Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

COLIFIN 1 AND 2 MEGA INTERNATIONAL UNITS POWDER FOR NEBULISER SOLUTION (COLISTIMETHATE SODIUM)

Procedure No: UK/H/1824/001-2/DC

UK Licence No: PL 32288/0001-2

PARI Pharma GmbH

LAY SUMMARY

On 12th February 2010, the MHRA granted PARI Pharma GmbH Marketing Authorisations (licences) for the medicinal products ColiFin 1 and 2 MIU Powder for Nebuliser Solution (PL 32288/0001-2). These are prescription-only medicines (POM).

ColiFin is an antibiotic powder for patients with Cystic Fibrosis to treat lung infections caused by the bacteria Pseudomonas aeruginosa. COLIFIN is inhaled using a nebuliser.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking ColiFin 1 and 2 MIU Powder for Nebuliser Solution outweigh the risks, hence Marketing Authorisations have been granted.

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Module 1

Product Name	ColiFin 1 and 2 MIU Powder for Nebuliser Solution
Type of Application	Generic, Article 10.3
Active Substances	Colistimethate sodium
Form	Powder for Nebuliser Solution
Strength	1 and 2 MIU Powder for Nebuliser Solution
MA Holder	PARI Pharma GmbH Moosstr. 3 Starnberg D-82319 Germany
Reference Member State (RMS)	UK
CMS	DE and NL
Procedure Number	UK/H/1824/01-2/DC
Timetable	Day 210 – 26 November 2009

Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
ColiFin 1 MIU Powder for Nebuliser Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 10 ml vial contains 1 MIU equivalent to ~80 mg of Colistimethate sodium (CMS).

There is no excipient in this medicinal product.

3 PHARMACEUTICAL FORM
Powder for Nebuliser Solution.

White powder

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
ColiFin is indicated for the treatment by inhalation of *Pseudomonas aeruginosa* lung infection in patients with cystic fibrosis (CF).

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

4.2 Posology and method of administration
Inhalation use

The following recommended doses are for guidance only and should be adjusted according to clinical response:

Adults:	1 or 2 MIU twice daily
Children (2 -11 years) and adolescents (12-17 years):	1 or 2 MIU twice daily
Children < 2 years:	1 MIU twice daily

In premature and newborn infants special care should be employed as renal function is only insufficiently developed in this population.

The dose may be varied across this range depending on the condition being treated. *Pseudomonas aeruginosa* resistance should be tested prior to first use.

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

For frequent, recurrent infections (Less than three positive cultures of *Pseudomonas aeruginosa* sensitive to Colistimethate sodium in a six month period) the dose may be increased up to a maximum of 2 MIU three times daily for up to 3 months, in conjunction with other parenteral or oral antibiotics.

Chronic colonisation (Three or more positive cultures of *Pseudomonas aeruginosa* sensitive to Colistimethate sodium in a 6 month period) may require long term therapy with 1 to 2 MIU twice daily. Additional parenteral or oral antibiotics may need to be administered to treat acute exacerbations of pulmonary infection**.**

Renal impairment
Colistimethate sodium is renally excreted and is nephrotoxic if high serum concentrations are achieved. Whilst this is unlikely during inhalation therapy, serum concentration estimations are recommended especially in patients with renal impairment.
Where there is renal impairment, excretion may be delayed and the daily dosage (magnitude of dose and dose interval) must be adjusted in relation to renal function to prevent accumulation of Colistimethate sodium as indicated in the table.

SUGGESTED DOSAGE ADJUSTMENT IN RENAL IMPAIRMENT

Grade	Creatinine clearance (ml/min)	Over 60kg bodyweight
Mild	20-50	1-2 MIU every 8hr
Moderate	10-20	1 MIU every 12-18 hr
Severe	<10	1 MIU every 18-24 hr

Nebulised ColiFin should be administered after physiotherapy and other inhaled treatments, where used. Other inhaled therapies may include agents to reduce the viscoelasticity of sputum and bronchodilators (see section 4.4).

The content of a vial of ColiFin 1 MIU should be dissolved in 3 ml of isotonic sodium chloride solution.

For instructions on dilution of the product before administration, see section 6.6.

Predicted drug delivery characteristics as studied in vitro (in vivo) with different nebuliser devices for ColiFIN 1.0 MIU dissolved in 3 ml of isotonic sodium chloride. (min – max)

Nebuliser system	PARI LC SPRINT with PARI Boy S compressor	eFlow®*rapid* nebuliser
Total Drug Delivered	25 mg CMS (22.1 – 27.2)	27 mg CMS (19.9 – 30.5)
Fine Particle Mass < 5 µm	15 mg CMS (12.7 – 16.8)	18 mg CMS (13.0 – 20.8)
Drug Delivery Rate	4.6 mg CMS/ min (4.3 – 5.0)	7.0 mg CMS/ min (5.2 – 7.7)
Mass Median Aerodynamic Diameter	3.8 µm (3.3 -4.3)	4.1 µm (4.0 – 4.4)
Geometric Standard Deviation	2.2	1.6

80 mg CMS corresponds approximately to1 MIU.

- The nebulisation time may increase during 60 cycles of nebulisation from ~ 3 minutes to ~ 4.5 minutes with eFlow®*rapid* nebuliser handset.
- The nebuliser must be kept horizontally during operation.
- The patient should sit in an upright position during inhalation. Inhalation should be performed applying a normal breathing pattern without interruption.
- The nebuliser must be cleaned and disinfected after use as described in the instructions of use of the corresponding nebuliser.

4.3 Contraindications
Hypersensitivity to Colistimethate sodium or to polymyxin B.
Colistimethate sodium is known to reduce the amount of acetylcholine released from the pre-synaptic neuromuscular junction and therefore must not be used in patients with myasthenia gravis.

4.4 Special warnings and precautions for use
Coughing and bronchospasm may occur on inhalation of antibiotics.

It is recommended to administer the first dose under medical supervision. Pre-dosing with a bronchodilator is recommended and should be routine, especially if this is part of the patient's current therapeutic regimen. FEV_1 should be evaluated pre and post dosing. If there is evidence of

Colistimethate sodium induced bronchial hyper reactivity in a patient not receiving pre-treatment bronchodilators the test should be repeated on a separate occasion using a bronchodilator. Evidence of bronchial hyper reactivity in the presence of a bronchodilator may indicate an allergic response and ColiFin should be discontinued. Bronchospasm that occurs should be treated as medically indicated.
Bronchial hyper reactivity in response to Colistimethate sodium may develop with continued use over time and it is recommended that pre and post treatment FEV_1s are evaluated at regular clinic visits.
In case of hypersensibility with respect to the recommended doses and volumes more diluted solutions should be used by adding about 1 - 3 ml isotonic saline to the recommended volumes and dose strengths.

Use with extreme caution in patients with porphyria.

Nephrotoxicity or neurotoxicity may occur if the recommended parenteral dose is exceeded. The risk is reduced due to the low bioavailability during inhalation, but ColiFin should be used with caution in patients with renal impairment (see section 4.2). Appearance of neurotoxic reactions as well as the renal function should be monitored.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of Colistimethate sodium with other medicinal products of neurotoxic and/or nephrotoxic potential (e.g. cephalosporins, aminoglycosides, ciclosporin) including those which are administered by the IV or IM routes should be avoided.

During concomitant use of inhalation narcotics (e.g. ether, halothan), muscle relaxants and aminoglycosids with ColiFin appearance of neurotoxic reactions should be thoroughly monitored due to prolongation effect of the inhaltion of narcotics.

Due to the effects of colistimethate sodium on the release of acetylcholine, non-depolarising muscle relaxants should be used with extreme caution in patients receiving ColiFin as their effects could be prolonged.

4.6 Pregnancy and lactation

There are no adequate data from the use of colistimethate sodium in pregnant women. Single dose studies in human pregnancy showed that colistimethate sodium crosses the placental barrier and there may be a risk of fetal toxicity if repeated doses are given to pregnant patients. Animal studies are insufficient with respect to the effect of colistimethate sodium on reproduction and development (see section 5.3). Colistimethate sodium should not be used in pregnancy unless the benefit to the mother outweighs the potential risk to the fetus.

Colistimethate sodium is secreted in breast milk. Colistimethate sodium should be administered to breastfeeding women only when clearly indicated and the benefit to the mother outweighs the potential risk to the child.

4.7 Effects on ability to drive and use machines

ColiFin has moderate influence on the ability to drive and use machines. During treatment with Colistimethate sodium neurotoxicity may occur with the possibility of dizziness, confusion or visual disturbance. Patients should be warned not to drive or operate machinery if these effects occur.

