SUMMARY OF PRODUCT CHARACTERISTICS

1.NAME OF THE MEDICINAL PRODUCT

COFIBCOL 4,500,000 IU Lyophilized powder and solvent for solution for IM/IV injection and inhalation
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:
Active substance:
Colistimethate sodium 384.62 mg (equivalent to 150 mg (4,500,000 I.U.) of colistin base)
When reconstituted with 2 ml of water for injection, 1 ml of solution contains 2,250,000 I.U. of colistin base.

Excipient(s):
For excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Lyophilised powder and solvent for preparing 4,500,000 IU IM/IV injection and inhalation solution
White to light yellow, free from foreign particles, lyophilised cake mass (*lyophilised powder*)
After reconstitution: a colourless or slightly yellow, clear solution free from visible undissolved residues and visible foreign particles

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

COFIBCOL is used in the treatment of acute or chronic infections caused by susceptible Gram-negative bacilli. It is particularly indicated for infections caused by susceptible strains of *Pseudomonas* aeruginosa. This antibiotic is not used in *Proteus* or *Neisseria* infections. COFIBCOL has been clinically proven to be effective in the treatment of infections caused by the following Gram-negative organisms: *Enterobacter aerogenes, Escherichia coli, Klebsiella pneumoniae*, *Pseudomonas aeruginosa,* and *Acinetobacter baumannii.*

COFIBCOL may be used in the initial treatment of serious infections caused by Gram-negative pathogens, which are thought to be associated with Gram-negative organisms.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of COFIBCOL and other antibacterial drugs, COFIBCOL should be used only to treat or prevent infections that are suspected or proven to be caused by multiply resistant bacteria.

Additionally, COFIBCOL is used by inhalation to treat lung infections caused by *Pseudomonas* aeruginosa in patients with cystic fibrosis, including paediatric patients, and is indicated under the following conditions:

- When *Pseudomonas aeruginosa* is isolated from respiratory tract cultures for the first time, regardless of whether the patient has symptoms, it should be used as a long-term inhalation therapy in combination with systemic antibiotic therapy.
- In patients under 6 years of age with *Pseudomonas aeruginosa* colonisation, if symptoms develop, long-term inhalation therapy is indicated.
- Long-term inhalation therapy when the isolated *Pseudomonas aeruginosa* strain is resistant to tobramycin.

4.2. Posology and method of administration

Posology:

Systemic administration

Loading dose: Independent of creatinine clearance, for ALL PATIENTS; 150,000 I.U./kg is administered as a single dose, and the maintenance dose is started 12 hours later.

Maintenance dose: For patients with normal renal function (creatinine clearance ≥70 mL/min), the total daily dose is calculated to be 150,000 I.U./kg/day. The total dose is administered in 2 or 3 divided doses. The recommended maximum daily dose is 14,250,000 IU. In obese patients, the dose will be adjusted according to ideal body weight.

Cystic fibrosis IV dose: 90,000-240,000 IU/kg/day (calculated based on ideal body weight, administered in 3 equal doses every 8 hours).

Posology/frequency and duration of administration:

Administered 2 to 3 times daily. A treatment duration of at least 5 days is generally recommended.

The duration of treatment in patients with cystic fibrosis may be extended up to 6 months depending on the patient's response to treatment.

Method of administration:

Intravenous or intramuscular administration.

COFIBCOL (4.5 M.I.U./vial) is dissolved in 2 ml of water for injection. The solution prepared by dilution contains colistimethate sodium at a concentration equivalent to 2,250,000 I.U./ml of colistin base activity.

To prevent foaming, gently swirl during reconstitution.

The prepared solution should be visually inspected for particulate matter and discolouration prior to use. Clear and particulate-free solutions should be used.

Intrathecal/Intraventricular Administration:

Meningitis, intrathecal or intravenous dosage: 300,000 I.U./day (the intrathecal dose is usually administered together with IV polymyxin).

Inhalation Administration:
For the local treatment of lower respiratory tract infections, 1,500,000-2,250,000 I.U. is administered via nebuliser 2-3 times daily in 3-4 mL of physiological saline.

Additional information on specific populations
Liver impairment:
There are no data available for patients with hepatic impairment. Caution should be exercised when administering colistimethate sodium to these patients.

Renal impairment:
Dose adjustment is necessary in renal impairment. Pharmacokinetic data for patients with renal dysfunction are very limited.

The daily dose should be reduced in patients with renal impairment.

