

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 1,662,500 IU, which is approximately equal to 125 mg of colistimethate sodium.

3. PHARMACEUTICAL FORM

Inhalation powder, hard capsule (inhalation powder)
Hard transparent PEG-gelatin capsules containing a fine white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 (see section 5.1). Consideration should be given to official guidance on the appropriate use of antibacterial active substances.

4.2 Posology and method of administration

Posology

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.

Renal impairment

No dose adjustment is considered to be necessary (see section 5.2).

Hepatic impairment

No dose adjustment is considered to be necessary (see section 5.2).

Paediatric population

The safety and efficacy of Colobreathe in children under 6 years of age have not been established. No data are available.

Method of administration

For inhalation use only.

Colobreathe capsules are to be used only with the Turbospin powder inhaler.

The capsules must not be swallowed.

To ensure proper administration of the medicinal product, the patient should be shown how to use the inhaler by a physician or other health professional, with the first dose being given under medical supervision.

If other treatments are being taken, they should be taken in the following order:

Inhaled bronchodilators

Chest physiotherapy

Other inhaled medicinal products

Colobreathe

4.3 Contraindications

Hypersensitivity to the active substance, colistin sulphate or polymyxin B.

4.4 Special warnings and precautions for use

Bronchospasm and coughing

Bronchospasm or coughing may occur on inhalation. These reactions usually disappear or significantly diminish with continued use and may be ameliorated by appropriate treatment with beta₂-agonists prior to or following dry powder colistimethate sodium inhalation. If bronchospasm or coughing remain problematic, withdrawal of treatment should be considered.

Haemoptysis

Haemoptysis is a complication in cystic fibrosis and is more frequent in adults. The use of colistimethate sodium in patients with clinically significant haemoptysis should be undertaken or continued only if the benefits of treatment are considered to outweigh the risks of inducing further haemorrhage.

Acute respiratory exacerbation

If acute respiratory exacerbations develop additional intravenous or oral antibacterial agent therapy should be considered.

Oral fungal super-infection

After each inhalation of Colobreathe, the mouth should be rinsed with water. The rinse should not be swallowed. Rinsing may reduce the risk of developing oral fungal super-infection during treatment and may also reduce the unpleasant taste associated with colistimethate sodium.

Nephrotoxicity/neurotoxicity

There is very low transpulmonary absorption of colistimethate after inhalation of Colobreathe (see section 5.2). Care should still be taken in administering Colobreathe to patients who are known to have a propensity for nephrotoxic or neurotoxic events.

Caution should be taken with concomitant use of Colobreathe and parenteral or nebulised colistimethate sodium.

Caution should be taken with concomitant use of colistimethate sodium and potential nephrotoxic or neurotoxic medicinal products, including non-depolarising muscle relaxants (see section 4.5).

Other

Colobreathe should be used with extreme caution in patients with myasthenia gravis because of potential for drug induced neuromuscular blockade.

Colistimethate sodium should be used with extreme caution in patients with porphyria.

Safety and efficacy have been assessed in controlled studies for up to 24 weeks. (see section 5.1).

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

There is no experience of using Colobreathe concurrently with other inhaled antibacterial agents.

Caution should be taken with concomitant use with other formulations of colistimethate sodium as there is little experience and there is a possibility of summative toxicity.

No *in-vivo* interaction studies have been performed.

Colistimethate sodium and colistin have been investigated *in vitro* to determine the effects on the expression of cytochrome P450 (CYP) enzymes on treating primary cultures of fresh human hepatocytes. Treatment with colistimethate sodium or colistin did not induce the activity of any enzyme tested (CYP1A2, 2B6, 2C8, 2C9, 2C19 and 3A4/5).

Concomitant use of inhaled colistimethate sodium with other medicinal products that are potentially nephrotoxic or neurotoxic, such as aminoglycosides, or neuromuscular blocking products, such as curariform agents should be undertaken with caution.