4.8 Undesirable effects

The most common undesirable effects following nebulisation of Colistimethate sodium are coughing and bronchospasm in approximately 10% of patients. In cystic fibrosis patients treated by IV or IM injection neurological events have been reported in up to 27% of patients.

The likelihood of adverse events may be related to the age, renal function and condition of the patient.

The frequency of adverse reactions listed below is to be used and is defined using the following convention:
Very common (>1/10); common *(≥1/100 to <1/10)*; uncommon *(≥1/1,000 to <1/100)* ; rare *(≥1/10,000 to <1/1,000)* , very rare (<1/10000), not known (cannot be estimated from the available data).

Frequency	**Body Class**	**Adverse Reaction** (MedDRA preferred term)
Very common	Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain, pharyngolaryngeal discomfort, cough, dyspnoea, wheezing, shortness of breath, forced expiratory volume decreased, apnoea
Unknown. Patients with severe renal impairment and higher dosages may experience side effects known for intravenous administration	Renal and urinary disorders	Renal failure
	Nervous system disorders	Paraesthesia, dysarthria, autonomic nervous system imbalance
	Ear and labyrinth disorders	Vertigo
	Eye disorders	Visual disturbance
	Psychiatric disorders	Confusional state, psychotic disorder

4.9 Overdose

Symptoms:
Overdose may cause muscular weakness, apnoea and possible respiratory arrest as well as acute renal failure characterised by decreased urine output and increased serum concentrations of BUN and creatinine.
There is no specific antidote.

Treatment:
Management of overdose is by means of supportive treatment and measures to increase the rate of elimination of colistin such as mannitol diuresis, prolonged haemodialysis or peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antibacterials, polymyxins, ATC code: J01X B01

Mode of action
Colistimethate sodium is a cyclic polypeptide antibiotic derived from Bacillus polymyxa var. colistinus. The polymyxin antibiotics are cationic agents that work by damaging the cell membrane. The resulting physiological effects are lethal to the bacterium. Polymyxins are selective for Gram-negative bacteria that have a hydrophobic outer membrane.

Breakpoints
Susceptible (S) ≤ 4 mg/L Resistant (R) ≥ 8 mg/L

Resistance
Resistant bacteria are characterised by modification of the phosphate groups of lipopolysaccharide that 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.

Colistimethate sodium acquired resistance in mucoid Pseudomonas aeruginosa has been reported to be approximately 3%. Susceptibility testing should be performed on patients who are treated on a long term basis.

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

Susceptibility
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species
Acinetobacter species* Citrobacter species Escherichia coli Haemophilus influenzae Pseudomonas aeruginosa
Species for which acquired resistance may be a problem
Enterobacter species Klebsiella species
Inherently resistant organisms
Brucella species Burkholderia cepacia and related species. Neisseria species Proteus species Providencia species Serratia species Anaerobes All Gram positive organisms

*In-vitro results may not correlate with clinical responses in the case of Acinetobacter spp.

PARI LC PLUS and PARI LC STAR are nebulisers which had been used in the past for nebulisation of Colistimethate sodium. These jet nebulisers were compared with the eFlow *rapid* for the nebulisation of 1 MIU Colistimethate sodium dissolved in 3 ml of isotonic saline solution by in-vitro testing:

Nebuliser:	eFlow *rapid*	PARI LC PLUS	PARI LC STAR
Total Drug Delivered [mg ± 95% CI]	26.6 ±1.62	26.0 ± 0.33	27.5 ± 2.06
Drug Delivery Rate [mg/min ± 95% CI]	7.0 ± 0.39	4.3 ± 0.14	3.2 ± 0.27

5.2 Pharmacokinetic properties

Absorption
Absorption from the gastrointestinal tract is neglible.
When given by nebulisation, variable absorption has been reported that may depend on the aerosol particle size, nebuliser system and lung status. Studies in healthy volunteers and patients with various infections have reported serum levels from nil to potentially therapeutic concentrations of 4mg/l or more. Therefore, the possibility of systemic absorption should always be borne in mind when treating patients by inhalation.

Distribution
After the administration to patients with cystic fibrosis of 7.5 mg/kg/day in divided doses given as 30-min intravenous infusions to steady state the C max was determined to be 23 ± 6 mg/l and C min at 8 h was 4.5 ± 4 mg/l. In another study in similar patients given 2 million units every 8 hours for 12 days the C max was 12.9 mg/l (5.7 – 29.6 mg/l) and the C min was 2.76 mg/l (1.0 – 6.2 mg/l). In healthy volunteers given a bolus injection of 150mg (2 MIU approx.) peak serum levels of 18 mg/l were observed 10 minutes after injection.

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 the dose can be recovered unchanged in the urine, and there is no biliary excretion, it can be assumed that the remaining active substance is active in the tissues. The mechanism is unknown.

Elimination
The main route of elimination after parenteral administration is by renal excretion with 40% of a parenteral dose recovered in the urine within 8 hours and around 80% in 24 hours. Because Colistimethate sodium is largely excreted in the urine, dose reduction is required in renal impairment to prevent accumulation. Refer to the table in Section 4.2.
After intravenous administration to healthy adults the elimination half-life is around 1.5 hrs. In a study in cystic fibrosis patients given a single 30-minute intravenous infusion the elimination half-life was 3.4 ± 1.4 hrs.
The elimination of Colistimethate sodium following inhalation has not been studied. A study in cystic fibrosis patients failed to detect any Colistimethate sodium in the urine after 1 MIU were inhaled twice daily for 3 months.
Colistimethate sodium kinetics appear to be similar in children and adults, including the elderly, provided renal function is normal. Limited data are available on use in neonates which suggest kinetics are similar to children and adults but the possibility of higher peak serum levels and prolonged half-life in these patients should be considered and serum levels monitored.

Serum concentrations and pharmacokinetics in 5 patients receiving inhaled colistimethate sodium

Parameter	160 mg (Approximately 2 MIU) Nebulised Colistimethate Sodium
AUC_{0-4} (h/mg/L)	165.9 ± 76.5
C_{max} (mg/L)	0.051 ± 0.0244
T_{max} (h)	1.9 ± 1.2
Ka (h^{-1})	3.0 ± 1.8
$t_{½}$ (h)	10.4 ± 3.6
Cl/F	0.27 ± 0.15

5.3 Preclinical safety data

Data on potential genotoxicity are limited and carcinogenicity data for Colistimethate sodium are lacking. Colistimethate sodium has been shown to induce chromosomal aberrations in human lymphocytes, in vitro. This effect may be related to a reduction in mitotic index, which was also observed.

Reproductive toxicity studies in rats and mice do not indicate teratogenic properties. However, Colistimethate sodium given intramuscularly during organogenesis to rabbits at 4.15 and 9.3 mg/kg resulted in talipes varus in 2.6 and 2.9% of fetuses respectively. These doses are 0.5 and 1.2 times the maximum daily human dose. In addition, increased resorption occured at 9.3 mg/kg.

There are no other preclinical safety data of relevance to the prescriber which are additional to safety data derived from patient exposure and already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
None.

6.2 Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life
3 years

Reconstituted solutions:
ColiFin can be stored after reconstitution with 0.9% saline solution for 24 hours below 25°C. Storage for more than 24 hours is not recommended due to the risk of microbial contamination of the reconstituted solution.

Please follow the manufacturer´s instructions on correct use of a nebuliser selected to be used with ColiFin solution.

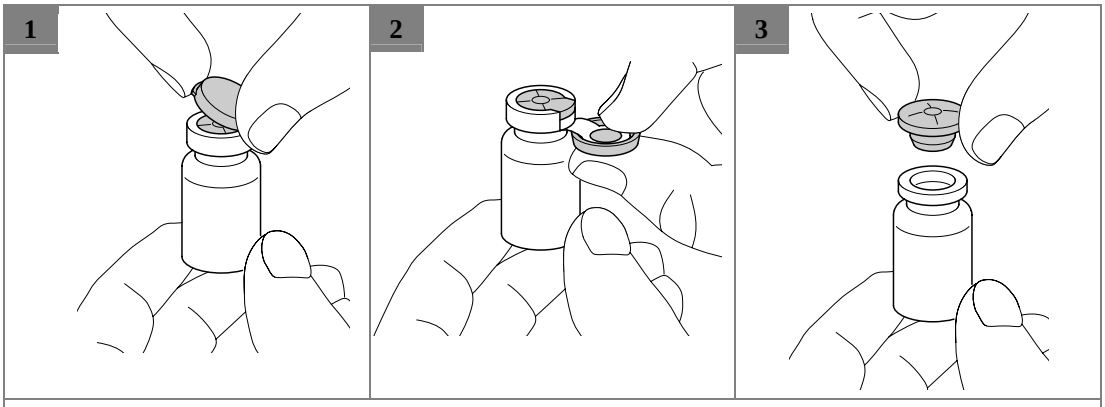
6.4 Special precautions for storage
Do not store above 25°C. Keep the vials in the outer carton.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container
ColiFin 1MIU: 10ml colourless glass vials with red flip-tear-off caps.