Recommended dosage adjustments for patients with renal impairment are listed in the table below:

Creatinine clearance (mL/min)	Daily total dose*		Administration Frequency
	Minimum	Maximum	
60	9,000,000 I.U.	12,600,000 I.U.	Once every 12 hours
50	7,875,000 IU	11,025,000 IU	
40	6,750,000 IU	9,450,000 IU	
30	5,625,000 IU	7,875,000 IU	
20	4,500,000 IU	6,300,000 IU	
≤10	3,375,000 IU	4,725,000 IU	

*Total daily dose = Target blood concentration (mg/L) x [(1.5 x CrC_{ln}) + 30] (target blood concentrations are taken as 75,000 I.U./L for minimum doses and 105,000 I.U./L for maximum doses). Doses are calculated based on an individual with a body surface area (BSA) of 1.73m^2 (average 70 kg). For a complete calculation, creatinine clearance adjusted for BSA should be used ($CrCl_n$= CrCl x BSA/1.73m^2)

The dosage and dosage range for COFIBCOL 4,500,000 IU Lyophilized powder and solvent for solution for IM/IV injection and inhalation, which is to be used in patients undergoing haemodialysis, are listed in the table below:

Haemodialysis	On non-haemodialysis days, a total daily dose of 3,150,000 IU is administered every 12 hours. On dialysis days, the total dose of 4,500,000 IU is divided into two parts, with the first half administered

	during the final hour of haemodialysis and the second half administered 12 hours later.
Continuous Ambulatory Peritoneal Dialysis (CAPD)	A single daily dose of 4,800,000 IU.
Continuous Renal Replacement Therapy (CRRT)	The total dose for an average serum steady-state concentration of 3.5 mcg/mL is 20,160,000 I.U. The dose is divided into doses administered every 12 hours.

Paediatric population:
In clinical studies, colistimethate sodium has been used in the paediatric population. Although similar side effects are seen in adults and the paediatric population, subjective symptoms of toxicity may not be reported in the paediatric population. Therefore, close clinical monitoring is recommended for paediatric patients.

Higher doses may be required to maintain therapeutic serum levels in patients with cystic fibrosis who exhibit abnormal distribution.

Geriatric population:
In clinical studies conducted to determine whether elderly patients aged 65 years and older respond differently to colistimethate sodium than adults, the number of patients was insufficient. Other reported clinical studies have not shown differences between the elderly and adults. In general, caution should be exercised in selecting doses for the geriatric population, starting with the lowest dose range and taking into account the importance of low renal, hepatic and cardiac function and the frequency of concomitant disease or other drug therapy. A significant portion of COFIBCOL is excreted by the kidneys. The risk of toxic reactions to COFIBCOL may be greater in patients with renal impairment, as geriatric patients have lower renal function. Precautions should be taken in dose selection and renal function should be monitored.

4.3. Contraindications
Colistimethate sodium is contraindicated in patients with hypersensitivity to colistin or any component of the formulation. It is contraindicated in patients with hypersensitivity to polymyxin B.

4.4. Special warnings and precautions for use
Intravenous colistimethate sodium should be administered with caution in combination with another antibacterial agent whenever possible, taking into account the remaining susceptibility of the pathogens being treated. Since resistance to intravenous colistin develops particularly when used as monotherapy, its use in combination with other antibacterials should also be considered to prevent the development of resistance.

There is limited clinical data on the efficacy and safety of intravenous colistimethate sodium. The recommended doses in all subpopulations are based on limited data (clinical and pharmacokinetic/pharmacodynamic data). In particular, there are limited safety data on the use of high doses (> 6MIU/day) and loading doses, and on special populations (patients with renal impairment and the paediatric population). Colistimethate sodium should only be used when other more commonly used antibiotics are ineffective or unsuitable.

Monitoring of renal function should be performed in all patients at the beginning of treatment and regularly during treatment. The colistimethate sodium dose should be adjusted according to creatinine clearance (see Section 4.2). The risk of nephrotoxicity due to colistin is increased in hypovolaemic patients or those receiving other potentially nephrotoxic drugs (see Sections 4.5 and 4.8). Some studies have reported a relationship between nephrotoxicity and cumulative dose and duration of treatment. The benefit of prolonged treatment duration should be balanced against the potential increased risk of renal toxicity.

As kidney functions are not fully developed in infants under 1 year of age, caution is advised when administering colistimethate sodium to this age group. Furthermore, the effect of immature kidney and metabolic functions on the conversion of colistimethate sodium to colistin is not known.

