic fibrosis (CF). It is now considered preventable but still contributes considerable morbidity in children. Malnutrition is linked to poorer pulmonary function, reduced survival and quality of life. As the anticipated lifespan of children with CF continues to lengthen, the prevention of malnutrition attains greater importance.

Disease	Incidence	Prevalence	Mortality
Distal Intestinal Obstruction Syndrome (DIOS)	DIOS occurs mainly in adolescents and adults, but all age groups can be affected, with an overall incidence of approximately 15%. Up to 3.5% of patients will have recurrences. (Cystic Fibrosis Medicine., 2011b).	See incidence statement	DIOS has been reported as a major cause of mortality in mice with CF but no figures relating to mortality in CF patients can be located.
Hepatic Diseases	Hepatic steatosis occurs in approximately 30% of patients with CF and may be found at any age. Focal biliary cirrhosis develops in up to 40% of patients with CF and is pathogenomic of CF related liver disease. Approximately 1% of CF patients with biliary cirrhosis progress clinically to portal hypertension and end-stage liver disease. Cholelithiasis is also a relatively common co-morbidity, occurring in 12%-24% of CF patients. (Review Anon).	See incidence statement	Early studies suggested that patients with CFLD had a shorter life expectancy, with a reported mean duration of survival of 4.5 years from diagnosis of liver disease. In contrast, more recent studies, both in children and adults, suggest that CFLD does not affect mortality or morbidity. However, in one study, after a fixed follow-up of 7 years, 9.4% (7 of 36) of CFLD participants had died or underwent liver transplantation compared with 8.3% (3 of 36) of CF controls. (Rowland et al., 2011).

Part II: Module SII - Non-Clinical Part of the Safety Specification

Key safety findings from non-clinical studies and relevance to human usage:

Colistimethate sodium has been established in the treatment of *Pseudomonas aeruginosa* lung infection in CF patients for a number of years, largely by the nebulized route but also by intravenous administration.

Fifty years of clinical use in a variety of infections have not revealed any toxicological issues beyond those in the proposed Summary of Product Characteristics. As the non-clinical toxicity of the active ingredient has been comprehensively described in the literature, no non-clinical studies have been specifically undertaken with Colobreathe®.

Toxicity

Table 3: Non-Clinical Part of the Safety Specification

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
Toxicity	

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
Inhalation studies/ Local toxicity	Toxicology studies following inhalation administration have not been conducted for Colobreathe®. However, the safety profile of colistimethate sodium is well characterized as a result of extensive human inhaled and intravenous use over the last 50 years. A pharmacokinetic study in Sprague- Dawley rats has been conducted to bridge the exposure in animals via intravenous administration with the human experience via inhalation administration.
Reproductive Toxicity	Colistimethate sodium given intramuscularly during organogenesis to rabbits at 4.15 and 9.3 mg/kg resulted in talipes varus (club foot) in 2.6% and 2.9% of fetuses, respectively. These doses are 0.25 and 0.55 times the maximum daily human dose based on mg/m2. In addition, an increase in the incidence of resorptions occurred at 9.3 mg/kg. In subsequent rabbit embryo/fetal development studies and in similar studies in mice and rats, these findings were not reproduced. Colistimethate sodium was not teratogenic in rats at 4.15 or 9.3 mg/kg. These doses are 0.13 and 0.30 times the maximum daily human dose based on mg/m2. Although talipus varus was similar to the anticipated spontaneous rate of occurrence in rabbits, and not reproducible in subsequent rabbit or rodent studies, it was dose dependent; and while its relation to colistimethate sodium is unlikely, it cannot be ruled out. There were no effects observed in the survival, growth development or fertility of offspring of rats administered colistimethate sodium a few days prior to birth through lactation. Additionally, it has been reported in the literature that parenteral administration of colistimethate sodium resulted in no effect on the fertility, or reproductive performance of rats or mice.
	There are no adequate and well-controlled studies in pregnant women. A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with Colobreathe® should be made taking into account the benefit of breastfeeding to the child balanced against the benefit of Colobreathe® therapy to the woman.
Genotoxicity	The genotoxic potential of colistimethate sodium has been evaluated in vitro and in vivo. The preponderance of the data taken as a whole indicates that colistimethate sodium is not genotoxic.
Carcinogenicity	Although formal animal carcinogenicity tests have not been performed with colistin, there is no reason to suppose either from chemical structure or clinical experience that the compound is likely to possess significant carcinogenic potential.

Table 4: Conclusion on Non-Clinical Data

Safety Concerns (Conclusion on Non-Clinical Data)
Important identified risks (confirmed by clinical data) • None
Important potential risks (not refuted by clinical data or which are of unknown significance) • Foetal Development There are no adequate and well-controlled studies in pregnant women and there is no evidence from the extensive clinical IV and inhalational use of colistimethate sodium to suggest that it has significant adverse effects on fertility or development. Colistimethate sodium is transferred across the placental barrier in humans; however given the low amounts of colistimethate sodium systemically absorbed following inhalation it is unlikely that Colobreathe® would affect the development of offspring. • Lactational Transfer Although minimal amounts of colisimethate sodium are systemically absorbed, that which is absorbed may be secreted in breast milk. A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with Colobreathe® should be made taking into account the benefit of breastfeeding to the child balanced against the benefit of Colobreathe® therapy to the woman.

Safety Concerns (Conclusion on Non-Clinical Data)
Missing information • None

Part II: Module SIII - Clinical Trial Exposure

Brief Overview of Development

Colistimethate sodium (colistin) is one of the polymyxin antibiotics produced by *Bacillus colistinus*. Polymyxins were discovered in 1947 and Forest Laboratories, UK has marketed colistin for over 50 years as Colomycin® for injection or inhalation for the treatment of severe systemic infections caused by sensitive Gram-negative organisms. In particular colistin has been used to treat *Pseudomonas aeruginosa* lung infections in patients with cystic fibrosis (CF). The impetus behind the development of a dry powder inhaled colistin was to enhance patient acceptability of dosing by reducing the time required to administer this effective inhaled antibiotic medication.