Co-treatment with colistimethate sodium and macrolides such as azithromycin and clarithromycin, or fluoroquinolones such as norfloxacin and ciprofloxacin should be undertaken with caution in patients with myasthenia gravis (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of 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 foetal toxicity if administered during pregnancy.

Colistimethate sodium is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

Physico-chemical data suggest excretion of colistimethate sodium in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from colistimethate sodium therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

Colistimethate sodium has no notable effects on fertility in male or female rats or mice.

4.7 Effects on ability to drive and use machines

Based on the safety profile of colistimethate sodium, neurotoxicity may occur with the possibility of dizziness, confusion or visual disturbances. Patients should be warned not to drive or operate machines if this occurs.

4.8 Undesirable effects

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 beta₂ 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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ 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, crackles lung	Chest pain, dyspnoea exacerbated, pharyngolaryngeal pain, epistaxis, sputum purulent, abnormal chest sound, increased upper airway secretion

System Organ Class	Very Common	Common	Uncommon
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 that 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%).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Symptoms

Currently there is no experience of overdose with the use of Colobreathe. However, overdose may possibly result in higher systemic exposure.

Overdose is unlikely by the inhaled route but has been recognised after systemic use. More common signs and symptoms of intravenous overdose include unsteadiness, paraesthesia and dizziness. It can also result in neuromuscular blockade that can lead to muscular weakness, apnoea and possible respiratory arrest. Overdose can also cause acute renal failure characterised by decreased urine output and increased serum concentrations of BUN and creatinine.

Management

There is no specific antidote, therefore management should be done by supportive treatment. Measures to increase the rate of elimination of colistimethate sodium e.g. mannitol diuresis, prolonged haemodialysis or peritoneal dialysis may be tried, but effectiveness is unknown.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemic use, other antibacterials.

ATC Code: J01XB01

Mechanism of action

Colistimethate sodium (CMS) is a cyclic polypeptide antibacterial active substance that is derived from *Bacillus polymyxa var. colistinus* and belongs to the polymyxin group. Polymyxins work by damaging the cell membrane and the resulting physiological effects are lethal to the bacterium. Polymyxins are selective for Gram-negative bacteria that have a hydrophobic outer membrane.

Resistance

Resistant bacteria are characterised by modification of the phosphate groups of lipopolysaccharide, which become substituted with ethanolamine or aminoarabinose. Naturally resistant Gram-negative bacteria, such as *Proteus mirabilis* and *Burkholderia cepacia*, show complete substitution of their lipid phosphate by ethanolamine or aminoarabinose.

Cross resistance

Cross resistance between colistimethate sodium and polymyxin B is expected. Since the mechanism of action of the polymyxins is different from that of other antibacterial agents, resistance to colistin and polymyxin by the above mechanism alone would not be expected to result in resistance to other drug classes.

The epidemiological cut off value for colistimethate sodium for *Pseudomonas aeruginosa*, distinguishing the wild type population from isolates with acquired resistance traits, is 4 mg/l.

Clinical efficacy

The Phase 3 clinical study was a randomised, open-label active comparator study comparing the efficacy of colistimethate sodium 1,662,500 IU dry powder for inhalation to tobramycin nebuliser solution for inhalation, 300 mg/5 ml, in 380 subjects with documented cystic fibrosis complicated by chronic pulmonary infection with *Pseudomonas aeruginosa*. The subjects were aged 6 years and above and had an FEV₁% predicted of 25-75%. All subjects were also required to have successfully completed a minimum of two cycles of nebulised tobramycin solution run-in prior to randomisation. Subjects were randomised to receive either one 1,662,500 IU capsule of colistimethate sodium twice daily, or 300 mg of tobramycin, twice daily. It should be noted that treatment was not interrupted when patients received concomitant parenteral antibacterial active substances.

Efficacy was measured by the change in FEV₁ % predicted compared to baseline after a 24-week treatment period.