In case of an allergic reaction, treatment with colistimethate sodium should be discontinued and appropriate measures taken.

High serum concentrations of colistimethate sodium, which may be associated with incorrect dose reduction in patients with overdose or renal impairment, have been reported to cause neurotoxic effects such as facial paraesthesia, muscle weakness, vertigo, slurred speech, vasomotor imbalance, visual disturbances, confusion, psychosis, and apnoea. Perioral paresthesia and paresthesia in the extremities, which are symptoms of overdose, should be monitored (see Section 4.9).

It is known that colistimethate sodium reduces the presynaptic release of acetylcholine at the neuromuscular junction and should be used with extreme caution in patients with myasthenia gravis, only when clearly indicated.

Respiratory arrest has been reported following the intramuscular administration of colistimethate sodium.

Impaired renal function increases the likelihood of apnoea and neuromuscular blockade following administration of colistimethate sodium.

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

Antibiotic-associated colitis and pseudomembranous colitis have been reported with almost all antibacterial agents and may occur with colistimethate sodium. Its severity can range from mild to life-threatening. It is important to consider this diagnosis in patients who develop diarrhoea during or after colistimethate sodium use (see Section 4.8). Discontinuation of therapy and specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be administered.

Intravenous colistimethate sodium does not cross the blood-brain barrier to a clinically significant degree. The use of intrathecal or intraventricular colistimethate sodium in the treatment of meningitis has not been systematically investigated in clinical trials and is supported only by case reports. Data supporting the posology are very limited. The most commonly observed side effect of colistimethate sodium administration is aseptic meningitis (see Section 4.8).

Bronchospasm may occur with antibiotics used for inhalation. This can be prevented or treated with appropriate beta2-agonist. If it is very bothersome, treatment is discontinued.

COFIBCOL contains 1.1 mmol (or 25.28 mg) of sodium per vial. This should be taken into account for patients on a controlled sodium diet.

4.5. Interaction with other medicinal products and other forms of interaction

Great caution should be exercised when intravenous colistimethate sodium is used concomitantly with other drugs that are potentially nephrotoxic or neurotoxic.

Due to limited experience and the potential for general toxicity, caution should be exercised when used concomitantly with other colistimethate sodium formulations.

In vivo interaction studies have not been conducted. The mechanism by which the active ingredient of colistimethat sodium is converted to colistin has not been characterised. The mechanism of colistin clearance, including in kidney transplants, is equally unknown. Neither colistimethate sodium nor colistin induced any P450 (CYP) enzyme activity (CYP1A2, 2B6, 2C8, 2C9, 2C19, and 3A4/5) tested in in vitro studies in human hepatocytes.

Potential drug-drug interactions should be considered when COFIBCOL is administered concomitantly with drugs known to be substrates for renal transporter mechanisms or drugs known to induce or inhibit drug-metabolising enzymes.

Due to colistin's effects on acetylcholine release, non-depolarising muscle relaxants should be used with caution in patients receiving colistimethate sodium, as they may prolong its effects (see Section 4.4).

The concomitant use of colistimethate sodium with macrolides such as azithromycin and clarithromycin or fluoroquinolones such as norfloxacin and ciprofloxacin should be administered with caution in patients with myasthenia gravis (see Section 4.4).

The simultaneous use of colistimethate sodium with other potentially neurotoxic and/or nephrotoxic drugs should be avoided. These include aminoglycoside antibiotics such as gentamicin, amikacin, netilmicin and tobramycin. The risk of nephrotoxicity may increase when administered concomitantly with cephalosporin antibiotics.

Additional information for special populations
No clinical interaction studies have been conducted in special populations.

Paediatric population
No clinical interaction studies have been conducted in the paediatric population.

4.6. Pregnancy and lactation
General advice
Pregnancy category: C

Women of childbearing potential/ Contraception
COFIBCOL should be used with caution in women of childbearing potential.
Due to insufficient data, women of childbearing potential should use an effective method of contraception while taking this medicine.

Pregnancy
There is insufficient data on the use of colistimethate sodium in pregnant women. Single-dose studies in human pregnancies indicate that colistimethate sodium crosses the placental barrier and that repeated doses to pregnant patients may pose a risk of foetal toxicity. Animal studies are insufficient regarding the effects of colistimethate sodium on reproduction and development (see Section 5.3). Colistimethate sodium should only be used during pregnancy if the benefit to the mother outweighs the potential risk to the foetus.

COFIBCOL should be administered to a pregnant woman only if the doctor decides that the risk-benefit ratio is acceptable in a medically necessary situation.