The indication for Colomycin®, treatment by inhalation of *Pseudomonas aeruginosa* lung infection in patients with CF, was also sought for the colistimethate sodium dry powder inhaler (DPI), Colobreathe®. The route of administration, via oral inhalation, remained the same.

The CF patient population remained the same for Colobreathe® but due to the physical constraints attendant on the use of a DPI the lower age limit was set at 6 years. A study is proposed in CF patients who are infected early (acute as opposed to chronically infected) with *Pseudomonas aeruginosa*. The end point is to look at the percentage of patients with eradication at the end of therapy i.e. eradication rate.

Clinical Trial Exposure

Table 5: Duration of Exposure (totals)*

Duration of exposure (at least)	Persons	Person time (years)
0 weeks	223	77.1
4 weeks	179	76
8 weeks	169	74.8
12 weeks	153	72.2
16 weeks	152	71.9
20 weeks	150	71.2
24 weeks	125	60.0
28 weeks	3	2.6
Unknown	14	0.0
Total	**1,168**	**505.8**

*Due to database limitations, studies COLO/DPI/98/01, COLO/DPI/98/02, and PPL-252 are not included in the table above.

Table 6: Dose (totals)*

Dose of exposure	Study numbers	Persons	Person time (years)
Multiple Dosing 1,662,500 IU bid for up to 28 days	COLO/DPI/02/05	15	2.2
Multiple Dosing 1,662,500 IU bid for up to 24 weeks	COLO/DPI/02/06	174	74.2
Multiple Dosing 1,662,500 IU bid for 7 days in cystic fibrosis patients	COLO/DPI/02/11	34	0.7
Total		**223**	**77.1**

*Due to database limitations, studies COLO/DPI/98/01, COLO/DPI/98/02, and PPL-252 are not included in the table above

Table 7: Age Group and Gender (totals)*

Total population: 237				
Age group	**Persons**		**Person time (years)**	
Sex	**M**	**F**	**M**	**F**
6-17 years	51	55	18.1	14.9
≥18 years	77	54	27	17.1
Total	**128**	**109**	**45.1**	**32**

*Due to database limitations, studies COLO/DPI/98/01, COLO/DPI/98/02, and PPL-252 are not included in the table above

The patients included in these studies were mostly Caucasian as this disease is uncommon in people of African or Asian origin. Please note that information on ethnicity or racial origin is not available for study number COLO/DPI/02/06.

Table 8: Ethnic Origin (totals)*

Ethnic/racial origin	Persons	Person time (years)
Asian	1	0.0
Caucasian	49	2.9
Total	**50**	**2.9**

*Due to database limitations, studies COLO/DPI/98/01, COLO/DPI/98/02, and PPL-252 are not included in the table above

There is no clinical trial exposure for special populations including pregnant women, lactating women, renal/hepatic/cardiac impairment, sub-populations with genetic polymorphisms or immuno-compromised.

Part II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Criterion	Reason for exclusion	Is it considered to be included as missing information	Rationale
Patients with predicted FEV1 outside the range 25-75%	The DPI 0206 study population included patients with an FEV1 % predicted between 25-75%. Only 5 patients who had pulmonary function out with the range specified (25-75%) for FEV1 predicted were available for safety evaluation. There is no rationale for a safety concern if greater than 75% and if less than 25% predicted the only issue might be difficulty in inhaling the powder with consequent reduction in efficacy.	No	Not a safety issue.
Patients with imminent heart lung transplant	This population typically represents a worse clinical status, and as such the benefits of medications would be considered to exceed the potential risks.	No	Not a safety issue.
Children under the age of 6 years	It is not envisaged that children under the age of 6 will use the product as they may not possess the motor skills required to use the Turbospin device for administration of Colobreathe®. Use of Colobreathe® in children under the age of 6 is the subject of a Paediatric Implementation Plan Waiver.	No	Product is indicated in patients with cystic fibrosis (CF) aged 6 years and older.
Elderly patients	Colobreathe® is not likely to be used extensively in elderly patients, as the average of age at death of CF patients is about 40 years. The age range of the patients in the studies is representative of the patients for whom the product is intended, and who are most likely to use the product.	No	There are no theoretical additional risks to administration in patients over 65 years of age.

Criterion	Reason for exclusion	Is it considered to be included as missing information	Rationale
Pregnant and lactating women	There were no pregnancies noted during the clinical development program. As with all medications, the risk to the unborn child must be balanced against the benefits of medication to the patients. As there are low levels of systemic absorption of Colobreathe®, the risk to the fetus is felt to be minimal, but there is no prospective data in pregnant patients to date. The SmPC Section 4.6 Pregnancy and lactation states: Pregnancy There are no adequate data from the use of inhaled colistimethate sodium in pregnant women. Studies in animals using parenteral administration have shown reproductive toxicity (see Section 5.3). Single dose intravenous studies in human pregnancy show that colistimethate sodium crosses the placenta and consequently there is potential for fetal toxicity if administered during pregnancy. Colistimethate sodium should be used in pregnancy only if the benefit to the mother outweighs the potential risk to the fetus. Breastfeeding Absorbed colistimethate sodium may be secreted in breast milk. A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with Colobreathe® should be made taking into account the benefit of breastfeeding to the child balanced against the benefit of Colobreathe® therapy to the woman.	Yes	Not applicable (included as missing information).