Pack size supplied:
- Cardboard box containing 8 cardboard boxes of 7 vials each (56 vials)

6.6 Special precautions for disposal and other handling
The required dose of ColiFin should be dissolved under gentle shaking in the respective volume of sterile isotonic sodium chloride solution. Due to the foaming properties of ColiFin, vigorous shaking should be avoided. The resulting solution for nebulisation should be clear and carefully transferred into the medication reservoir of the nebuliser. For further instructions for handling and use consult the instructions for use of the nebuliser.



Vial content should be dissolved with isotonic saline solution

- Nebulisation should take place in a well ventilated room.
- The solution is for single use only and any remaining solution should be discarded.
- For more detailed information on the device refer to the instruction manual of the nebuliser.
- For instructions on dilution of the product before administration, see section 4.2. The appearance of the solution after reconstitution should be clear.

7 MARKETING AUTHORISATION HOLDER

PARI Pharma GmbH,
Moosstr. 3
82319 Starnberg
Germany

8 MARKETING AUTHORISATION NUMBER(S)

PL 32288/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/02/2010

10 DATE OF REVISION OF THE TEXT

12/02/2010

1 NAME OF THE MEDICINAL PRODUCT

ColiFin 2 MIU Powder for Nebuliser Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 ml vial contains 2 MIU equivalent to ~160 mg of Colistimethate sodium (CMS).

There is no excipient in this medicinal product.

3 PHARMACEUTICAL FORM

Powder for Nebuliser Solution.

White powder

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ColiFin is indicated for the treatment by inhalation of *Pseudomonas aeruginosa* lung infection in patients with cystic fibrosis (CF).

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

4.2 Posology and method of administration

Inhalation use

The following recommended doses are for guidance only and should be adjusted according to clinical response:

Adults:	1 or 2 MIU twice daily
Children (2 – 11 years) and adolescents (12 – 17 years):	1 or 2 MIU twice daily
Children < 2 years:	1 MIU twice daily

In premature and newborn infants special care should be employed as renal function is only insufficiently developed in this population.

ColiFin is not recommended for use in children younger than 4 weeks due to insufficient data on safety and efficacy.

The dose may be varied across this range depending on the condition being treated. *Pseudomonas aeruginosa* resistance should be tested prior to first use.

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

For frequent, recurrent infections (Less than three positive cultures of *Pseudomonas aeruginosa* sensitive to Colistimethate sodium in a six month period) the dose may be increased up to a maximum of 2 MIU three times daily for up to 3 months, in conjunction with other parenteral or oral antibiotics.

Chronic colonisation (Three or more positive cultures of *Pseudomonas aeruginosa* sensitive to Colistimethate sodium in a 6 month period) may require long term therapy with 1 to 2 MIU twice daily. Additional parenteral or oral antibiotics may need to be administered to treat acute exacerbations of pulmonary infection**.**

Renal impairment
Colistimethate sodium is renally excreted and is nephrotoxic if high serum concentrations are achieved. Whilst this is unlikely during inhalation therapy, serum concentration estimations are recommended especially in patients with renal impairment.
Where there is renal impairment, excretion may be delayed and the daily dosage (magnitude of dose and dose interval) must be adjusted in relation to renal function to prevent accumulation of Colistimethate sodium as indicated in the table.

SUGGESTED DOSAGE ADJUSTMENT IN RENAL IMPAIRMENT

Grade	Creatinine clearance (ml/min)	Over 60kg bodyweight
Mild	20-50	1-2 MIU every 8hr
Moderate	10-20	1 MIU every 12-18 hr
Severe	<10	1 MIU every 18-24 hr

Nebulised ColiFin should be administered after physiotherapy and other inhaled treatments, where used. Other inhaled therapies may include agents to reduce the viscoelasticity of sputum and bronchodilators (see section 4.4).

The content of a vial of ColiFin 2 MIU should be dissolved in 4 ml of isotonic sodium chloride solution.

For instructions on dilution of the product before administration, see section 6.6.

Predicted drug delivery characteristics as studied in vitro (in vivo) with different nebuliser devices for ColiFIN 2.0 MIU dissolved in 4 ml of isotonic sodium chloride. (min – max)

Nebuliser system	PARI LC SPRINT with PARI Boy S compressor	eFlow®*rapid* nebuliser
Total Drug Delivered	65 mg CMS (59.9 – 72.5)	58 mg CMS (54.6 – 62.5)
Fine Particle Mass < 5 µm	39.1 mg CMS (36.0 – 45.8)	40 mg CMS (36.8 – 43.2)
Drug Delivery Rate	6.7 mg CMS/min (5.7 – 8.6)	9.5 mg CMS/min (8.1 - 10.7)
Mass Median Aerodynamic Diameter	4.1 µm (3.9 – 4.4)	4.0 µm (3.8 – 4.3)
Geometric Standard Deviation	2.1	1.6

160 mg CMS corresponds approximately to2 MIU.

- The nebulisation time may increase during 60 cycles of nebulisation from ~ 3 minutes to ~ 4.5 minutes with eFlow® *rapid* nebuliser handset.
- The nebuliser must be kept horizontally during operation.
- The patient should sit in an upright position during inhalation. Inhalation should be performed applying a normal breathing pattern without interruption.
- The nebuliser must be cleaned and disinfected after use as described in the instructions of use of the corresponding nebuliser.

4.3 Contraindications
Hypersensitivity to Colistimethate sodium or to polymyxin B.
Colistimethate sodium is known to reduce the amount of acetylcholine released from the pre-synaptic neuromuscular junction and therefore must not be used in patients with myasthenia gravis.

4.4 Special warnings and precautions for use
Coughing and bronchospasm may occur on inhalation of antibiotics.

It is recommended to administer the first dose under medical supervision. Pre-dosing with a bronchodilator is recommended and should be routine, especially if this is part of the patient's current therapeutic regimen. FEV_1 should be evaluated pre and post dosing. If there is evidence of Colistimethate sodium induced bronchial hyper reactivity in a patient not receiving pre-treatment bronchodilators the test should be repeated on a separate occasion using a bronchodilator. Evidence of

bronchial hyper reactivity in the presence of a bronchodilator may indicate an allergic response and ColiFin should be discontinued. Bronchospasm that occurs should be treated as medically indicated.
Bronchial hyper reactivity in response to Colistimethate sodium may develop with continued use over time and it is recommended that pre and post treatment FEV_1s are evaluated at regular clinic visits.
In case of hypersensibility with respect to the recommended doses and volumes more diluted solutions should be used by adding about 1 - 3 ml isotonic saline to the recommended volumes and dose strengths.

Use with extreme caution in patients with porphyria.

Nephrotoxicity or neurotoxicity may occur if the recommended parenteral dose is exceeded. The risk is reduced due to the low bioavailability during inhalation, but ColiFin should be used with caution in patients with renal impairment (see section 4.2). Appearance of neurotoxic reactions as well as the renal function should be monitored.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of Colistimethate sodium with other medicinal products of neurotoxic and/or nephrotoxic potential (e.g. cephalosporins, aminoglycosides, ciclosporin) including those which are administered by the IV or IM routes should be avoided.

During concomitant use of inhalation narcotics (e.g. ether, halothan), muscle relaxants and aminoglycosids with ColiFin appearance of neurotoxic reactions should be thoroughly monitored due to prolongation effect of the inhaltion of narcotics.

Due to the effects of colistimethate sodium on the release of acetylcholine, non-depolarising muscle relaxants should be used with extreme caution in patients receiving ColiFin as their effects could be prolonged.

4.6 Pregnancy and lactation

There are no adequate data from the use of colistimethate sodium in pregnant women. Single dose studies in human pregnancy showed that colistimethate sodium crosses the placental barrier and there may be a risk of fetal toxicity if repeated doses are given to pregnant patients. Animal studies are insufficient with respect to the effect of colistimethate sodium on reproduction and development (see section 5.3). Colistimethate sodium should not be used in pregnancy unless the benefit to the mother outweighs the potential risk to the fetus.

Colistimethate sodium is secreted in breast milk. Colistimethate sodium should be administered to breastfeeding women only when clearly indicated and the benefit to the mother outweighs the potential risk to the child.