Animal studies are insufficient with regard to effects on pregnancy and/or embryonic/foetal development and/or birth and/or postnatal development. The potential risk to humans is not known.

COFIBCOL should not be used during pregnancy unless absolutely necessary.

Lactation

Colistimethate sodium passes into breast milk. Colistimethate sodium should only be administered to breastfeeding women when necessary.

The excretion of colistimethate sodium in milk has not been studied in animals. When deciding whether to discontinue breastfeeding or to discontinue/avoid COFIBCOL treatment, the benefits of breastfeeding for the child and the benefits of COFIBCOL treatment for the breastfeeding mother should be taken into account. It should not be used during breastfeeding unless necessary.

Reproductive ability/Fertility
Long-term animal carcinogenicity studies and genetic toxicity studies have not been conducted with sodium colistimethate. No adverse effects on fertility and reproductive ability were observed in mice given a dose of 279,000 IU/kg/day.

4.7. Effects on the ability to drive and use machines
Neurotoxicity may occur during treatment with COFIBCOL, along with the possibility of dizziness, confusion, or visual disturbances.
Vehicles and machinery should not be operated during the use of COFIBCOL.

4.8. Undesirable effects
Adverse events are listed according to system organ class and frequency as follows: 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) and very rare (<1/10,000), not known (cannot be estimated from the available data).

Systemic treatment
The likelihood of side effects may be related to age, renal function, and the patient's condition.

Neurological events have been reported in 27% of patients with cystic fibrosis. These are generally mild and resolve during or shortly after treatment.

Neurotoxicity may be associated with overdose, inability to reduce the dose in patients with renal failure, and concomitant use of neuromuscular blocking agents or other drugs with similar neurological effects. Reducing the dose may alleviate symptoms. Effects may include apnoea, transient sensory disturbances (such as facial paraesthesia and vertigo), and, rarely, vasomotor instability, slurred speech, visual disturbances, confusion, or psychosis.

Adverse effects on renal function have been reported in patients with normal renal function when doses exceed the recommended levels, in patients with renal impairment when dose reduction fails, or following concomitant use of other nephrotoxic drugs. These effects are generally reversible upon discontinuation of treatment.

Nephrotoxicity is rarely seen in cystic fibrosis patients treated within the recommended dose limits (less than 1%). In seriously ill hospitalised patients without cystic fibrosis, nephrotoxicity findings have been reported in approximately 20% of patients.
Hypersensitivity reactions such as skin redness and drug fever have been reported. If these occur, treatment should be discontinued.

Local irritation may occur at the injection site.

Immune system disorders
Not known: Hypersensitivity reactions such as skin rash and angioedema

Nervous system disorders
Very common: Neurotoxicity such as facial, oral, and perioral paraesthesia, headache, and muscle weakness
Unknown: Dizziness, ataxia

Skin and subcutaneous tissue disorders
Very common: Itching

Kidney and urinary tract disorders
Very common: Renal failure manifested by increased blood creatinine and/or urea and/or decreased creatinine renal clearance
Rare: Renal failure

General disorders and administration site conditions
Not known: Injection site reaction

Inhalation therapy
Mouth or throat pain has been reported and may be related to *Candida albicans* infection or hypersensitivity. Skin rash may also indicate hypersensitivity; if this occurs, treatment should be discontinued.

Immune system disorders
Not known: Hypersensitivity reactions such as skin rash

Respiratory, thoracic disorders, and mediastinal diseases
Very common: Cough, chest tightness, bronchoconstriction, or bronchospasm

General disorders and administration site conditions
Not known: Sore throat and mouth pain.

If hypersensitivity reactions such as skin rash occur during treatment with sodium colistimethate, the drug should be discontinued.

Inhalation administration
Coughing and bronchospasm may occur with inhalation.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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.

4.9.Overdose and Treatment
Overdose may result in neuromuscular blockade, which can lead to renal failure, muscle weakness, apnoea, dizziness, slurred speech, vasomotor instability, visual disturbances, confusion, psychosis, and possible respiratory arrest. Overdose may also cause acute renal failure, characterised by decreased urine output and increased serum BUN and creatinine concentrations.
There is no specific antidote; treatment is supportive. Measures to increase the elimination rate of colistin, e.g. mannitol diuresis, prolonged haemodialysis or peritoneal dialysis, may be attempted, but their efficacy is unknown.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties
Pharmacotherapeutic group: Antibacterials for systemic use, Polymyxins
ATC code: J01XB01

Mechanism of action
Colistin is a cyclic polypeptide antibacterial agent belonging to the polymyxin group. Polymyxin antibiotics act by damaging the cell membrane, and the resulting physiological effects are lethal to bacteria. Polymyxins are selective for Aerobic Gram-negative bacteria with a hydrophobic outer membrane.

Resistance
Resistant bacteria are characterised by the alteration of the phosphate groups of lipopolysaccharides through binding with ethanolamine or aminoarabinos. Resistant Gram-negative bacteria, such as *Proteus mirabilis* and *Burkholderia cepacia*, show complete binding to phospholipids with ethanolamine or aminoarabinos.

Cross-resistance between colistin (polymyxin E) and polymyxin B may be expected. Since the mechanism of action of polymyxins differs from that of other antibiotics, resistance to colistin

and polymyxin developed through the above mechanism alone may not necessarily develop against other drug classes.

Pharmacokinetic/Pharmacodynamic relationship

Polymyxins have been reported to have a concentration-dependent bactericidal effect on susceptible bacteria. The fAUC/MIC is thought to be related to clinical efficacy.

EUCAST Breakpoints	Susceptible (S)	Resistant (R)[a]
Acinetobacter	S ≤ 2	R > 2 mg/L
Enterobacteriaceae	S ≤ 2	R > 2 mg/L
Pseudomonas spp	S ≤ 4	R > 4 mg/L

[a]A cut-off point is applied to 2-3 MIU x 3 doses. A loading dose *(9 MIU)* may be required.

Susceptibility

The prevalence of acquired resistance may vary geographically and over time for selected species, and local information on resistance is desirable, particularly when treating severe infections. When the local prevalence of resistance is such that the use of agents is questionable for at least some types of infection, expert advice should be sought if necessary.

Commonly susceptible species
Acinetobacter baumannii *Haemophilus influenzae* *Klebsiella spp* *Pseudomonas aeruginosa*
Species that may pose an acquired **resistance problem**
Stenotrophomonas maltophilia *Achromobacter xylosoxidans (formerly Alcaligenes xylosoxidans)*
Intrinsically resistant organisms
Burkholderia cepacia and related species. *Proteus species* *Providencia species* *Serratia species*

5.2. Pharmacokinetic properties

General characteristics

Colistimethate sodium is a white or almost white, odourless, hygroscopic powder. It is highly soluble in water, slightly soluble in alcohol, and practically insoluble in acetone and ether.

Absorption

Information regarding the pharmacokinetics of colistimethate sodium and colistin is limited. There are indications that the pharmacokinetics in critically ill patients differ from those in patients with less severe physiological impairment and in healthy volunteers. The following data are based on studies using YBSK to determine colistimethate sodium/colistin plasma concentrations.

Following colistimethate sodium infusion, the inactive prodrug is converted to active colistin. Peak plasma concentrations of colistin have been shown to occur 7 hours after colistimethate sodium administration in critically ill patients.
Absorption from the gastrointestinal tract is negligible in healthy individuals.
When administered by nebulisation, variable absorption has been reported depending on aerosol particle size, nebuliser system, and lung condition. Studies in healthy volunteers and patients with various infections have reported that therapeutic concentrations of 4 mg/L or higher serum potential have been achieved. Therefore, the possibility of systemic absorption should be kept in mind when treating patients via inhalation.

Distribution
In healthy subjects, the distribution volume of colistin is low and corresponds approximately to the extracellular fluid (ECF). The distribution volume is appropriately expanded in critical illnesses. Protein binding is moderate and decreases at higher concentrations. In the absence of meningeal inflammation, penetration into cerebrospinal fluid (CSF) is minimal, but increases in the presence of meningeal inflammation.

Both colistimethate sodium and colistin exhibit clinically relevant linear pharmacokinetics within the dose range.

Elimination
In healthy subjects, approximately 30% of colistimethate sodium is converted to colistin, its clearance is dependent on creatinine clearance, and it is estimated that a larger proportion of colistimethate sodium is converted to colistin when renal function is impaired. In patients with severely impaired renal function (creatinine clearance <30 ml/min), the extent of conversion may be as high as 60% to 70%.
Colistimethate sodium is eliminated by the kidneys, primarily via glomerular filtration. In healthy subjects, 60 to 70% of colistimethate sodium is excreted unchanged in the urine within 24 hours.