Criterion	Reason for exclusion	Is it considered to be included as missing information	Rationale
Patients with renal or hepatic impairment	By definition, all patients with CF have a collection of co-morbidities. Use of nephrotoxic medicines may also impair renal function. Hepatic dysfunction is common (including CF related cirrhosis of the liver), and some medications have hepatotoxic potential e.g. macrolide antibiotics. During the clinical trial program for Colobreathe®, such abnormalities consistent with the underlying disease were admissible, and the patient population included was representative of CF patients in general. The applicant therefore proposes that no additional data be generated for co-morbidity. Data generated to date suggest that the transpulmonary absorption of the active is low and is unlikely to constitute a problem. Due to very low systemic exposure concomitant use with other formulations of colistimethate is not contraindicated but caution should be exercised as there little experience and there is a possibility of summative toxicity.	No	The proposed SmPC Section 4.2 recommends that no dose adjustment is considered to be necessary in patients with renal or hepatic impairment. The proposed SmPC Section 4.4 Special warnings and precautions for use states the following: "There is very low transpulmonary absorption of colistimethate after inhalation of Colobreathe®. Care should still be taken in administering Colobreathe® to patients who are known to have a propensity for nephrotoxic events." Use in patients with renal or hepatic impairment is adequately discussed under 'Special warnings and precautions for use' in the SmPC.
Acute respiratory exacerbation	Need to establish baseline.	No	Indication is for the management of same when secondary to infection with *P. aeruginosa.*
Investigational product administered within 28-days of study start	Risk of drug/drug interaction and need to establish baseline.	No	Investigational products are administered at the discretion of the prescribing physician.
Administration of other antibiotic, anti-Pseudomonas vaccine or gene therapy	Need to establish baseline.	No	May form part of the physician approved medication program.

Criterion	Reason for exclusion	Is it considered to be included as missing information	Rationale
Presence of Burkholderia or allergic bronchopulmonary aspergillosis	Complication of interpretation of primary variable.	No	Not a safety issue.
Compatibility with study procedures	Need to keep protocol.	No	Not a safety issue.
Laboratory parameters outside expected normal ranges (investigator decision)	Standardization of patient management for safety determined through physician's judgment.	No	Physician's judgment always employed in prescribing a medication.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 9: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	Pregnant females were excluded from the studies. There were no pregnancies noted during the clinical development program. As with all medications, the risk to the unborn child must be balanced against the benefits of medication to the patients. As there are low levels of systemic absorption of Colobreathe®, the risk to the fetus is felt to be minimal, but there are no prospective data in pregnant patients to date. Absorbed colistimethate sodium may be secreted in breast milk. A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with Colobreathe® should be made taking into account the benefit of breastfeeding to the child balanced against the benefit of Colobreathe® therapy to the woman.
Breastfeeding women	
Patients with relevant comorbidities:	Not applicable as there was no exclusion based on other co-morbidities.
Patients with hepatic impairment	By definition, all patients with CF have a collection of co-morbidities. Hepatic dysfunction is common (including CF related cirrhosis of the liver), and some medications have hepatotoxic potential e.g. macrolide antibiotics. During the clinical trial program for Colobreathe®, such abnormalities consistent with the underlying disease were admissible, and the patient population included was representative of CF patients in general. Colobreathe® has not been tested specifically in subjects with hepatic impairment but no dose adjustment is considered to be necessary with Colobreathe® administration.

Type of special population	Exposure
Patients with renal impairment	Systemic administration of colistimethate sodium may lead to nephrotoxicity. However, as there is only low systemic availability after administration of Colobreathe® by the oral inhalation route it is not proposed that additional data be generated on renally impaired patients. Instead this issue has been dealt with in the proposed SmPC Section 4.4 Special Warnings and Precautions wherein it states: 'There is very low transpulmonary absorption of colistimethate sodium after inhalation of Colobreathe®. Care should still be taken in administering Colobreathe® to patients who are known to have a propensity for nephrotoxic or neurotoxic events.
Patients with cardiovascular impairment	Not included in the clinical development program.
Immunocompromised patients	Not included in the clinical development program.
Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable as there was no exclusion bases on disease severity.
Population with relevant different ethnic origin	Cystic fibrosis occurs most commonly among Caucasians of Northern European descent; an estimated 1 in 2,500 Caucasian births are affected. It is estimated that 1 in 15,100 African Americans are diagnosed with cystic fibrosis.In the US Cystic Fibrosis Foundation's Patient Registry only 4.2 percent were African American. The incidence in Asians is very low amounting to no more than 1 in 31,000 to 100,000. The patients studied in the Colobreathe® program were overwhelmingly Caucasian in origin and therefore reflect the demographics of the CF population.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program
Children under age of 6 years	No children under the age of 6 years were recruited into the Colobreathe® clinical studies. However, it is not envisaged that children under the age of 6 years will use the product due to coordination issues in using a DPI. A waiver has been granted in the Pediatric Investigation Plan for pre-term, newborns, infants and children less than 6-years old.
Elderly	As Colobreathe® is expected to be used in the CF population, with a mean predicted age of survival of approximately 40 years of age, it is likely it would not be used extensively in patients 60 years and older.

Part II: Module SV - Post-Authorisation Experience

SV.1 Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Sales data up to 12 February 2019 were used to estimate the patient exposure.

An estimate of patients exposed to colistimethate sodium was calculated in patient-years by assuming a daily dose (DD) of two capsules per day and an average number of 365 days (730 capsules), as per the SmPC.

SV.1.2 Exposure

Table 10: Exposure Table

Period	No. of DDs[1]	Estimation of patient-years
Cumulative	2,193,717	6,027

[1] DD = 2 capsules per day

Part II: Module SVI - Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

Colobreathe® is an anti-infective agent to be used in the treatment of *Pseudomonas aeruginosa* infections in cystic fibrosis patients. There is no data that suggests a potential for illicit drug use or use as a recreational drug. The potential for misuse for illegal purposes is therefore considered negligible, and no special coloring or packaging is required.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Not applicable. This is not the initial RMP submission.