4.7 Effects on ability to drive and use machines

ColiFin has moderate influence on the ability to drive and use machines. During treatment with Colistimethate sodium neurotoxicity may occur with the possibility of dizziness, confusion or visual disturbance. Patients should be warned not to drive or operate machinery if these effects occur.

4.8 Undesirable effects

The most common undesirable effects following nebulisation of Colistimethate sodium are coughing and bronchospasm in approximately 10% of patients. In cystic fibrosis patients treated by IV or IM injection neurological events have been reported in up to 27% of patients.

The likelihood of adverse events may be related to the age, renal function and condition of the patient.

The frequency of adverse reactions listed below is to be used and is defined using the following convention:
Very common (>1/10); common *(≥1/100 to <1/10*); uncommon *(≥1/1,000 to <1/100)* ; rare *(≥1/10,000 to <1/1,000)* , very rare (<1/10000), not known (cannot be estimated from the available data).

Frequency	**Body Class**	**Adverse Reaction** (MedDRA preferred term)
Very common	Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain, pharyngolaryngeal discomfort, cough, dyspnoea, wheezing, shortness of breath, forced expiratory volume decreased, apnoea
Unknown. Patients with severe renal impairment and higher dosages may experience side effects known for intravenous administration	Renal and urinary disorders	Renal failure
	Nervous system disorders	Paraesthesia, dysarthria, autonomic nervous system imbalance
	Ear and labyrinth disorders	Vertigo
	Eye disorders	Visual disturbance
	Psychiatric disorders	Confusional state, psychotic disorder

4.9 Overdose

Symptoms
Overdose may cause muscular weakness, apnoea and possible respiratory arrest as well as acute renal failure characterised by decreased urine output and increased serum concentrations of BUN and creatinine.
There is no specific antidote.

Treatment
Management of overdose is by means of supportive treatment and measures to increase the rate of elimination of colistin such as mannitol diuresis, prolonged haemodialysis or peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antibacterials, polymyxins, ATC code: J01X B01

Mode of action
Colistimethate sodium is a cyclic polypeptide antibiotic derived from Bacillus polymyxa var. colistinus. The polymyxin antibiotics are cationic agents that work by damaging the cell membrane. The resulting physiological effects are lethal to the bacterium. Polymyxins are selective for Gram-negative bacteria that have a hydrophobic outer membrane.

Breakpoints
Susceptible (S) ≤ 4 mg/L Resistant (R) ≥ 8 mg/L

Resistance
Resistant bacteria are characterised by modification of the phosphate groups of lipopolysaccharide that 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.

Colistimethate sodium acquired resistance in mucoid Pseudomonas aeruginosa has been reported to be approximately 3%. Susceptibility testing should be performed on patients who are treated on a long term basis.

Cross resistance
Cross resistance between colistimethate sodium and polymyxin B would be expected. Since the mechanism of action of the polymyxins is different from that of other antibiotics, resistance to

colistimethate sodium and polymixin by the above mechanism alone would not be expected to result in resistance to other antibiotic classes.

Susceptibility
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species
Acinetobacter species* Citrobacter species Escherichia coli Haemophilus influenzae Pseudomonas aeruginosa
Species for which acquired resistance may be a problem
Enterobacter species Klebsiella species
Inherently resistant organisms
Brucella species Burkholderia cepacia and related species. Neisseria species Proteus species Providencia species Serratia species Anaerobes All Gram positive organisms

*In-vitro results may not correlate with clinical responses in the case of Acinetobacter spp.

PARI LC PLUS and PARI LC STAR are nebulisers which had been used in the past for nebulisation of Colistimethate sodium. These jet nebulisers were compared with the eFlow *rapid* for the nebulisation of 2 MIU Colistimethate sodium dissolved in 4 ml of isotonic saline solution by in-vitro testing:

Nebuliser	eFlow *rapid*	PARILCPLUS	PARI LC STAR
Total Drug Delivered [mg ± 95% CI]	57.8 ±1.56	61.3 ± 1.25	60.1 ± 1.20
Drug Delivery Rate [mg/min ± 95% CI]	9.5 ± 0.51	6.6 ± 0.41	4.1 ± 0.15

5.2 Pharmacokinetic properties

Absorption
Absorption from the gastrointestinal tract is neglible.
When given by nebulisation, variable absorption has been reported that may depend on the aerosol particle size, nebuliser system and lung status. Studies in healthy volunteers and patients with various infections have reported serum levels from nil to potentially therapeutic concentrations of 4mg/l or more. Therefore, the possibility of systemic absorption should always be borne in mind when treating patients by inhalation.

Distribution
After the administration to patients with cystic fibrosis of 7.5 mg/kg/day in divided doses given as 30-min intravenous infusions to steady state the C max was determined to be 23 ± 6 mg/l and C min at 8 h was 4.5 ± 4 mg/l. In another study in similar patients given 2 million units every 8 hours for 12 days the C max was 12.9 mg/l (5.7 – 29.6 mg/l) and the C min was 2.76 mg/l (1.0 – 6.2 mg/l). In healthy volunteers given a bolus injection of 150mg (2 MIU approx.) peak serum levels of 18 mg/l were observed 10 minutes after injection.
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 the dose can be recovered unchanged in the urine, and there is no biliary excretion, it can be assumed that the remaining active substance is active in the tissues. The mechanism is unknown.

Elimination
The main route of elimination after parenteral administration is by renal excretion with 40% of a parenteral dose recovered in the urine within 8 hours and around 80% in 24 hours. Because Colistimethate sodium is largely excreted in the urine, dose reduction is required in renal impairment to prevent accumulation. Refer to the table in Section 4.2.
After intravenous administration to healthy adults the elimination half-life is around 1.5 hrs. In a study in cystic fibrosis patients given a single 30-minute intravenous infusion the elimination half-life was 3.4 ± 1.4 hrs.
The elimination of Colistimethate sodium following inhalation has not been studied. A study in cystic fibrosis patients failed to detect any Colistimethate sodium in the urine after 1 MIU were inhaled twice daily for 3 months.
Colistimethate sodium kinetics appear to be similar in children and adults, including the elderly, provided renal function is normal. Limited data are available on use in neonates which suggest kinetics are similar to children and adults but the possibility of higher peak serum levels and prolonged half-life in these patients should be considered and serum levels monitored.

Serum concentrations and pharmacokinetics in 5 patients receiving inhaled colistimethate sodium

Parameter	160 mg (Approximately 2 MIU) Nebulised Colistimethate Sodium
AUC_{0-4} (h/mg/L)	165.9 ± 76.5
C_{max} (mg/L)	0.051 ± 0.0244
T_{max} (h)	1.9 ± 1.2
Ka (h^{-1})	3.0 ± 1.8
$t_{½}$ (h)	10.4 ± 3.6
Cl/F	0.27 ± 0.15

5.3 Preclinical safety data

Data on potential genotoxicity are limited and carcinogenicity data for Colistimethate sodium are lacking. Colistimethate sodium has been shown to induce chromosomal aberrations in human lymphocytes, in vitro. This effect may be related to a reduction in mitotic index, which was also observed.

Reproductive toxicity studies in rats and mice do not indicate teratogenic properties. However, Colistimethate sodium given intramuscularly during organogenesis to rabbits at 4.15 and 9.3 mg/kg resulted in talipes varus in 2.6 and 2.9% of fetuses respectively. These doses are 0.5 and 1.2 times the maximum daily human dose. In addition, increased resorption occured at 9.3 mg/kg.

There are no other preclinical safety data of relevance to the prescriber which are additional to safety data derived from patient exposure and already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
None.

6.2 Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life
3 years

Reconstituted solutions:
ColiFin can be stored after reconstitution with 0.9% saline solution for 24 hours below 25°C. Storage for more than 24 hours is not recommended due to the risk of microbial contamination of the reconstituted solution.

Please follow the manufacturer's instructions on correct use of a nebuliser selected to be used with ColiFin solution.