The results of the Intent-To-Treat (ITT) population for the primary efficacy outcome are shown below:

Change in FEV₁ (% predicted) from baseline at Week 24 (ITT Population)

Patient group	Colobreathe (Mean)	Tobramycin (Mean)	Adjusted Treatment difference	95% CI
All patients using LOCF	-0.90 (n=183)	0.35 (n=190)	-0.97	-2.74, 0.86
Completed patients	0.39 (n=153)	0.78 (n=171)	-0.29	-2.21, 1.71

The data from the primary outcome parameter, change in FEV₁ % predicted, are not normally distributed. The adjusted treatment difference and 95% confidence interval have been back transformed from log transformed data. The ITT population excluded patients who had been treated but demonstrated no evidence of chronic infection.

The European Medicines Agency has deferred the obligation to submit the results of studies with Colobreathe in one or more subsets of the paediatric population in *Pseudomonas aeruginosa* pulmonary infection/colonisation in patients with cystic fibrosis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Colistimethate is not significantly absorbed from the lung after inhalation of Colobreathe. After administration of 1,662, 500IU twice daily for 7 days in adult, adolescent and paediatric cystic fibrosis patients mean C_{max} values of total colistimethate of up to 455ng/ml (adult mean) were observed. T_{max} for total colistimethate occurred between 0.5 and 1 hour post-dose. Although the population PK analysis showed that age is a statistically significant covariate, the AUC₀₋₆ and dose adjusted AUC₀₋₆ (AUC₀₋₆/D) for total CMS and total free colistin were similar between children and adolescents, while higher AUC₀₋₆ was observed in the adult group. When AUC₀₋₆ was adjusted by dose and body weight, a slightly higher AUC₀₋₆/D/W for total CMS and total free colistin was observed in children. High PK variability was observed in all three groups. Therefore, dose adjustment in low age groups is considered not necessary.

High concentrations of total free colistin (mean 23.5mg/L) and total colistimethate (mean 178mg/L) were observed in sputum at 1 hour post-dose on Day 8 following BID dosing for 7 days across all age groups.

Absorption of colistimethate from the gastro-intestinal tract does not occur to any appreciable extent in the normal individual.

Distribution

Protein binding is low. Polymyxins persist in the liver, kidney, brain, heart and muscle. One study in cystic fibrosis patients gives the steady-state volume of distribution as 0.09 l/kg.

Biotransformation

Colistimethate sodium is converted to the base *in vivo*. As 80% of a parenteral dose can be recovered unchanged in the urine, and there is no biliary excretion, it can be assumed that the remaining drug is inactivated in the tissues. The mechanism is unknown.

Elimination

A systemic absorption study showed minimal urinary excretion with less than 3% of the dose of Colobreathe excreted in the urine as colistimethate sodium and colistin. Therefore, dose adjustment in patients with renal impairment is not considered necessary. The estimated mean terminal half-lives for total CMS and total free colistin were 3.0 and 6.4 h, respectively.

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on conventional studies of genotoxicity. Animal studies of safety pharmacology, repeated dose toxicity or toxicity to reproduction, employing routes assuring systemic exposure, showed no particular hazard. There were no notable effects on fertility or general reproductive performance in male or female rats or mice. In embryo-fetal development studies in mice, resorptions and reduced ossification were seen, and in rats reduced fetal weights, reduced ossification and at the high dose of 10 mg colistin base per day, reduced post-natal survival. An embryo-fetal study in rabbits reported no effects at intravenous doses up to 80 mg/kg colistimethate sodium (32 mg colistin base/kg).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Components of the PEG-gelatin hard capsules:

Gelatin
Polyethylene glycol
Purified water
Sodium lauryl sulfate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original package until immediately before use in order to protect from moisture.

6.5 Nature and contents of container

The capsules are contained in oPA/aluminium/pvc blisters with a peelable lidding foil composed of polyester/aluminium of either 8 or 14 hard capsules in each blister.

Colobreathe is available in packs containing either 8 or 56 hard capsules.