Based on the established safety profile, the list of safety concerns for Colistimethate sodium (Colobreathe®) has been agreed by the Competent Authorities taking into consideration the following aspects: impact on the individual, the seriousness of the risk, and the impact on public health. In addition, the risks which whilst not normally serious enough to require specific warnings or precautions but which occur in a significant proportion of the treated population, affect the quality of the treated person's life, and which could lead to serious consequences if untreated were also considered for inclusion.

The main reasons for considering the risk as an important identified or important potential risk are presented in section SVII.3 under "Evidence source(s) and strength of evidence".

Table 11: Colistimethate sodium (Colobreathe®) Safety Concerns

Important identified risks	• Cough / Productive cough • Throat irritation • Chest discomfort/pain • Wheezing / Bronchospasm • Dyspnoea • Lower respiratory tract infection • Dysgeusia
Important potential risks	• Exacerbation of myasthenia gravis • Oropharyngeal infection with Candida albicans or other yeast like organisms • Nephrotoxicity

Important identified risks	• Cough / Productive cough • Throat irritation • Chest discomfort/pain • Wheezing / Bronchospasm • Dyspnoea • Lower respiratory tract infection • Dysgeusia
	• Neurotoxicity • Hepatotoxicity • Increased sensitisation to colistimethate due to inhaled route of administration • Capsule fragmentation
Missing information	• Pregnancy / Foetal harm • Lactating women

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

The product Colobreathe has been on the market and in clinical use for over a decade. As discussed in the last PSUR, the safety profile is considered well-established and HCPs and patients alike are well acquainted with its method of administration and most common adverse reactions. Taking into consideration the GVP Module 5 (revision 2) guideline and its definition on what constitutes important risks and missing information, the following modifications in the list of safety concerns is proposed:

Important identified risks	• Cough / Productive cough • Throat irritation • Wheezing / Bronchospasm • Dysgeusia
Important potential risks	• None
Missing information	• None

Rationale for removing important identified risks

Chest discomfort/pain

Dyspnea

These AEs are a common occurrence in patients with CF. The events are listed in Colobreathe's SmPC. The analysis of the reported AEs which was performed in the last PSUR showed that the peak reporting of this event occurred in 2014 and that many of the report were related to capsule fragmentation, an issue that was resolved by the previous MAH (Teva) by replacing the hard gelatine capsules with PEG-gelatine capsules in 2020. Since then, the reporting rates of the PTs (chest discomfort, chest pain and dyspnea) have been significantly lower than the ones stated in

the SmPC and stable over time. This indicates that the risks are well-characterized and adequately managed by the HCPs and patients. The risks are also adequately addressed in the product information and the MAH proposes to further monitor this risk through routine pharmacovigilance activities. No aRMM is considered necessary to manage these events.

Lower respiratory tract infection

Patients with CF are especially vulnerable to respiratory tract infections, which can be fatal if left untreated. During clinical trials, the use of colistimethate sodium was associated with an increased time to lower respiratory tract infection, which indicates that the drug may actually act protective. During the review of data, presented in the last PSUR, no outstanding patterns of occurrence were observed, with only 1 case reported in 2023. The reporting rates are therefore significantly lower than the ones defined in the product's SmPC.

The risk is considered to be well-characterized, and the information provided to the HCPs and patients in the product information is sufficient to manage the risk. Therefore, the MAH proposes to remove the risk from the RMP. No aRMMs are required to manage the event.

Important potential risks

As discussed in the latest PSUR, most of the important potential risks have not been confirmed and were only associated with the systemic use of colistimethate sodium. The absorption of Colobreathe after inhalation is minimal and therefore the risks are considered not to be directly related to this product. The risk of capsule fragmentation has already been adequately addressed by formulation change. The risks do not plausibly affect the benefit-risk balance of the product and do not require further evaluation as part of the pharmacovigilance plan.

Missing information

The safety of Colobreathe in pregnant and lactating women has been followed for over a decade and during this period, no safety signals have been identified. Therefore, this risk is considered to be well-characterized and should be further managed via routine pharmacovigilance activities.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

Table 12: Presentation of Important Identified Risk: Cough/Productive Cough

Important Identified risk	Cough/Productive cough
Characterisation of risk	Severity and reversibility of risk Cough tends to be an acute reaction to the use of the Dry Powder Inhaler (DPI) administration of Colobreathe®, which resolves shortly after dose administration. This is not a serious event, except in very isolated cases. Chronic productive cough is common in patients with cystic fibrosis. Long-term outcomes and impact on the quality of life Extensive coughing can be a burden for those with cystic fibrosis and it can also place strain on family members, friends and co-workers.

Important Identified risk	Cough/Productive cough
Risk groups or risk factors	Patients with cystic fibrosis are likely to have sensitive airways and thus any substance inhaled by such patients may cause cough.
Potential mechanisms	Cough is a physiological phenomenon which exists to protect the airways from harmful irritants. It is a reflex arc.
Preventability	It is not possible to prevent this risk as it is related to the route of administration of the product. However, the SmPC recommends that this may be ameliorated with appropriate pre-treatment with a bronchodilator (beta2- agonist) prior to inhalation (see SmPC sections 4.2 and 4.4).
Impact on the risk-benefit balance of the product	There are ARMMs in place to minimise the risk and to ensure positive benefit-risk balance. PASS is being conducted with aim to better characterise this risk and to evaluate the impact on risk-benefit balance.
Potential public health impact of safety concern	It is most unlikely that there is any public health impact secondary to cough. In theory there is the possibility of reduced efficacy as a result of coughing out Colobreathe®. However, in the pivotal trial COLO/DPI/02/06, the primary efficacy endpoint was met, as it was in earlier studies, despite the majority of patients suffering cough during the early phases of treatment. Thus, reduced efficacy is not considered at all likely. It should also be noted that the incidence of cough decreases rapidly after the first 28 days of treatment. In pivotal trial COLO/DPI/02/06 the incidence of cough was reported in 58% of Colobreathe® treated patients during the first 28 days, reducing to 13% during the second 28 day period and remaining at this level for the remainder of the study.
Evidence source	Marketing authorisation application (MAA) for Colobreathe® (clinical trials)

Table 13: Presentation of Important Identified Risk: Throat Irritation

Important Identified risk	Throat Irritation
Characterisation of risk	<u>Severity and reversibility of the risk</u> This is a class effect following use of a dry powder inhalation. It could also be as a result of coughing. This is not a serious adverse event but could lead patients to discontinue treatment if it became severe and intolerable. <u>Long-term outcomes and impact on the quality of life</u> May result in under dosing or noncompliance.
Risk groups or risk factors	Patients with cystic fibrosis are likely to have sensitive airways and thus any substance inhaled by such patients may cause throat irritation
Potential mechanisms	Throat irritation is a mechanical class effect following use of dry powder inhalation. It could also occur as a result of coughing.
Preventability	No mechanism to prevent it.
Impact on the risk-benefit balance of the product	There are ARMMs in place to minimise the risk and to ensure positive benefit-risk balance. PASS is being conducted with aim to better characterise this risk and to evaluate the impact on risk-benefit balance.
Potential public health impact of safety concern	None.
Evidence source	MAA for Colobreathe® (clinical trials)

Table 14: Presentation of Important Identified Risk: Wheezing/Bronchospasm

Important Identified risk	Wheezing/Bronchospasm
Characterisation of risk	Severity and reversibility of the risk Wheezing/ bronchospasm are common symptoms in patients with respiratory diseases such as cystic fibrosis. Majority of wheezing / bronchospasm cases are not serious. But treatment may be required if they become severe or intolerable. Long-term outcomes and impact on the quality of life May result in under dosing or non-compliance.
Risk groups or risk factors	Patients with cystic fibrosis are likely to have sensitive airways and thus any substance inhaled may cause wheezing/ bronchospasm.
Potential mechanisms	Bronchospasm occurs due to the narrowing of the airways
Preventability	It is not possible to completely prevent this risk if it is related to the underlying disease and the route of administration of the product. However, the SmPC recommends pre-treatment with a bronchodilator (beta2-agonist) prior to inhalation (see SmPC sections 4.2 and 4.4) which may relieve cough or bronchospasm, and thus treat wheezing symptoms.
Impact on the risk-benefit balance of the product	There are ARMMs in place to minimise the risk and to ensure positive benefit-risk balance. PASS is being conducted with aim to better characterise this risk and to evaluate the impact on risk-benefit balance.
Potential public health impact of safety concern	None.
Evidence source	MAA for Colobreathe® (clinical trials)

Table 15: Presentation of Important Identified Risk: Dysgeusia

Important Identified risk	Dysgeusia
Characterisation of risk	Severity and reversibility of the risk Dysgeusia tends to be an acute reaction to the use of the Dry Powder Inhaler administration of Colobreathe®, which resolves shortly after dose administration. This is not a serious event though it can be unpleasant. The risk is more of discomfort and does not carry morbidity with it except for potential compliance issues. Long-term outcomes and impact on the quality of life May cause intolerance leading to discontinuation.
Risk groups or risk factors	This is potentially a disadvantage and could impact correct use of the product. However, medication of these patients is highly supervised and the patients are motivated to take the required medication.
Potential mechanisms	The event tends to be transient following dose administration, and probably results from powder being deposited in the oropharynx affecting the taste buds in the mouth.
Preventability	The SmPC advises that rinsing may reduce the unpleasant taste associated with colistimethate sodium.
Impact on the risk-benefit balance of the product	There are ARMMs in place to minimise the risk and to ensure positive benefit-risk balance. PASS is being conducted with aim to better characterise this risk and to evaluate the impact on risk-benefit balance.

Important Identified risk	Dysgeusia
Potential public health impact of safety concern	None. Alternative treatments which may not be as effective are available for the small proportion of patients who cannot tolerate the unpleasant taste.
Evidence source	MAA

Part II: Module SVIII - Summary of the Safety Concerns

Table 16: Summary of Safety Concerns

List of important risks and missing information	
Important identified risks	• Cough / productive cough • Throat irritation • Wheezing / bronchospasm • Dysgeusia
Important potential risks	• None
Missing information	• None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

In accordance with Article 8(3)(ia) of Directive 2001/83/EC as amended the Applicant has the services of a Qualified Person Responsible for Pharmacovigilance, an assigned Deputy and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third Country.

Routine pharmacovigilance activities are conducted, and processes and systems are in place to ensure that information on all suspected adverse reactions related Colobreathe and the active substance colistimethate sodium that are reported to the company are collected and collated in order to be accessible at least at one point within the EU.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

None.

Specific adverse reaction follow-up questionnaires for safety concerns:

Not applicable.

Other forms of routine pharmacovigilance activities for safety concerns:

Not applicable.

III.2 Additional pharmacovigilance activities

There are no additional pharmacovigilance activities proposed.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable since there are no additional pharmacovigilance activities proposed.