6.4 Special precautions for storage
Do not store above 25°C. Keep the vials in the outer carton.

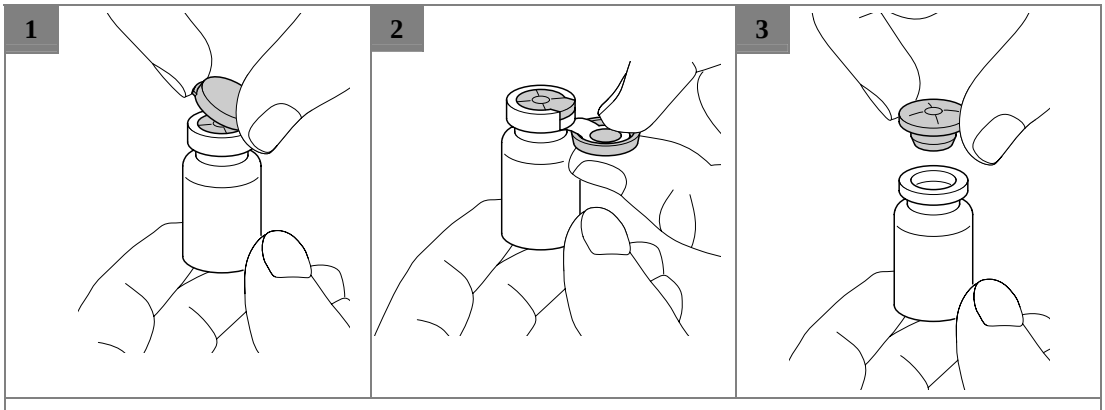
For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container
ColiFin 2 MIU: 10 ml colourless glass vials with lavender flip-tear-off caps.

Pack size supplied:

- Cardboard box containing 8 cardboard boxes of 7 vials each (56 vials)

6.6 Special precautions for disposal and other handling
The required dose of ColiFin should be dissolved under gentle shaking in the respective volume of sterile isotonic sodium chloride solution. Due to the foaming properties of ColiFin, vigorous shaking should be avoided. The resulting solution for nebulisation should be clear and carefully transferred into the medication reservoir of the nebuliser. For further instructions for handling and use consult the instructions for use of the nebuliser.



Vial content should be dissolved with isotonic saline solution

- Nebulisation should take place in a well ventilated room.
- The solution is for single use only and any remaining solution should be discarded.
- For more detailed information on the device refer to the instruction manual of the nebuliser.
- For instructions on dilution of the product before administration, see section 4.2. The appearance of the solution after reconstitution should be clear.

7 MARKETING AUTHORISATION HOLDER

PARI Pharma GmbH,
Moosstr. 3
82319 Starnberg
Germany

8 MARKETING AUTHORISATION NUMBER(S)

PL 32288/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/02/2010

10 DATE OF REVISION OF THE TEXT

12/02/2010

Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

ColiFin 1 Million International Units Powder for Nebuliser Solution

Colistimethate sodium

Read all of this leaflet carefully before you start taking this medicine.
- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What ColiFin is and what it is used for
2. Before you use ColiFin
3. How to use ColiFin
4. Possible side effects
5. How to store ColiFin
6. Further information

1. WHAT COLIFIN IS AND WHAT IT IS USED FOR

ColiFin is an antibiotic powder for patients with Cystic Fibrosis to treat lung infections caused by the bacteria *Pseudomonas aeruginosa*. COLIFIN is inhaled using a nebuliser.

2. BEFORE YOU USE COLIFIN

Do not use ColiFin
- if you are allergic (hypersensitive) to Colistimethate sodium
- if you suffer from serious muscle weakness (myasthenia gravis)

Take special care with ColiFin
- if you have kidney problems.
- if you are allergic to any antibiotics
- if you suffer from disruption of heme production (porphyria)

Coughing and chest tightness may lead to discontinuation. This may be relieved by using an inhaled bronchodilator (e.g. salbutamol) before using ColiFin. Your doctor will supervise your first dose of ColiFin and check your lung function before and after dosing.

If chest tightness occurs despite the use of a bronchodilator, please tell your doctor because this may indicate an allergic reaction and the treatment should be discontinued.

During treatment with ColiFin neurotoxicity may occur with the possibility of dizziness, confusion or visual disturbance. If you do experience any side effects such as dizziness or visual disturbance or also ones not listed in this patient information, please tell your doctor.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

If you are taking several medications to treat cystic fibrosis, the recommended order is as follows:

1. Bronchodilator (to expand the airways)
2. Chest physiotherapy
3. Any other inhaled medications

And finally

4. ColiFin

ColiFin should not be mixed with any other drugs in the nebuliser!

If you are taking any of the following medicines, ask your doctor or pharmacist for advice before using ColiFin.

- Are you taking other antibiotics called aminoglycosides (which include gentamicin, tobramycin, antikacin and netilmicin) or cephalosporins?
    - Having ColiFin at the same time as an aminoglycoside antibiotic can increase the risk of kidney problems or can affect parts of the nervous system.
    - Taking cephalosporin antibiotics at the same time as ColiFin can increase the risk of kidney problems.
- Are you receiving muscle relaxant medicines?
    - These are most usually used during a general anaesthetic so you should make sure that you tell the anaesthetist that you are taking ColiFin before you have an operation. Having a muscle relaxing drug and ColiFin together can increase and prolong the muscle relaxing effects.
- If you are likely to be given ether for any reason, please tell your doctor that you are also being treated with ColiFin.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

ColiFin has moderate influence on the ability to drive and use machines. During treatment with ColiFin neurotoxicity may occur with the possibility of dizziness, confusion or visual disturbance. If you do experience any side effects, such as dizziness or visual disturbance do not drive or operate machines and talk to your doctor or pharmacist.

HOW TO USE COLIFIN

ColiFin is for inhalation use.

Always use ColiFin exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Dosing

	Proposed Dose	**Maximum dose per day**
Adults	1 to 2 Million International Units (MIU) twice daily	2 MIU three times a day
Children (age 2 years to 11 years) and **Adolescents** (age 12 years to 17 years)	1 to 2 Million International Units (MIU) twice daily	2 MIU twice a day
Children younger than 2 years	1 Million International Units (MIU) twice daily	2 MIU

Please note ColiFin is also available as 2 MIU vial.

Your doctor will tell you how long your treatment with ColiFin will last. Do not stop treatment early because when treating bacterial infections it is important to complete the full course of treatment to reduce the risk of resistance formation of the infectious bacteria.

Preparation for inhalation treatment

If you are treating yourself at home, your doctor or nurse will show you how to use ColiFin in your nebuliser when you first start this treatment.

To start your treatment, you will need the following:

- **One clear-glass vial of ColiFin 1 MIU**
- **Isotonic saline solution (0.9 % w/w sodium chloride) for dissolving the powder**
- **A nebuliser appropriate for inhalation use of ColiFin (e.g. eFlow *rapid*® or PARI LC SPRINT®)**

It is important that your nebuliser system functions properly before starting your treatment with ColiFin. **Read carefully the instructions for use of the nebuliser for further information on handling the nebuliser system.**

Place the components of your nebuliser on a clean flat surface and follow the manufacturer's instructions for use.

Preparing your ColiFin for Inhalation

ColiFin must be used immediately after dissolution. Do not dissolve ColiFin until ready to administer a dose (see also section 5).

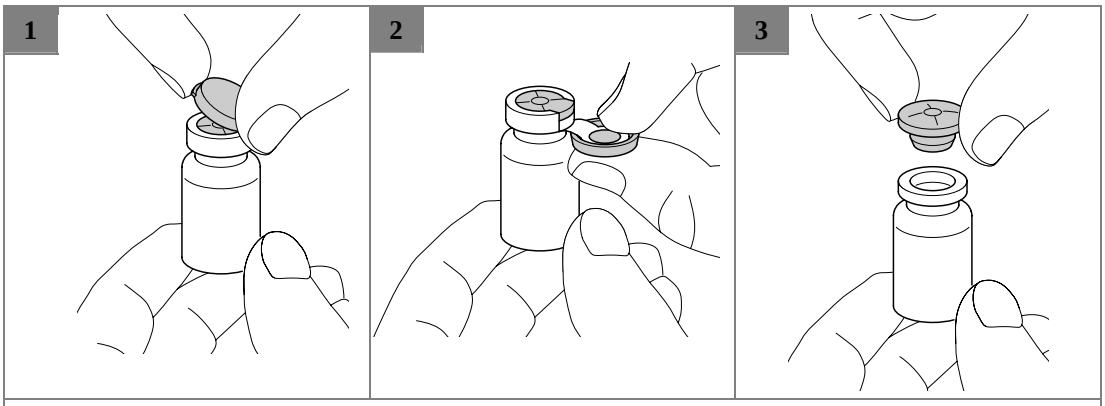
Step 1: Take one vial of ColiFin and gently tap the glass vial so that the powder settles to the bottom. This helps ensure you get the proper dose of medication. Open the drug vial by lifting up the plastic overcap on the top (Figure 1).

Step 2: Pull down to carefully remove the entire plastic overcap together with metal ring from the vial (Figure 2). Safely dispose of the ring and overcap.