Each 56 capsule pack contains one Turbospin powder inhaler device and 7 blisters of 8 capsules or one Turbospin powder inhaler device and 4 blisters of 14 capsules (56 hard capsules) sufficient for 4 weeks use.

Each 8 capsule pack contains one Turbospin powder inhaler device and 1 blister of 8 hard capsules sufficient for 4 days use.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Capsules: no special requirements for disposal. The Turbospin device should be discarded after completion of the treatment pack.

Colobreathe capsules should only be administered using the Turbospin inhaler device.

Taking Colobreathe using the Turbospin inhaler

The following instructions should be adhered to by the patient when taking Colobreathe:

Preparing the Turbospin

1. Remove the cap. It comes away with a gentle pull.
2. Unscrew the mouthpiece, exposing the chamber of the Turbospin inhaler.
3. Remove a single capsule from the blister pack. Once you have removed the capsule it must be used immediately.
4. Gently insert the capsule into the chamber with the widest end first. No force is required.
5. Now replace the mouthpiece by screwing it back into place.

Piercing the capsule and inhaling the medicine

6. To pierce the capsule:
 - Hold the inhaler with the mouthpiece upright, gently push the piston upwards until the visible line is reached – you will feel resistance at this point and this will lock the capsule in place ready for piercing. Hold that position before continuing to follow through with the piercing.
 - Now, with the capsule locked in place, continue pushing the piston as far as it will go and then release.
 - The capsule is now pierced and the contents can be inhaled.
 - Do **not** pierce the capsule more than once. You may see a small amount of powder released from the capsule chamber after the capsule is pierced, this is normal.
7. Breathe out slowly. Place the mouthpiece between your lips and teeth. Ensure there is a seal between your lips and the mouthpiece. Take care not to cover the air slits with your fingers or mouth during inhalation.
8. Then, breathe in slowly and deeply through your mouth at a rate sufficient for you to hear or feel the capsule spinning.
9. Remove the Turbospin inhaler from your mouth and hold your breath for about 10 seconds or for as long as is comfortable, then breathe out slowly.
10. If you do not hear the capsule spinning, the capsule may be stuck in the compartment. If this occurs, you can loosen the capsule by gently tapping the chamber of the inhaler. Do not try to loosen the capsule by repeatedly pressing the piston. If the capsule cannot be loosened and the powder cannot be inhaled, dispose of the broken capsule and any powder remaining in it and use another.
11. Inhale the medicine again by repeating Steps 7 and 8 to ensure you have emptied the capsule.
12. You can check whether the capsule is empty by unscrewing the mouthpiece and checking the capsule. If it is not empty, repeat steps 7, 8 and 9 until you have inhaled all of the contents.
13. Once all the contents have been inhaled, rinse your mouth out well with water and spit out.

Removing the empty capsule from the Turbospin

14. When the capsule is empty, unscrew the mouthpiece, then remove and discard the empty capsule.

Additional information

As you breathe in slowly, you suck air through the body of the Turbospin inhaler into the capsule chamber. The tiny particles of medicine in the capsule are picked up by the airflow and carried down your airway into your lungs.

Occasionally, very small pieces of the capsule shell can get into your mouth or airways.

- If this happens, you may be able to feel these pieces on your tongue or in your airways.
- The capsule shell is made of gelatin, which is harmless to humans if swallowed or inhaled.
- The chances of the capsule breaking into pieces are increased if the capsule is pierced more than once during Step 6.