Part IV: Plans for **post-authorisation efficacy studies**

Not applicable as no post-authorisation efficacy study is imposed for the reference product.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table 17: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
IMPORTANT IDENTIFIED RISKS	
Cough/ productive cough	Routine risk communication: Risk is listed in SmPC section 4.4 and 4.8. Described in PL section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine.
Throat irritation	Routine risk communication: Risk is listed in SmPC section 4.8. Described in PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine.
Wheezing/ Bronchospasm	Routine risk communication: Risk is listed in SmPC section 4.4 and 4.8. Described in PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine.

Safety concern	Routine risk minimisation activities
Dysgeusia	Routine risk communication: Risk is listed in SmPC section 4.8. Described in PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine.

Table 18: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
IMPORTANT POTENTIAL RISKS	
None	

Table 19: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
MISSING INFORMATION	
None	

V.2. Additional Risk Minimisation Measures

An additional risk minimization measure was implemented with the initial MAA (**Table 20**).
No updates were made to the aRMM since its implementation. The aRMM is provided in form of a DVD and an information leaflet for patients and HCPs.
The content of the educational materials fully reflects the information included in the SmPC and PIL and do not confer any additional information related to the product's mode of administration and/or safety.
Based on the revised safety profile of the product, over a decade of experience with the product, no safety concerns identified with its administration and the obsolete nature of the distribution medium (DVD and paper leaflet) the MAH proposes to discontinue the aRMM and to manage all important identified risk via routine pharmacovigilance activities.

Table 1: An Educational DVD and Patient and Healthcare Professional Guide in Leaflet Form

Objectives	Helping patients and HCPs to understand the risk of cough/productive cough, throat irritation, wheezing/bronchospasm, dysgeusia and the procedures related to the appropriate management of these risks to minimize their occurrence and severity
Rationale for the additional risk minimisation activity	These materials have been developed for use by patients, caregivers and health care professionals and describe clearly the technique to be used to deliver Colobreathe® using the Turbospin device and provide reassurance with respect to continuous use. The following themes have been included in the DVD: Introduction to the product: shows what should be in the box and explains that 28 days treatment is 56 capsules and 1 device. Explains that device is discarded after 28 days. Explanation of the Turbospin and how it works. Introduction to the need to comply with the treatment in order to maximise the potential benefits and explain that using inhaled antibiotics can reduce the need for intravenous antibiotics. Detailed instructions about how to use the medication starting from unpacking the product and ending up at disposing of the used capsule. Some detail about cleaning the Turbospin. Discussion about common side effects, particularly cough and taste abnormality. Goes on to say that these are nuisance value for most patients and that patients should persist. States that cough decreases with repeated use of the product and should settle down after the first month or so. Emphasises the need to persist with the product.
Target audience and planned distribution path	Healthcare professionals (those within the MultiDisciplinary Teams, MDTs) and patients with cystic fibrosis/caregivers. They were designed to be as simple and as easy to follow as possible. The method/process of distribution are to be agreed at national level with each Competent Authority.
Plans to evaluate the effectiveness of the interventions and criteria for success	The success of proposed additional risk minimization activities will be measured by monitoring process indicator – risk minimization tool implementation. The implementation will be considered successful if MAH fulfilled obligation(s). Potential increase in the relevant cases will be criteria for judging the success of the proposed additional risk minimization measures (ARMMs). The ARMMs will be considered successful if no significant increase in the period after ARMMs implementation compared to previous period, without an alternative explanation, is noticed. Results of effectiveness evaluation will be presented in periodic reports. Additionally, effectiveness was evaluated in the PASS CLB-MD-08. The results of this study indicate that the majority of HCPs were aware of, received, and utilised the Colobreathe educational materials. Overall, knowledge levels of the side effects and the proper usage of Colobreathe and the Turbospin inhaler were high. This indicates that the majority of the HCPs and patients have a high level of awareness of the risks associated with Colobreathe, and proper use of Colobreathe to minimise these risks. Based on the results of this study, it appears that the Colobreathe educational materials did effectively educate and inform HCPs and patients on the risks associated with Colobreathe and proper use to minimise these risks.

V.3 Summary of risk minimisation measures

Table 21: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
IMPORTANT IDENTIFIED RISKS		
Cough/ productive cough	**Routine risk minimisation measures:** SmPC section 4.4 and 4.8. PL section 2. Prescription only medicine. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Throat irritation	**Routine risk minimisation measures:** SmPC section 4.8. PL section 4. Prescription only medicine. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Wheezing/ Bronchospasm	**Routine risk minimisation measures:** SmPC section 4.4 and 4.8. PL section 4. Prescription only medicine. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Dysgeusia	**Routine risk minimisation measures:** SmPC section 4.8. PL section 4. Prescription only medicine. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.

Table 22: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
IMPORTANT POTENTIAL RISKS		
None		

Table 23: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
MISSING INFORMATION		
None		

Part VI: Summary of the risk management plan

Summary of risk management plan for Colistimethate sodium (Colobreathe®)

This is a summary of the risk management plan (RMP) for Colistimethate sodium (Colobreathe®). The RMP details important risks of Colistimethate sodium (Colobreathe®), how these risks can be minimised, and how more information will be obtained about Colistimethate sodium (Colobreathe®)'s risks and uncertainties (missing information).

Colistimethate sodium (Colobreathe®)'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Colistimethate sodium (Colobreathe®) should be used.

This summary of the RMP for Colistimethate sodium (Colobreathe®) should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Colistimethate sodium (Colobreathe®)'s RMP.

I. The medicine and what it is used for

Colistimethate sodium (Colobreathe®) is authorised for control of persistent lung infections caused by bacterium *Pseudomonas aeruginosa* in adult patients and children aged 6 years and older with cystic fibrosis (see SmPC for the full indication). It contains colistimethate as the active substance and it is given as inhalation powder.