Step 3: Carefully remove the rubber stopper (Figure 3). Add the following volume of isotonic saline solution to the corresponding vial to dissolve the powder:

- **Add 3 mL of isotonic saline solution to ColiFin 1 MIU vial (red cap)**

In order to avoid foaming, shake the vial gently until all powder is dissolved. Do not use ColiFin if you notice visible particles in the solution after dissolution.



Vial content should be dissolved with isotonic saline solution

Using your ColiFin

ColiFin is for inhalation use with an appropriate nebuliser (e.g. eFlow *rapid*® or PARI LC SPRINT®).
For more detailed information on correct use of the selected nebuliser follow the instruction manual of the nebuliser.
Inhalation should take place in a well ventilated room.

After inhalation of ColiFin

Please refer to the manufacturer's instructions for use of the nebuliser for cleaning and disinfecting instructions.

If you use more ColiFin than you should

If you have used more ColiFin than you should, talk to a doctor or pharmacist immediately. If too much ColiFin is accidentally given, the effects can be serious and can include kidney problems, muscle weakness and difficult (or even stopping) breathing.

If you forget to use ColiFin

If you are treating yourself and have missed any doses, you should give the missed dose as soon as you remember and then give the next dose at 8 or 12 hours later and carry on from there as instructed.

Do not use a double dose to make up for a forgotten dose.

If you stop using ColiFin

You should not stop using ColiFin as prescribed without first consulting with your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, ColiFin can cause side effects, although not everybody gets them.

Tell your doctor if you have any of the following effects:

Very common:	affects more than 1 user in 10
Common:	affects 1 to 10 users in 100
Uncommon:	affects 1 to 10 users in 1,000
Rare:	affects 1 to 10 users in 10,000
Very rare:	affects less than 1 user in 10,000
not known:	frequency cannot be estimated from the available data

Frequency	**Side Effects**
Very common	Coughing, a feeling of tightness in the chest due to narrowing of the airways (may not always be a true allergic reaction), sore mouth or throat
Unknown.	Patients with severe renal impairment and higher dosages may experience side effects known for intravenous administration
	Visual disturbance
	An allergic reaction is possible. Serious allergic reactions can happen even with the very first dose and can include rapid development of rashes, swelling of face, tongue and neck, inability to breath due to narrowing of airways and loss of consciousness. Urgent medical attention is needed. **If you think you are having an allergic reaction to ColiFin tell your doctor immediately.**

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE COLIFIN

Keep out of the reach and sight of children.

Do not use ColiFin after the expiry date which is stated on the carton and on the vial label. The expiry date refers to the last day of that month.

Do not store above 25°C.
Keep the vials in the outer carton.

ColiFin solution for nebulisation should be used immediately after preparation. If this is not possible, a ColiFin solution should not be stored above 25°C and not longer than 24 hours.

Any remaining solution should be discarded.

For single use only.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What ColiFin contains

- The active substance is Colistimethate sodium
- There are no other ingredients

What ColiFin looks like and contents of the pack

ColiFin is a powder for nebuliser solution.

1 MIU/vial:	White powder in a 10-ml colourless glass vial with a red cap.
Also available:	
2 MIU/vial:	White powder in a 10-ml colourless glass vial with a lavender cap.

<u>The product is available in the following pack size:</u>

Cardboard box containing 8 cardboard boxes of 7 vials each (56 vials)

Marketing Authorisation Holder and Manufacturer

PARI Pharma GmbH,
Moosstr. 3
82319 Starnberg
Germany
Tel.: +49 (0) 81 51 / 279-0
Fax: +49 (0) 81 51 / 279-101 E-Mail: info@pari.de

For any information about this medicine, please contact the Marketing Authorisation Holder:

Deutschland: Tel.: +49 (0)89/74 28 46 – 47

This medicinal product is authorised in the Member States of the EEA under the following names:

United Kingdom	ColiFin 1 MIU Powder for Nebuliser Solution
Germany	ColiFin 1 Mio. I.E. Pulver zur Herstellung einer Lösung für einen Vernebler.
Netherlands	ColiFin 1 Mio I.U.

This leaflet was last approved in {MM/YYYY}.

PACKAGE LEAFLET: INFORMATION FOR THE USER

ColiFin 2 Million International Units Powder for Nebuliser Solution

Colistimethate sodium

Read all of this leaflet carefully before you start taking this medicine.
- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What ColiFin is and what it is used for
2. Before you use ColiFin
3. How to use ColiFin
4. Possible side effects
5. How to store ColiFin
6. Further information

2. WHAT COLIFIN IS AND WHAT IT IS USED FOR

ColiFin is an antibiotic powder for patients with Cystic Fibrosis to treat lung infections caused by the bacteria *Pseudomonas aeruginosa*. COLIFIN is inhaled using a nebuliser.

3. BEFORE YOU USE COLIFIN

Do not use ColiFin
- if you are allergic (hypersensitive) to Colistimethate sodium
- if you suffer from serious muscle weakness (myasthenia gravis)

Take special care with ColiFin
- if you have kidney problems.
- if you are allergic to any antibiotics
- if you suffer from disruption of heme production (porphyria)

Coughing and chest tightness may lead to discontinuation. This may be relieved by using an inhaled bronchodilator (e.g. salbutamol) before using ColiFin. Your doctor will supervise your first dose of ColiFin and check your lung function before and after dosing.

If chest tightness occurs despite the use of a bronchodilator, please tell your doctor because this may indicate an allergic reaction and the treatment should be discontinued.

During treatment with ColiFin neurotoxicity may occur with the possibility of dizziness, confusion or visual disturbance. If you do experience any side effects such as dizziness or visual disturbance or also ones not listed in this patient information, please tell your doctor.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

If you are taking several medications to treat cystic fibrosis, the recommended order is as follows:

1. Bronchodilator (to expand the airways)
2. Chest physiotherapy
3. Any other inhaled medications

And finally

4. ColiFin

ColiFin should not be mixed with any other drugs in the nebuliser!

If you are taking any of the following medicines, ask your doctor or pharmacist for advice before using ColiFin.

- Are you taking other antibiotics called aminoglycosides (which include gentamicin, tobramycin, antikacin and netilmicin) or cephalosporins?
    - Having ColiFin at the same time as an aminoglycoside antibiotic can increase the risk of kidney problems or can affect parts of the nervous system.
    - Taking cephalosporin antibiotics at the same time as ColiFin can increase the risk of kidney problems.
- Are you receiving muscle relaxant medicines?
    - These are most usually used during a general anaesthetic so you should make sure that you tell the anaesthetist that you are taking ColiFin before you have an operation. Having a muscle relaxing drug and ColiFin together can increase and prolong the muscle relaxing effects.
- If you are likely to be given ether for any reason, please tell your doctor that you are also being treated with ColiFin.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

ColiFin has moderate influence on the ability to drive and use machines. During treatment with ColiFin neurotoxicity may occur with the possibility of dizziness, confusion or visual disturbance. If you do experience any side effects, such as dizziness or visual disturbance do not drive or operate machines and talk to your doctor or pharmacist.

HOW TO USE COLIFIN

ColiFin is for inhalation use.

Always use ColiFin exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Dosing

	Proposed Dose	**Maximum dose per day**
Adults	1 to 2 Million International Units (MIU) twice daily	2 MIU three times a day
Children (age 2 years to 11 years) and **Adolescents** (age 12 years to 17 years)	1 to 2 Million International Units (MIU) twice daily	2 MIU twice a day
Children younger than 2 years	1 Million International Units (MIU) twice daily	2 MIU

Please note ColiFin is also available as 1 MIU vial.

Your doctor will tell you how long your treatment with ColiFin will last. Do not stop treatment early because when treating bacterial infections it is important to complete the full course of treatment to reduce the risk of resistance formation of the infectious bacteria.

Preparation for inhalation treatment

If you are treating yourself at home, your doctor or nurse will show you how to use ColiFin in your nebuliser when you first start this treatment.

To start your treatment, you will need the following:

- **One clear-glass vial of ColiFin 2 MIU**
- **Isotonic saline solution (0.9 % w/w sodium chloride) for dissolving the powder**
- **A nebuliser appropriate for inhalation use of ColiFin (e.g. eFlow *rapid*® or PARI LC SPRINT®)**

It is important that your nebuliser system functions properly before starting your treatment with ColiFin. **Read carefully the instructions for use of the nebuliser for further information on handling the nebuliser system.**

Place the components of your nebuliser on a clean flat surface and follow the manufacturer's instructions for use.

Preparing your ColiFin for Inhalation

ColiFin must be used immediately after dissolution. Do not dissolve ColiFin until ready to administer a dose (see also section 5).