7. MARKETING AUTHORISATION HOLDER

Essential Pharma Limited,
Vision Exchange Building
Triq it-Territorjals, Zone 1,
Central Business District,
Birkirkara, CBD 1070, Malta

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/747/001 56 hard capsules (4 blisters of 14 capsules)

EU/1/11/747/002 8 hard capsules (1 blister of 8 capsules)

EU/1/11/747/003 56 hard capsules (7 blisters of 8 capsules)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13/02/2012

Date of latest renewal: 26/09/2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Teva Pharmaceuticals Europe BV
Swensweg 5
2031 GA Haarlem
The Netherlands

Millmount Healthcare Limited
Block 7, City North Business Campus
Stamullen
Co Meath
K32 YD60
Ireland

Merckle GmbH
Ludwig-Merckle-Str-3
89143 Blaubeuren
Germany

Laboratorios Liconsa, S.A.
Avda. Miralcampo, 7, Pol. Ind.
Miralcampo
19200 Azuqueca de Henares (Guadalajara)
Spain

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall agree the format and content of the healthcare professional and patient educational pack with the National Competent Authority prior to launch in the Member State.

The MAH shall ensure that all physicians who are expected to prescribe or use Colobreathe are provided with a healthcare professional and patient educational pack containing the following:

- The Summary of Product Characteristics
- The Patient Information Leaflet
- The “Physician DVD”
- The “Patient DVD”
- “Physician DVD” information in “leaflet form” for those physicians who do not have access to a DVD player
- “Patient DVD” information in “leaflet form” for those patients who do not have access to a DVD player

The Physician and patient “DVDs/leaflet forms” should contain the following key elements and messages:

- Introduction to the product: provide information on the contents of the box ie that 28 days treatment is 56 capsules and 1 device. Explain that the device should be discarded after 28 days. Explanation of the Turbospin and how it works.
- Information on the need to comply with the treatment in order to maximise the potential benefits. Explanation that using inhaled antibiotics can reduce the need for intravenous antibiotics.
- Detailed instructions about how to use the medication: starting from unpacking of the product and finishing with disposal of the used capsule and device. Some detail about cleaning the Turbospin device.
- Discussion about common side effects and in particular cough and taste abnormality: Explanation that:
 - these are only of nuisance value for most patients
 - emphasise that patients should persist with the treatment.
 - that cough decreases with repeated use of the product and should stabilize after the first month or so.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Colobreathe 1,662,500 IU inhalation powder, hard capsules
colistimethate sodium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 1,662,500 IU (approximately equal to 125 mg) colistimethate sodium.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, hard capsule.

8 capsules with 1 Turbospin inhaler (1 strip of 8 capsules)
56 capsules with 1 Turbospin inhaler (4 strips of 14 capsules)
56 capsules with 1 Turbospin inhaler (7 strips of 8 capsules)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Inhalation use only.
Use as directed by the physician.
Do not swallow the capsules.
For use with the Turbospin inhaler only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store in the original package until immediately before use in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Essential Pharma Limited,
Vision Exchange Building
Triq it-Territorjals, Zone 1,
Central Business District,
Birkirkara, CBD 1070, Malta

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/747/001 56 hard capsules (4 strips of 14 capsules)
EU/1/11/747/002 8 hard capsules (1 strip of 8 capsules)
EU/1/11/747/003 56 hard capsules (7 strips of 8 capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Colobreathe

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Colobreathe 1,662,500 IU inhalation powder
colistimethate sodium
Inhalation use

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Essential Pharma Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Colobreathe 1,662,500 IU inhalation powder, hard capsules colistimethate sodium

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Colobreathe is and what it is used for
2. What you need to know before you use Colobreathe
3. How to use Colobreathe
4. Possible side effects
5. How to store Colobreathe
6. Contents of the pack and other information

1. What Colobreathe is and what it is used for

Colobreathe contains colistimethate sodium, a type of antibiotic called a polymyxin.

Colobreathe is used to control persistent lung infections caused by the bacterium *Pseudomonas aeruginosa* in adult patients and children aged 6 years and older with cystic fibrosis. *Pseudomonas aeruginosa* is a very common bacterium that infects nearly all cystic fibrosis patients at some time during their lives. Some people will get this infection whilst very young but for others it will be much later. If this infection is not properly controlled it will cause damage to the lungs.

How it works

Colobreathe works by destroying the bacterial cell membrane, having a lethal effect on them.