Further information about the evaluation of Colistimethate sodium (Colobreathe®)'s benefits can be found in Colistimethate sodium (Colobreathe®)'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001225/human_med_001507.jsp&mid=WC0b01ac058001d124.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Colistimethate sodium (Colobreathe®), together with measures to minimise such risks and the proposed studies for learning more about Colistimethate sodium (Colobreathe®)'s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

II.A List of important risks and missing information

Important risks of Colistimethate sodium (Colobreathe®) are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Colistimethate sodium (Colobreathe®). Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 24: Summary of Safety Concerns

List of important risks and missing information	
Important identified risks	• Cough / productive cough • Throat irritation • Wheezing / bronchospasm • Dysgeusia
Important potential risks	None
Missing information	None

II.B Summary of important risks

Table 2: Summary of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Important identified risk: Cough/Productive cough	
Evidence for linking the risk to the medicine	MAA (clinical trials: Cough was one of the most commonly reported adverse reactions of all Colobreathe® treated patients). Coughing may occur on inhalation.
Risk factors and risk groups	Patients with cystic fibrosis are likely to have sensitive airways and thus any substance inhaled by such patients may cause cough.

Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and 4.8. PL section 2. Prescription only medicine. Additional risk minimisation measures: An educational DVD and Colobreathe® patient and healthcare professional guide in leaflet form are distributed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.
Important identified risk: Throat irritation	
Evidence for linking the risk to the medicine	MAA (clinical trials: Throat irritation was one of the most commonly reported adverse reactions of all Colobreathe® treated patients). This is a class effect following use of a dry powder inhalation. Sore throat or mouth has been reported with nebulised colistimethate sodium and may occur with Colobreathe®.
Risk factors and risk groups	Patients with cystic fibrosis are likely to have sensitive airways and thus any substance inhaled by such patients may cause throat irritation.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8. PL section 4. Prescription only medicine. Additional risk minimisation measures: An educational DVD and Colobreathe® patient and healthcare professional guide in leaflet form are distributed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.
Important identified risk: Wheezing/Bronchospasm	
Evidence for linking the risk to the medicine	MAA (clinical trials). Bronchospasm may occur with inhalation.
Risk factors and risk groups	Patients with cystic fibrosis are likely to have sensitive airways and thus any substance inhaled may cause wheezing/bronchospasm.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8. PL section 4. Prescription only medicine. Additional risk minimisation measures: An educational DVD and Colobreathe® patient and healthcare professional guide in leaflet form are distributed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.
Important identified risk: Dysgeusia	

Evidence for linking the risk to the medicine	MAA (clinical trials: Unpleasant taste was the most commonly reported adverse reactions of all Colobreathe® treated patients).
Risk factors and risk groups	This is potentially a disadvantage and could impact correct use of the product. However, medication of these patients is highly supervised and the patients are motivated to take the required medication.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8. PL section 4. Prescription only medicine. Additional risk minimisation measures: An educational DVD and Colobreathe® patient and healthcare professional guide in leaflet form are distributed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation of Colistimethate sodium (Colobreathe®).

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Colistimethate sodium (Colobreathe®).

Part VII: Annexes

Table of contents

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable.

Draft/approved key messages of the additional risk minimisation measures

Not applicable.

Annex 7 - Other supporting data (including referenced material)

Akata D and Akhan O. Liver manifestations of Cystic Fibrosis. European Journal of Radiology. 2007; 61: 11-17

Anon (Accessed 2011) Gastrointestinal Manifestations of Cystic Fibrosis Radiologic-Pathologic Correlation. Archives of the AFIP. Accessed online at: http://www.rsna.org/reg/publications/rg/afip/privatem/1996/0016/0004/0871/6.htm#topAnchor

Beringer M. The clinical use of colistin in patients with cystic fibrosis. Current Opinion in Pulmonary Medicine. 2001; 7: 434-440

CHMP. Guideline on Reporting of Suspected Transmission of any Infectious Agent via a Medicinal Product (Doc. Ref. EMEA/CHMP/296412/2005) London: EMEA, 23 January 2006.

CHMP. Guideline on Risk Management Systems for Medicinal Products for Human Use (Doc. Ref. EMEA/CHMP/96268/2005 London: EMEA, 14 November 2005.

Cohn JA et al. Relation between mutations of the cystic fibrosis gene and idiopathic pancreatitis. N. Engl. J. Med. 1998; 339 (10): 653–8.

Cystic Fibrosis Trust, Standards of Care 2001 (Accessed on 9 February 2011 online at http://www.cftrust.org.uk/aboutcf/publications/consensusdoc/C_3000Standards_of_Care.pdf

Cystic Fibrosis Medicine (Accessed 2011a) Vitamins (Taken from the Leeds Method of Management April 2008). Accessed online at http://www.cfmedicine.com/cfdocs/cftext/vitamins.htm

Cystic Fibrosis Medicine (Accessed 2011b) Treatment of Distal Intestinal Obstruction Syndrome (Taken from the Leeds Method of Management April 2008). Accessed online at http://www.cfmedicine.com/cfdocs/cftext/dios.htm

Escobar MA et al. (2005) Surgical considerations in cystic fibrosis: a 32-year evaluation of outcomes. Surgery. Oct;138(4):560-71; discussion 571-2. Abstract accessed online at: http://www.surgjournal.com/article/S0039-6060(05)00425-3/abstract

Feranchak AP et al. (1999) Perspective long term study of fat soluble vitamin status in children with cystic fibrosis identified by newborn screening. J Pediatr ; 135: 601-610 Abstract Accessed online at: http://www.ncbi.nlm.nih.gov/pubmed/10547249?dopt=AbstractPlus

Frederiksen B et al. Antibiotic Treatment of Initial Colonisation with Pseudomonas aeruginosa Postpones Chronic Infection and Prevents Deterioration of Pulmonary Function in Cystic Fibrosis. Pediatric Pulmonology, 1997; 23: 330-335

Heubi J (2007) Treatment of Exocrine Pancreatic Insufficiency in Cystic Fibrosis Patients. US Respiratory Disease. October 2007:48-50 Accessed online at: http://www.touchrespiratory.com/files/article_pdfs/resp_7761

Hodson M et al. A randomised clinical trial of nebulized tobramycin or colistin in cystic fibrosis. European Respiratory Journal 2001; 20:658-664 (Accessed 9 February 2011 online at http://erj.ersjournals.com/content/20/3/658.full)

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ICH Harmonised Tripartite Guideline Pharmacovigilance Planning E2E Current Step 4 version 18 November 2004.