The elimination of active colistin is characterised by deficiency. Colistin undergoes extensive renal tubular reabsorption and, with its potential for renal accumulation, is either cleared by non-renal means or undergoes renal metabolism. Colistin clearance decreases in renal failure, probably due to increased colistin sodium conversion.

In healthy subjects and those with cystic fibrosis, the half-life of colistin is approximately 3 hours and 4 hours, respectively, and a total clearance of approximately 3 L/hour has been reported. In critically ill patients, a prolonged half-life of approximately 9-18 hours has been reported.

Linearity/Non-linearity

There is insufficient data to determine whether colistimethate sodium is linear.

Characteristic features in patients

Renal impairment:

As a significant portion of COFIBCOL is excreted via the kidneys, dosage adjustment should be made in patients with renal impairment, and it should be used under controlled conditions with appropriate precautions.

Paediatric population:

Although similar side effects are seen in adults and the paediatric population, subjective symptoms of toxicity may not be reported in the paediatric population. Therefore, close clinical monitoring is recommended for paediatric patients.

Geriatric population:

As a significant portion of COFIBCOL is excreted by the kidneys, the risk of toxic reactions to COFIBCOL may be greater in patients with renal impairment. In addition, geriatric patients have lower renal function. Therefore, precautions should be taken in dose selection and renal function should be monitored.

5.3. Preclinical safety data

Potential genotoxicity data for sodium colistimethate are limited, and carcinogenicity data are not available. Sodium colistimethate has caused chromosomal aberrations in human lymphocytes in vitro. This effect may be related to the previously observed decrease in mitotic content.

Reproductive toxicity studies in mice and rats did not reveal teratogenic properties. However, following intramuscular administration of 4.15 and 9.3 mg/kg colistimethate sodium to rabbits during organogenesis, talipes varus occurred in 2.6% and 2.9% of foetuses, respectively. These doses are 0.5 and 1.2 times the maximum daily human dose. In addition, increased absorption occurred at the 9.3 mg/kg dose.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Solvent ampoule: Injection water

6.2. Incompatibilities

COFIBCOL solution should not be mixed with other medicines. The addition of other antibiotics such as erythromycin, tetracycline, or cefalexin sodium to COFIBCOL solution may cause precipitation.

6.3. Shelf life

Shelf life before first opening: 24 months

Shelf life after reconstitution: 7 days

6.4. Special precautions for storage
Store at room temperature below 25°C.
Our product must be used within 7 days after reconstitution, provided it is stored in a refrigerator (2°C -8°C).

6.5. Nature and contents of container
The primary packaging material for our product is a transparent, 10 mL Type I glass vial with a lyophilisation stopper. An aluminium safety ring and a blue flip-off cap are used to seal the vials. Our product is presented in a cardboard box with a cardboard separator, containing one vial of the product, one diluent ampoule containing 2 mL of water for injection, and package leaflet.

6.6. Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

INTRAVENOUS USE
Intermittent Direct Use: Half of the total daily dose is slowly injected IV every 12 hours over a period of 3-5 minutes.

Continuous Infusion: The remaining half of the total dose is slowly injected intravenously over 3-5 minutes. The remaining half of the total daily dose of COFIBCOL is added to one of the following solutions:

- 0.9% NaCl
- 0.9% NaCl in 5% dextrose
- 5% dextrose in water
- 5% dextrose in 0.45% NaCl
- 5% dextrose in 0.225% NaCl
- Lactated Ringer's solution
- 10% invert sugar solution

There is no significant information regarding the use of other drugs in combination with COFIBCOL or in combination with the infusion solutions mentioned above.

The other half of the daily total dose is administered as a slow intravenous infusion over 22-23 hours, 1-2 hours after the initial dose. In cases of renal impairment, the infusion frequency is reduced depending on the degree of renal failure.

The choice of intravenous solution and the volume used are determined by the requirements of fluid and electrolyte management.

The infusion solution containing sodium colistimethate should be freshly prepared and used within 24 hours.

For nebulisation use, it should be reconstituted with injectable water and administered immediately. It is administered via a nebuliser in physiological saline.

7. MARKETING AUTHORISATION HOLDER

Deva Holding A.S.
Halkalı Merkez Mah. Basın Ekspres Cad.
34303 No:1 Küçükçekmece-İSTANBUL/TÜRKİYE
Tel: 0212 692 92 92
Fax: 0212 697 00 24
Email: deva@devaholding.com.tr

8. MARKETING AUTHORISATION NUMBER(S)

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Date of latest renewal:

10. DATE OF REVISION OF THE TEXT