2. What you need to know before you use Colobreathe

Do not use Colobreathe

- if you/your child are allergic to colistimethate sodium, colistin sulphate or polymyxins.

Warnings and precautions

Talk to your doctor or pharmacist before using Colobreathe.

Tell your doctor if you/your child has ever had any of the following conditions

- have reacted badly to inhaled dry powder medicines previously unless this has already been discussed with your doctor.
- already have a muscle condition known as myasthenia gravis or the inherited condition, porphyria
- blood in your sputum (the substance you cough up)

After each inhalation of Colobreathe, the mouth should be rinsed with water. The rinse should not be swallowed. Rinsing may reduce the risk of developing oral fungal super-infection during treatment and may also reduce the unpleasant taste associated with colistimethate sodium.

When you/your child start using Colobreathe, you/your child may find they have cough, breathlessness, tightness of chest or wheezing. The number of these side-effects may reduce as you continue to use the inhaler or your doctor may prescribe a bronchodilator to use before or after taking Colobreathe. If any of these effects become a problem, please contact your doctor who may change your treatment.

If you/your child has any problems with your kidneys or nerves, care should be taken when administering Colobreathe but your doctor should be aware of this.

If you/your child needs to have other forms of colistimethate either by injection or nebulisation caution should be used but your doctor should be aware of this.

Children

Do not give Colobreathe to children under the age of 6 years as it is not suitable for them.

Other medicines and Colobreathe

Tell your doctor if you/your child are taking, have recently taken or might take any other medicines, and in particular:

- if you/your child are taking aminoglycoside antibiotics used to treat infections caution must be taken;
- if you/your child suffer from myasthenia gravis and are taking macrolide type antibiotics such as azithromycin and clarithromycin, or fluoroquinolones such as norfloxacin and ciprofloxacin. Taking these at the same time as Colobreathe may cause problems with muscle weakness;
- if you/your child are taking colistimethate by injection or nebulisation caution must be taken;
- if you/your child need to have a general anaesthetic caution must be taken.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

There is no information about the safety of Colobreathe in pregnant women. Your doctor should advise you before using Colobreathe whether the benefits of the medicine exceed the risks.

Colistimethate sodium may be secreted in the breast milk. Please discuss the use of Colobreathe with your doctor.

Driving and using machines

It is possible while using Colobreathe that you may experience dizziness, confusion or have problems with your sight. Do not drive or use any machines until the symptoms have gone away.

Colobreathe contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

3. How to use Colobreathe

Always use this medicine exactly as your doctor has told you. Check with your doctor if you/your child are not sure.

The first dose should be given under medical supervision.

The recommended dose is

Adults and children 6 years of age and older

- The contents of one Colobreathe capsule should be inhaled twice a day using the Turbospin inhaler.
- There should be a 12 hour gap between doses.

The order in which other treatments should be taken or carried out

If you/your child are taking other treatments for cystic fibrosis you/your child should take them in the following order:

- Inhaled bronchodilators
- Chest physiotherapy
- Other inhaled medicines
- Then Colobreathe

You/your child should confirm the order of your treatments with your doctor.



Method of administration

Colobreathe is inhaled into the lungs as a powder from the capsule using the hand-held inhaler called the Turbospin. Colobreathe can only be administered using this device.

Do not swallow Colobreathe capsules.

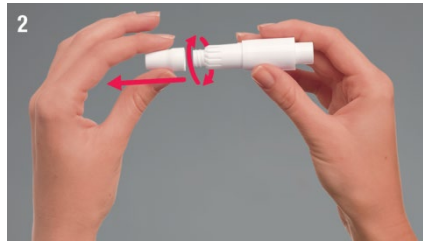
To inhale Colobreathe from the capsule through the Turbospin inhaler follow the procedure described below. Your doctor, pharmacist or nurse should show you/your child how to inhale the medicine when you/your child first start treatment:

Taking Colobreathe using the Turbospin inhaler

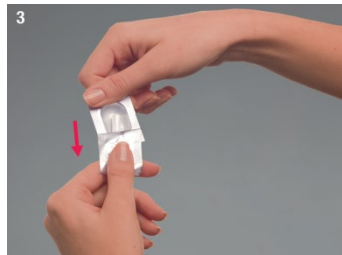
Preparing the Turbospin



1. Remove the cap. It comes away with a gentle pull.



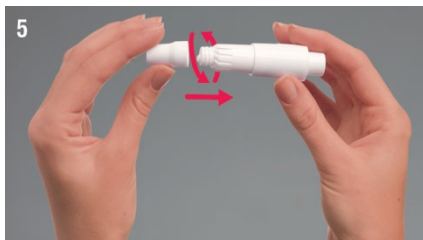
2. Unscrew the mouthpiece, exposing the chamber of the Turbospin inhaler.



3. Remove a single capsule from the blister. Once you have removed the capsule it must be used immediately.

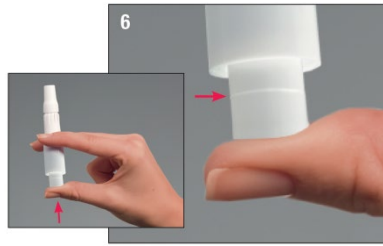


4. Gently insert the capsule into the chamber with the widest end first. No force is required.



5. Now replace the mouthpiece by screwing it back into place.

Piercing the capsule and inhaling the medicine



6. To pierce the capsule:

- Hold the inhaler with the mouthpiece upright, gently push the piston upwards until the visible line is reached – you will feel resistance at this point and this will lock the capsule in place ready for piercing. Hold that position before continuing to follow through with the piercing.
- Now, with the capsule locked in place, continue pushing the piston as far as it will go and then release.
- The capsule is now pierced and the contents can be inhaled.
- Do **not** pierce the capsule more than once. You may see a small amount of powder released from the capsule chamber after the capsule is pierced, this is normal.



7. Breathe out slowly. Place the mouthpiece between your lips and teeth. Ensure there is a seal between your lips and the mouthpiece. Take care not to cover the air slits with your fingers or mouth during inhalation.
8. Then, breathe in slowly and deeply through your mouth at a rate sufficient for you to hear or feel the capsule spinning.
9. Remove the Turbospin inhaler from your mouth and hold your breath for about 10 seconds or for as long as is comfortable, then breathe out slowly.
10. If you do not hear the capsule spinning, the capsule may be stuck in the compartment. If this occurs, you can loosen the capsule by gently tapping the chamber of the inhaler. Do not try to loosen the capsule by repeatedly pressing the piston. If the capsule cannot be loosened and the powder cannot be inhaled, dispose of the broken capsule and any powder remaining in it and use another.
11. Inhale the medicine again by repeating Steps 7 and 8 to ensure you have emptied the capsule.
12. You can check whether the capsule is empty by unscrewing the mouthpiece and checking the capsule. If it is not empty, repeat steps 7, 8 and 9 until you have inhaled all of the contents.
13. Once all the contents have been inhaled, rinse your mouth out well with water and spit out.

Removing the empty capsule from the Turbospin

14. When the capsule is empty, unscrew the mouthpiece, then remove and discard the empty capsule.

Additional information

As you breathe in slowly, you suck air through the body of the Turbospin inhaler into the capsule chamber. The tiny particles of medication in the capsule are picked up by the airflow and carried down your airway into your lungs.

Occasionally, very small pieces of the capsule shell can get into your mouth or airways.

- If this happens, you may be able to feel these pieces on your tongue or in your airways.
- The capsule shell is made of gelatin, which is harmless to humans if swallowed or inhaled.
- The chances of the capsule breaking into pieces are increased if the capsule is pierced more than once during Step 6.

Cleaning the Turbospin device

Clean the Turbospin inhaler after each dose using the following procedure:

1. Deeply press the piston a few times whilst keeping the chamber turned upside down.
2. Clean the chamber using a tissue or cotton bud. Do not use water.
3. Screw the mouthpiece firmly back into place, put the cap back on and the inhaler is ready to be used for your next dose.

If you/your child use more Colobreathe than you/your child should, or have accidentally swallowed the capsule, contact your doctor immediately for advice.

If you/your child forget to use Colobreathe

If you/your child forget to take a dose of Colobreathe then you/your child should take your missed dose as soon as you/your child remember. You/your child must not take 2 doses within 12 hours. Carry on from there as instructed.

If you/your child stop using Colobreathe

Do not stop your treatment early unless your doctor says you can. Your doctor will decide how long you/your child's treatment should last.

If you/your child have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines this medicine can cause side effects, although not everyone gets them.

Allergic reactions

An allergic reaction with Colobreathe is possible (typically serious allergic reactions may cause rashes, swelling of the face, tongue and neck, inability to breathe due to narrowing of the airways and loss of consciousness). **If you/your child experience signs of an allergic reaction you should seek urgent medical attention.**

Other possible side effects

You/your child may get an unpleasant taste in your mouth after inhaling Colobreathe.

Very common: may affect more than 1 in 10 people

- Difficulty in breathing
- Cough, throat irritation
- Hoarse or weak, or even loss of the voice
- Unpleasant taste

Common: may affect up to 1 in 10 people

- Headache
- Ringing or buzzing noises in the ear, problems with balance

- Coughing up blood, wheezing, chest discomfort, asthma, productive cough (a cough which brings up mucus), infection of the lungs, lung crackles (your doctor would hear this when listening to your lungs using a stethoscope)
- Vomiting, nausea
- Changes in how your lungs function (found by testing)
- Joint pains
- Lack of energy, tiredness
- Raised temperature

Uncommon: may affect up to 1 in 100 people

- Allergic (hypersensitivity) reactions, the signs may include rash and itching
- Weight fluctuations, decreased appetite
- Anxiety
- Fits
- Sleepiness
- Blockage in the ears
- Chest pain
- Shortness of breath
- Nose bleeds, catarrh (mucus in your nose, which may make you feel blocked up), coughing up thick green mucus, pain in the throat and sinuses
- Unusual noises in the chest (your doctor would hear this when listening to your lungs with a stethoscope)
- Diarrhoea, wind
- Excessive production of saliva
- Toothache
- Protein in the urine (found by testing)
- Thirst

The above side effects have been seen in people of all ages with similar frequency.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Colobreathe

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the outer carton and blister after EXP. The expiry date refers to the last date of that month.

Do not store Colobreathe above 25°C.

Store in the original package until immediately before use in order to protect from moisture.

If you/your child accidentally peel back the foil, and any capsules become exposed, please discard these capsules.

Discard the Turbospin inhaler after the completion of a treatment pack.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Colobreathe contains

The active substance is colistimethate sodium. Each capsule contains 1,662,500 IU (approximately equivalent to 125 mg) colistimethate sodium.

The other ingredients are:

Capsule Shell

Gelatin

polyethylene glycol

sodium lauryl sulfate

purified water

What Colobreathe looks like and contents of the pack

Colobreathe inhalation powder, hard capsule (inhalation powder) is supplied as small, hard, transparent gelatin capsules containing a fine white powder.

The Turbospin is an inspiratory flow driven dry powder inhaler made of polypropylene and stainless steel.

The capsules are packed in blister packs supplied in cartons containing:

- 56 hard capsules and one Turbospin powder inhaler device sufficient for 4 weeks use.
- 8 hard capsules and one Turbospin inhaler device sufficient for 4 days use.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Essential Pharma Limited,
Vision Exchange Building
Triq it-Territorjals, Zone 1,
Central Business District,
Birkirkara, CBD 1070, Malta

Manufacturer

Teva Pharmaceuticals Europe BV
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Block 7, City North Business Campus
Stamullen
Co Meath
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Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>. There are also links to other websites about rare diseases and treatments.