Irish M (2011) Surgical Aspects of Cystic Fibrosis and Meconium Ileus. Medscape Website Accessed online at http://emedicine.medscape.com/article/939603-overview#a1

Kerem E et al. Standards of care for patients with cystic fibrosis: A European consensus. Journal of Cystic Fibrosis 2005; 4: 7-26 (Accessed 14 February 2011 online at http://www.elsevier.com/framework_products/promis_misc/2005.pdf)

Konstan M et al. Safety, efficacy and convenience of tobramycin inhalation powder in cystic fibrosis patients: The EAGER trial. Journal of Cystic Fibrosis, 2011; 10: 54-61

Medicine online. Tobramycin Injection USP (Accessed 8 February 2011 online at: http://www.medicineonline.com/drugs/t/3502/TOBRAMYCIN-INJECTION-USP.html)

Kristidis P et al (1992) Genetic determination of exocrine pancreatic function in cystic fibrosis. Am J Hum Genet. 50(6):1178 – 1184 Accessed online at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1682557/pdf/ajhg00077-0033.pdf.

Lanng S et al (1995) Glucose tolerance in patients with cystic fibrosis: five year prospective study. British Medical Journal, 311:655-9. Abstract accessed at: http://www.joplink.net/prev/200807/ref/07-071.html

Liu M et al. Neuromuscular Blocking Effects of the Aminoglycoside Antibiotics Arbkacin, Astromicin, Isepamicin and Netilmicin on the Diaphragm and Limb Muscles of the Rabbit. I.J. Exp. Clin. Pharm. 2001; 63: 142-146. (Abstract only accessed on 1 March 2011 at http://content.karger.com/ProdukteDB/produkte.asp?Aktion=ShowAbstract&ArtikelNr=56125&Ausgabe=228204&ProduktNr=224274)

Michalopoulos A et al Pharmacokinetic evaluation of colistin sodium. Expert Opin Drug Metab Toxicol; 2011, 7: 245-255

Mitchell et al. Robbins basic pathology 2007. Saunders/Elsevier.

Pascuzzi R Medications and Myasthenia Gravis (A Reference for Health Care Professionals). 2000 Myasthenia Gravis Foundation of America (Revised 2007)

Moran A et al (2009) Cystic fibrosis-related diabetes: current trends in prevalence, incidence, and mortality. Diabetes Care. Sep, 32(9):1626-31. Accessed at http://www.ncbi.nlm.nih.gov/pubmed/19542209

Ratjen F et al. Pharmacokinetics of inhaled colistin in patients with cystic fibrosis. Journal of Antimicrobial Chemotherapy. 2006; 57: 306-311

Reddel S. Treatment of myasthenia gravis. Aust Prescr. 2007; 30: 156-160

Rowland M et al (2011) Outcome in Cystic Fibrosis Liver Disease Am J Gastroenterol;106:104–109. Accessed at: http://www.nature.com/ajg/journal/v106/n1/full/ajg2010316a.html#bib7#bib7

Schuster, A, Haliburn, C, Doring, G, Goldman MH. 2013 Safety, efficacy and convenience of colistimethate sodium dry powder for inhalation (Colobreathe® DPI) in patients with cystic fibrosis: a randomised study. Thorax. 68:344-350.

Sokol RJ et al. (1989) Fat soluble vitamin status during the first year of life in infants with cystic fibrosis identified by screening of newborns. Am J Clin Nutr; 50:1064-1071 Abstract accessed at: http://www.ncbi.nlm.nih.gov/pubmed/2816791?dopt=AbstractPlus

Stockley's Drug Interactions (accessed on line 16 July 2009 at http://www.medicinescomplete.com/mc/stockley)

The Leeds Method of Management (2008). Vitamins [online]. Leeds Regional Adult and Pediatric Cystic Fibrosis Units, St James's University Hospital, Leeds, UK Accessed at http://www.cfmedicine.com/cfdocs/cftext/vitamins.htm

Van Devanter D, Lai H, Eigen H, and Konstan M: Rates of lung function decline for Pseudomonas Aeruginosa infected placebo patients in the prednisone, ibuprofen and Tobramycin Solution for Inhalation (TOBI) cystic fibrosis (CF) trials. Poster presented at the 14th North American Cystic Fibrosis Conference, Baltimore, MD, USA, 9-12 November 2000

Van Devanter D, Rose L and Sprugel K. 28 day inhalation toxicology of Polymyxin E , the major active component of colistin, in rats and dogs. Poster presented at the European Cystic Fibrosis Congress, Vienna, Austria, 6-9 June 2001

Walters S. Clinical epidemiology of cystic fibrosis; in Hodson ME, Geddes DM (eds): Cystic Fibrosis, ed 2. Arnold Publishers, 2000; Chap 1a,p4

Westerman E et al Effects of nebulized colistin sulphate and colistin sulphomethate on lung function in patients with cystic fibrosis: a pilot study. Journal of Cystic Fibrosis, 2004, 3: 23-28