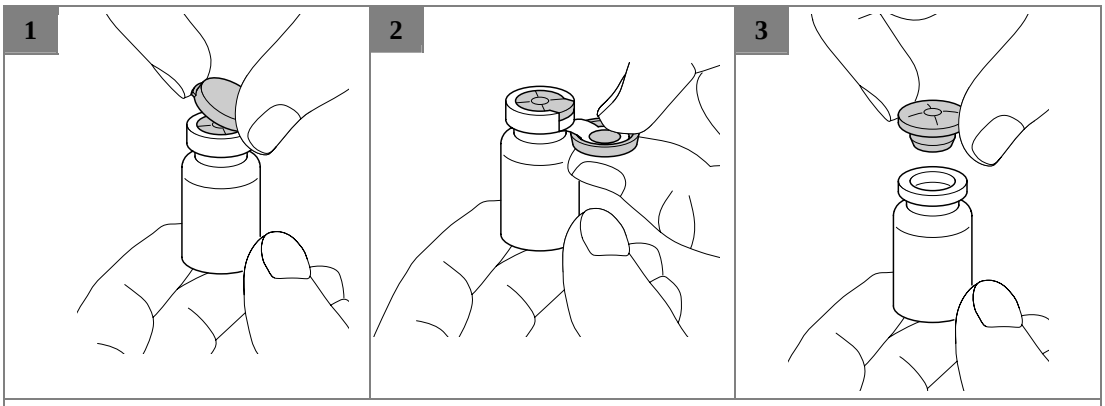
Step 1: Take one vial of ColiFin and gently tap the glass vial so that the powder settles to the bottom. This helps ensure you get the proper dose of medication. Open the drug vial by lifting up the plastic overcap on the top (Figure 1).

Step 2: Pull down to carefully remove the entire plastic overcap together with metal ring from the vial (Figure 2). Safely dispose of the ring and overcap.

Step 3: Carefully remove the rubber stopper (Figure 3). Add the following volume of isotonic saline solution to the corresponding vial to dissolve the powder:

- **Add 4 mL of isotonic saline solution to ColiFin 2 MIU vial (lavender cap)**

In order to avoid foaming, shake the vial gently until all powder is dissolved. Do not use ColiFin if you notice visible particles in the solution after dissolution.



Vial content should be dissolved with isotonic saline solution

Using your ColiFin

ColiFin is for inhalation use with an appropriate nebuliser (e.g. eFlow *rapid*® or PARI LC SPRINT®).
For more detailed information on correct use of the selected nebuliser follow the instruction manual of the nebuliser.
Inhalation should take place in a well ventilated room.

After inhalation of ColiFin

Please refer to the manufacturer's instructions for use of the nebuliser for cleaning and disinfecting instructions.

If you use more ColiFin than you should

If you have used more ColiFin than you should, talk to a doctor or pharmacist immediately. If too much ColiFin is accidentally given, the effects can be serious and can include kidney problems, muscle weakness and difficult (or even stopping) breathing.

If you forget to use ColiFin

If you are treating yourself and have missed any doses, you should give the missed dose as soon as you remember and then give the next dose at 8 or 12 hours later and carry on from there as instructed.

Do not use a double dose to make up for a forgotten dose.

If you stop using ColiFin

You should not stop using ColiFin as prescribed without first consulting with your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, ColiFin can cause side effects, although not everybody gets them.

Tell your doctor if you have any of the following effects:

Very common:	affects more than 1 user in 10
Common:	affects 1 to 10 users in 100
Uncommon:	affects 1 to 10 users in 1,000
Rare:	affects 1 to 10 users in 10,000
Very rare:	affects less than 1 user in 10,000
not known:	frequency cannot be estimated from the available data

Frequency	**Side Effects**
Very common	Coughing, a feeling of tightness in the chest due to narrowing of the airways (may not always be a true allergic reaction), sore mouth or throat
Unknown.	Patients with severe renal impairment and higher dosages may experience side effects known for intravenous administration
	Visual disturbance
	An allergic reaction is possible. Serious allergic reactions can happen even with the very first dose and can include rapid development of rashes, swelling of face, tongue and neck, inability to breath due to narrowing of airways and loss of consciousness. Urgent medical attention is needed. **If you think you are having an allergic reaction to ColiFin tell your doctor immediately.**

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE COLIFIN

Keep out of the reach and sight of children.

Do not use ColiFin after the expiry date which is stated on the carton and on the vial label. The expiry date refers to the last day of that month.

Do not store above 25°C.
Keep the vials in the outer carton.

ColiFin solution for nebulisation should be used immediately after preparation. If this is not possible, a ColiFin solution should not be stored above 25°C and not longer than 24 hours.

Any remaining solution should be discarded.

For single use only.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What ColiFin contains

- The active substance is Colistimethate sodium
- There are no other ingredients

What ColiFin looks like and contents of the pack

ColiFin is a powder for nebuliser solution.

2 MIU/vial:	White powder in a 10-ml colourless glass vial with a lavender cap.
Also available:	
1 MIU/vial:	White powder in a 10-ml colourless glass vial with a red cap.

<u>The product is available in the following pack size:</u>

Cardboard box containing 8 cardboard boxes of 7 vials each (56 vials)

Marketing Authorisation Holder and Manufacturer

PARI Pharma GmbH,
Moosstr. 3
82319 Starnberg
Germany
Tel.: +49 (0) 81 51 / 279-0
Fax: +49 (0) 81 51 / 279-101 E-Mail: info@pari.de

For any information about this medicine, please contact the Marketing Authorisation Holder:

Deutschland:

Tel.: +49 (0) 89/74 28 46 - 47

This medicinal product is authorised in the Member States of the EEA under the following names:

United Kingdom	ColiFin 2 MIU Powder for Nebuliser Solution
Germany	ColiFin 2 Mio. I.E. Pulver zur Herstellung einer Lösung für einen Vernebler.
Netherlands	ColiFin 2 Mio I.U.

This leaflet was last approved in {MM/YYYY}.

Module 4
Labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Paper Carton Box

1. NAME OF THE MEDICINAL PRODUCT

ColiFin 1 MIU Powder for Nebuliser Solution

Colistimethate Sodium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 10 ml vial contains 1 MIU equivalent to ~ 80 mg of Colistimethate Sodium (CMS).

3. LIST OF EXCIPIENTS

N/A

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for Nebuliser Solution
56 Vials as 8 boxes of 7 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For inhalation use after dissolving. Read the package leaflet before use. For use with a nebuliser.

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

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

N/A

8. EXPIRY DATE

EXP MM-YYYY

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C. Keep the vials in the outer carton.

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

The solution is for single use only and any remaining solution should be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

PARI Pharma GmbH,
Moosstr. 3
82319 Starnberg
Germany
Phone: +49 (0) 81 51 / 279-0
Fax: +49 (0) 81 51 / 279-101
E-Mail: info@pari.de

12. MARKETING AUTHORISATION NUMBER(S)

PL 32288/0001

13. BATCH NUMBER

Lot 000000

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

N/A

16. INFORMATION IN BRAILLE

ColiFin 1 MIU

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Paper Label of Bundle Pack

1. NAME OF THE MEDICINAL PRODUCT

ColiFin 1 MIU Powder for Nebuliser Solution

Colistimethate Sodium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 10 ml vial contains 1 MIU equivalent to ~ 80 mg of Colistimethate Sodium (CMS).

3. LIST OF EXCIPIENTS

N/A

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for Nebuliser Solution
56 Vials as 8 boxes of 7 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For inhalation use after dissolving. Read the package leaflet before use. For use with a nebuliser.

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

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

N/A

8. EXPIRY DATE

EXP MM-YYYY

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C. Keep the vials in the outer carton.

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

The solution is for single use only and any remaining solution should be discarded.

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12. MARKETING AUTHORISATION NUMBER(S)

PL 32288/0001

13. BATCH NUMBER

Lot 000000

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

N/A

16. INFORMATION IN BRAILLE

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

10 ml clear glass vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ColiFin 1 MIU Powder for Nebuliser Solution

2. METHOD OF ADMINISTRATION

For inhalation use after dissolving.

3. EXPIRY DATE

EXP MM-YYYY

4. BATCH NUMBER

Lot 000000

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Each 10 ml vial contains 1 MIU equivalent to ~ 80 mg of Colistimethate Sodium (CMS).

6. OTHER

Do not store above 25°C. Keep the vials in the outer carton.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Paper Carton Box

1. NAME OF THE MEDICINAL PRODUCT

ColiFin 2 MIU Powder for Nebuliser Solution

Colistimethate Sodium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 10 ml vial contains 2 MIU equivalent to ~160 mg of Colistimethate Sodium (CMS).

3. LIST OF EXCIPIENTS

Not applicable.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for Nebuliser Solution
56 vials as 8 boxes of 7 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For inhalation use after dissolving. Read the package leaflet before use. For use with a nebuliser.

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

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Not applicable.

8. EXPIRY DATE

EXP MM-YYYY

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C. Keep the vials in the outer carton.

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

The solution is for single use only and any remaining solution should be discarded.

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82319 Starnberg
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Fax: +49 (0) 81 51 / 279-101
E-Mail: info@pari.de

12. MARKETING AUTHORISATION NUMBER(S)

PL 32288/0002

13. BATCH NUMBER

Lot 000000

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Not applicable.

16. INFORMATION IN BRAILLE

ColiFin 2 MIU

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Paper Label of Bundle Pack

1. NAME OF THE MEDICINAL PRODUCT

ColiFin 2 MIU Powder for Nebuliser Solution

Colistimethate Sodium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 10 ml vial contains 2 MIU equivalent to ~ 160 mg of Colistimethate Sodium (CMS).

3. LIST OF EXCIPIENTS

Not applicable.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for Nebuliser Solution
56 vials as 8 boxes of 7 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For inhalation use after dissolving. Read the package leaflet before use. For use with a nebuliser.

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

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Not applicable.

8. EXPIRY DATE

EXP MM-YYYY

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C. Keep the vials in the outer carton.

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

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12. MARKETING AUTHORISATION NUMBER(S)

PL 32288/0002

13. BATCH NUMBER

Lot 000000

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Not applicable.

16. INFORMATION IN BRAILLE

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

10 ml clear glass vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ColiFin 2 MIU Powder for Nebuliser Solution

2. METHOD OF ADMINISTRATION

For inhalation use after dissolving.

3. EXPIRY DATE

EXP MM-YYYY

4. BATCH NUMBER

Lot 000000

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Each 10 ml vial contains 2 MIU equivalent to ~ 160 mg of Colistimethate Sodium.

6. OTHER

Do not store above 25°C. Keep the vials in the outer carton.

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considered that the applications for ColiFin 1 and 2 MIU Powder for Nebuliser Solution (PL 32288/0001-2; UK/H/1824/01-2/DC) could be approved. The products are prescription-only medicines in the treatment by inhalation of Pseudomonas aeruginosa lung infection in patients with cystic fibrosis (CF).

These applications for Colifin 1 and 2 MIU powder for nebuliser solution are submitted via the decentralised procedure under article 10(3) of directive 2001/83/EC, with UK acting as RMS and DE and NL as CMS. The reference product to which this application refers is Colomycin 1 MIU powder for nebuliser solution (PL 00108/5006R), licensed to Forest laboratories UK Ltd in 1986.

The polymyxins, a group of basic, cyclic polypeptide antibiotics with activity versus most Gram-negative pathogens, were first isolated from a *Bacillus spp.* in 1947. Five different chemical compounds (polymyxins A, B, C, D, and E) are included in this group of antibiotics. Polymyxin B and polymyxin E (colistin) are the two polymyxins that have been used therapeutically. Polymyxin B was isolated from *Bacillus polymyxa* in 1947, and polymyxin E, or colistin (or Colistimethate sodium), was isolated from *Bacillus colistinus* in 1950.

No new preclinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

No new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	ColiFin 1 and 2 MIU Powder for Nebuliser Solution
Name(s) of the active substance(s) (INN)	Colistimethate sodium
Pharmacotherapeutic classification (ATC code)	J01XB
Pharmaceutical form and strength(s)	1 and 2 MIU
Reference numbers for the Mutual Recognition Procedure	UK/H/1824/01-2/DC
Reference Member State	UK
Member States concerned	DE and NL
Marketing Authorisation Number(s)	PL 32288/0001-2
Name and address of the authorisation holder	PARI Pharma GmbH Lochhamer Schlag 21 82166 Gräfelfing Germany

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

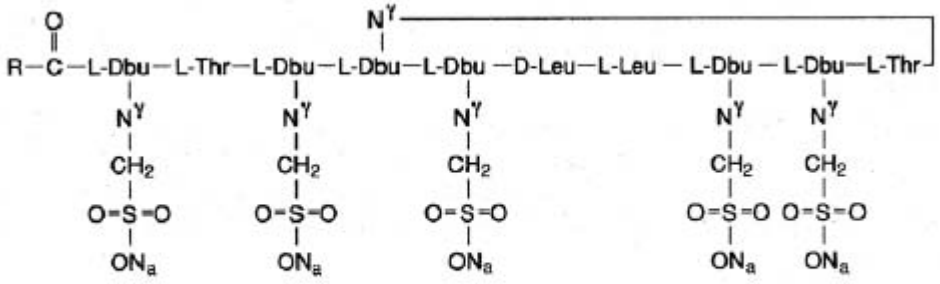
S. Active substance

INN: Colistimethane Sodium

Chemical Name: Pentasodium colistinmethanesulfonate

Molecular Formula: $C_{58}H_{105}N_{16}Na_5O_{28}S_5$ (colistin A component)
$C_{58}H_{105}N_{16}Na_5O_{28}S_5$ (colistin B component)

Chemical Structure:



Dbu is 2,4-diaminobutanoic acid; R is 5-methylheptyl in colistin A and 5-methylhexyl in colistin B

Molecular Weight
Colistin A component: 1749.82
Colistin B component: 1735.80

Appearance: White or almost white, hygroscopic powder. It is very soluble in water, slightly soluble in ethanol (96%), practically insoluble in acetone.

All aspects of the manufacture and control of the drug substance clistimethate sodium are covered by a European Directorate for the Quality of Medicines (EDQM) certificate of suitability.

P. Medicinal Product

Other Ingredients

There are no excipients present.

Pharmaceutical Development

The objective of the development programme was to formulate ColiFin powder for nebuliser solution containing qualitatively and quantitatively the same active substance to Colomycin 1 MIU powder for nebuliser solution (Forest laboratories, UK Ltd).

A satisfactory account of the pharmaceutical development has been provided.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of all strengths of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The finished product specifications proposed for both strengths are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

Container-Closure System
ColiFin 1 MIU is packaged in a glass vial with red flip-tear-off cap.
ColiFin 2 MIU is packaged in a glass vial with lavender flip-tear-off cap.

Pack size is supplied in cardboard box containing 8 cardboard boxes of 7 vials each (56 vials) The marketing authorisation holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with parenteral products.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years, with storage conditions of ‘Do not store above 25 degree C’ and ‘Keep the vials in the outer carton’.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a risk management plan for these products.

MAA forms
The MAA forms are pharmaceutically satisfactory.

Expert report

The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of marketing authorisations is recommended.

III.2 PRE-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of colistimethate sodium are well-known, no further studies are required and none have been provided.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products' pharmacology and toxicology.

An environmental risk assessment for colistimethate sodium has been submitted in support of these applications.

III.3 CLINICAL ASPECTS

Pharmacokinetics
No new data have been submitted and none are required for an application of this type.

ColiFin 1 and 2 MIU Powder for Nebuliser Solution is the generic version of Colomycin 1 MIU powder for nebuliser solution. The use of the reference product is well-established in the UK. Both products contain the same quantitative and qualitative composition of the active ingredient, colistimethate sodium.

According to CPMP guidelines, the applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance, in the same concentration as the currently authorised product (CPMP/EWP/1401/98, subpoint 5.1.6, Parenteral solutions).

Pharmacodynamics
No new data have been submitted and none are required for an application of this type.

Efficacy
No new data on the efficacy have been submitted and none are required for these types of applications.

Safety
No new data on the efficacy have been submitted and none are required for these types of applications.

SPC, PIL, Labels
The SPC, PIL and labels are medically acceptable. The SPCs are consistent with those for the originator products.

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion
The grant of marketing authorisations is recommended.

IV OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of ColiFin 1 and 2 MIU Powder for Nebuliser Solution are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the risk-benefit balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

No new data have been submitted and none are required for an application of this type.

ColiFin 1 and 2 MIU Powder for Nebuliser Solution is the generic version of Colomycin 1 MIU powder for nebuliser solution. The use of the reference product is well-established in the UK. Both products contain the same quantitative and qualitative composition of the active ingredient, colistimethate sodium.

According to CPMP guidelines, the applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance, in the same concentration as the currently authorised product (CPMP/EWP/1401/98, subpoint 5.1.6, Parenteral solutions).

No new safety data are supplied or required for this generic application. ColiFin has a well-established side-effect profile and is generally well-tolerated.

The SPC, PIL and labelling are satisfactory.

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable, and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant’s product and the innovator product are interchangeable. Extensive clinical experience with colistimethate sodium is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome