Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Colistimethate sodium 1 million IU powder for solution for injection, infusion and inhalation.

2. Qualitative and quantitative composition

Colistimethate sodium 1 million IU: Each vial contains 1 million International Units (IU) which is approximately equivalent to 80 mg of colistimethate sodium.

Excipient(s) with known effect

This medicinal product contains less than 1 mmol (23 mg) of sodium per dose and is therefore considered essentially sodium-free.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Powder for solution for injection, infusion or inhalation. White powder

4. Clinical particulars

4.1 Therapeutic indications

Intravenous route:

Colistimethate sodium is indicated in adults and children, including neonates for the treatment of serious infections due to selected aerobic Gram-negative pathogens in patients with limited treatment options (see sections 4.2, 4.4, 4.8 and 5.1).

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

Inhalation route:

Colistimethate sodium is indicated in adults and paediatric patients, for the treatment of pulmonary chronic infections caused by Pseudomonas aeruginosa in patients with cystic fibrosis (see section 5.1).

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

4.2 Posology and method of administration

Intravenous route:

The dose to be administered and the treatment duration should take into account the severity of the infection as well as the clinical response. Therapeutic guidelines should be adhered to.

The dose is expressed in international units (IU) of colistimethate sodium (CMS). A conversion table from CMS in IU to mg of CMS as well as to mg of colistin base activity (CBA) is included at the end of this section.

Posology

Adults and adolescents

Maintenance dose: 9 million IU/day in 2-3 divided doses.

In patients who are critically ill, a loading dose of 9 million IU (MIU) should be administered. The most appropriate time interval to the first maintenance dose has not been established.

Modelling suggests that loading and maintenance doses of up to 12 million IU may be required in patients with good renal function in some cases. Clinical experience with such doses is however extremely limited and safety has not been established.

The loading dose applies to patients with normal and impaired renal functions including those on renal replacement therapy.

Renal impairment

Dose adjustments in renal impairment are necessary, but pharmacokinetic data available for patients with impaired renal function is very limited.

The following dose adjustments are suggested as guidance.

Hepatic impairment

Dose adjustment is not considered necessary

Dose reductions are recommended for patients with creatinine clearance <50ml/min

Twice daily dosing is recommended

Creatinine clearance (mL/min)	**Daily dose**
< 50-30	5.5-7.5 MIU
< 30-10	4.5-5.5 MIU
<10	3.5-5.5 MIU

MIU = million IU

Haemodialysis and continuous haemo(dia)filtration

Colistin appears to be dialyzable through conventional haemodialysis and continuous venovenous haemo(dia)filtration (CVVHF, CVVHDF). There are extremely limited data from population pharmacokinetics studies from very small number of patients on renal replacement therapy. Firm dose recommendations cannot be made. The following dosage regimens could be considered.

Haemodialysis (HD)

No-HD days: 2.25 MIU/day (2.2-2.3 MIU/day). HD days: 3 MIU/day on haemodialysis days, to be given after the HD session.

Twice daily dosing is recommended.

CVVHF/ CVVHDF As in patients with normal renal function. Three times daily dosing is recommended.

Older people

No dose adjustment in older patients with normal renal function are considered necessary.

Paediatric population

The data supporting the dose regimen in paediatric patients are very limited. Renal maturity should be taken into account when selecting the dose. The dose should be based on lean body weight.

Children ≤ 40 kg

75,000-150,000 UI/kg/day divided into 3 doses. For children with a body weight above 40 kg, use of the dosing recommendation for adults should be considered.

The use of doses >150,000 IU/kg/day has been reported in children with cystic fibrosis. There are no data regarding the use or magnitude of a loading dose in critically ill children.
No dose recommendations have been established in children with impaired renal function.

Intrathecal and intraventricular administration
Based on limited data, the following dose is recommended in adults:

Intraventricular route
125,000 UI/day Intrathecally administered doses should not exceed those recommended for intraventricular use.
No specific dosing recommendation can be made in children for intrathecal or intraventricular routes of administration.

Method of administration
Colistimethate sodium is administered intravenously as slow infusion over 30-60 minutes.
Colistimethate sodium undergoes hydrolysis to the active substance colistin in aqueous solution. For dose preparation, particularly where combination of multiple vials is needed, reconstitution of the required dose must be performed using strict aseptic technique (see section 6.6).

• **Inhalation route:**
It is recommended to administer colistimethate sodium (CMS) under the supervision of physicians with appropriate experience in its use.

Posology
Dosage can be adjusted according to disease severity and clinical response.
Recommended dose interval:

Inhalation administration
Adults, adolescents and children ≥ 2 years of age 1-2 MIU two or three times a day (max. 6 MIU/day).

Children < 2 years of age 0.5-1 MIU twice a day (max. 2 MIU/day).

Relevant clinical posology guidelines should be followed, including treatment duration and frequency as well as combined administration of other antibacterial agents.

Older people
No dose adjustment is considered necessary.

Renal impairment
No dose adjustment is considered necessary; however, caution is advised in patients with renal impairment (see sections 4.4 and 5.2).

Hepatic impairment
No dose adjustment is considered necessary.

Method of administration
Inhalation route
Colistimethate sodium in aqueous solution is hydrolysed to the active substance colistin. Consult special preventive measures for the disposal and handling of reconstituted solutions in section 6.6.
If you are taking other treatments, you should take them in the order your doctor has prescribed.

Dose conversion table:
In the EU, the dose of colistimethate sodium (CMS) must be prescribed and administered only as International Units (IU). The product label states the number of IU per vial.
Confusion and medication errors have occurred due to the different expressions of the dose in terms of potency. The dose is expressed in the US, and other parts of the world, as milligrams of colistin base activity (mg CBA).
The following conversion table is prepared for information and values must be considered nominal and approximate only.

Table of CMS Conversion

Potency		≈ mass of CMS (mg)*
IU	≈ mg CBA	
12,500	0.4	1
150,000	5	12
1,000,000	34	80
4,500,000	150	360
9,000,000	300	720

Nominal potency of the drug substance = 12,500 IU/mg

4.3 Contraindications
Hypersensitivity to the active substance

4.4 Special warnings and precautions for use
Consideration should be given to co-administering intravenous colistimethate sodium with another antibacterial agent whenever this is possible, taking into account the remaining susceptibilities of the pathogen(s) under treatment. As the development of resistance to intravenous colistin has been reported, in particular when it is used as a monotherapy, the concomitant administration with other antibacterial should also be considered in order to prevent the emergence of resistance.
There are limited clinical data on the efficacy and safety of intravenous colistimethate sodium. The recommended doses in all subpopulations are equally based on limited data (clinical and pharmacokinetic/ pharmacodynamics data). In particular there are limited safety data for the use of high doses (> 6 MIU/day) and the use of a loading dose, and for special populations (patients with renal impairment and the paediatric population). Colistimethate sodium should only be used when other, more commonly prescribed antibiotics are not effective or not appropriate.

Bronchospasm

Nebulization of colistimethate sodium may cause cough or bronchospasm, so it is advisable to administer the first dose under medical supervision. Routine pre-administration of a bronchodilator is recommended, especially if it is part of the patient's current treatment regimen. FEV1 should be evaluated before and after nebulization (see section 4.2). If colistimethate sodium is found to produce bronchial hyper responsiveness in a patient not receiving bronchodilators, test should be repeated using a bronchodilator. Evidence of bronchospasm in bronchodilator therapy may indicate an allergic response; therefore, treatment with this medicine should be discontinued. Bronchospasm thus produced should be treated at medical discretion. Continue use of colistimethate sodium may lead to the development of bronchial hyper responsiveness; therefore, assessment of pre- and post-treatment FEV1 values during regular clinic visits is recommended.

Haemoptysis

Haemoptysis is complication of cystic fibrosis, and it is more common in adults. The use of this medicinal product in patients with clinically significant haemoptysis should be undertaken or continued only if benefits of treatment are considered to outweigh risks of inducing further haemorrhage.

Nephrotoxicity

Impairment of renal function has been reported, usually following use of higher than recommended intravenous or intramuscular doses in patients with normal renal function, or failure to reduce the intravenous or intramuscular dosage in patients with renal impairment or when used concomitantly with other nephrotoxic drugs (see section 4.5). The effect is usually reversible on discontinuation of therapy.

Renal function monitoring should be performed at the start of treatment and regularly during treatment in all patients. The dose of colistimethate sodium should be adjusted according to creatinine clearance (see section 4.2). Patients who are hypovolaemic or those receiving other potentially nephrotoxic drugs are at increased risk of nephrotoxicity from colistin (see sections 4.5 and 4.8). Nephrotoxicity has been reported to be associated with cumulative dose and treatment duration in some studies. The benefit of prolonged treatment duration should be balanced against the potentially increased risk of renal toxicity.

Caution is advised when administering colistimethate sodium to infants < 1 year of age as renal function is not fully matured in this age group. Further, the effect of immature renal and metabolic function on the conversion of colistimethate sodium to colistin is not known.

Although unlikely in the case of inhalation treatment, monitoring of serum concentrations is recommended, especially in patients with impaired renal function, so as to adjust dosage if necessary.

Hypersensitivity

n case of allergic reaction, treatment with colistimethate sodium must be discontinued and appropriate measures implemented.

Neurotoxicity

High serum concentrations of colistimethate sodium, which may be associated with overdosage or failure to reduce the dosage in patients with renal impairment, have been reported to lead to neurotoxic effects such as facial paresthesia, muscle weakness, vertigo, slurred speech, vasomotor instability, visual disturbances, confusion, psychosis and apnoea. Monitoring should be performed for perioral paresthesia and paresthesia in extremities, which are signs of overdose (see section 4.9).

Concomitant use with non-depolarising muscle relaxants or antibacterial with similar neurotoxic effects may also produce neurotoxicity. A reduced dose of colistimethate sodium may relieve symptoms.

Myasthenia gravis

Colistimethate sodium is known to reduce the presynaptic release of acetyl-choline at the neuromuscular junction and should be used in patients with myasthenia gravis with the greatest caution and only if clearly needed.

Intramuscular administration

Respiratory arrest has been reported following intramuscular administration of colistimethate sodium. Impaired renal function increases the possibility of apnoea and neuromuscular blockade following administration of colistimethate sodium.

Intrathecal or intraventricular administration

Intravenous colistimethate sodium does not cross the blood-brain barrier to a clinically relevant extent. The use of intrathecal or intraventricular administration of colistimethate sodium for the treatment of meningitis has not been systematically studied with clinical trials and is supported by case reports only. Data supporting posology are very limited. The most commonly observed adverse effect of CMS administration was aseptic meningitis (see section 4.8).

Porphyria

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

Clostridium difficile-associated disease

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

Microbial resistance

Colistimethate sodium acquired resistance in mucoid Pseudomonas aeruginosa during clinical use has been reported. Susceptibility testing should be performed on patients who are treated on a long-term basis, at regular clinic visits, and whenever a patient experiences an exacerbation (see section 5.1).

In the event of physiotherapy or other inhalation treatments, this medicinal product should be administered after such treatments are completed, see section 4.2.

Few cases of pseudo-Bartter syndrome have been reported in children and adults with the intravenous use of colistimethate sodium. Monitoring of serum electrolytes should be started in suspected cases and appropriate management should be implemented, however, normalisation of electrolyte imbalance might not be achieved without discontinuation of colistimethate sodium.

This medicinal product contains less than 1 mmol sodium (23 mg) per vial and is therefore considered to be essentially sodium-free.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of intravenous colistimethate sodium with other medications that are potentially nephrotoxic or neurotoxic should be undertaken with great caution.
Caution should be taken with concomitant use with other formulations of colistimethate sodium as there is little experience and there is a possibility of summative toxicity.

No in vivo interaction studies have been performed. The mechanism of conversion of colistimethate sodium to the active substance, colistin, is not characterised. The mechanism of colistin clearance, including renal handling, is equally unknown. Colistimethate sodium or colistin did not induce the activity of any P 450 (CYP) enzyme tested (CYP1A2, 2B6, 2C8, 2C9, 2C19 and 3A4/5) in in vitro studies in human hepatocytes.

The potential for drug-drug interactions should be borne in mind when Colistimethate sodium is co-administered with drugs known to inhibit or induce drug metabolising enzymes or drugs known to be substrates for renal carrier mechanisms.

Due to the effects of colistin on the release of acetylcholine, non-depolarising muscle relaxants should be used with caution in patients receiving colistimethate sodium as their effects could be prolonged (see section 4.4).
Co-treatment with colistimethate sodium and macrolides such as azithromycin and clarithromycin, or fluoroquinolones such as norfloxacin and ciprofloxacin should be undertaken with caution in patients with myasthenia gravis (see section 4.4).

Concomitant use of colistimethate sodium with other medicinal products of neurotoxic and/or nephrotoxic potential should be avoided. These include the aminoglycoside antibiotics such as gentamicin, amikacin, netilmicin and tobramycin. There may be an increased risk of nephrotoxicity if given concomitantly with cephalosporin antibiotics.

4.6 Pregnancy and Lactation

Fertility
There are no data on the effects of colistimethate sodium on human fertility. Animal studies do not indicate effects with respect to fertility (see section 5.3).
Pregnancy
Safety in human pregnancy has not been established. Animal studies are insufficient with respect to effects on reproduction and development (see section 5.3). Single dose studies in human pregnancy show that colistimethate sodium crosses the placental barrier and there may be a risk of foetal toxicity if repeated doses are given to pregnant patients.

Hence, Colistimethate sodium should only be given during pregnancy if the benefits outweigh any potential risk.

Breast-feeding

Colistimethate sodium is excreted in breast milk. Colistimethate sodium should be administered to breastfeeding women only when clearly needed.

4.7 Effects on ability to drive and use machines

Neurotoxicity, characterised by dizziness, confusion or visual disturbances have been reported following parenteral administration of colistimethate sodium.

If these effects occur patients should be warned against driving or operating machinery

4.8 Undesirable effects

Adverse reactions are included in the table below according to MedDRA System Organ and Frequency Classification. Frequencies are defined as Very common (≥ 1/10): common (≥ 1/100 to <1/10): uncommon (≥ 1/1,000 to <1/100): rare (≥ 1/10,000 to <1/1,000) and very rare (<1/10,000), not known (cannot be estimated from the available data)

The most commonly reported adverse reactions following intravenous administration are impaired renal function, and more rarely renal failure, usually following the use of higher than recommended doses in patients with normal renal function, or failure by reducing the dose in patients with impaired renal function or when used concomitantly with other nephrotoxic antibacterials. The effect is usually reversible when treatment is discontinued, and intervention is rarely required (dialysis).

Elevated serum concentrations of colistimethate sodium, which can be associated with overdose or failure to reduce dosage in patients with renal impairment, can produce neurotoxic effects such as facial paresthesia, muscle weakness, vertigo, poorly articulated speech, vasomotor instability, visual disturbances, confusion, psychosis and apnea. Concomitant use with other non-depolarising muscle relaxants or antibacterials with similar neurotoxic effects may also produce neurotoxicity. Reducing the dose of colistimethate sodium can relieve the symptoms.

Hypersensitivity reactions such as rash and angioedema are known to occur. In the event of these reactions, treatment with colistimethate sodium should be discontinued.

MedDRA System Organ Classification	Frequency	Reported adverse reactions
Immune system disorders	Not known	Hypersensitivity reactions such as rash and angioedema
Metabolism and nutrition disorders	Not known	Pseudo-Bartter syndrome (see section 4.4)
Nervous system disorders	Very common	Neurotoxicity as facial, buccal or peri-oral paraesthesia, headache, and muscle weakness
	Not known	Dizziness Ataxia
Skin and subcutaneous tissue disorders	Very common	Pruritus
Renal and urinary disorders	Very common	Renal impairment demonstrated by increased creatinine in blood and / or urea and / or decreased renal clearance of creatinine
	Rare	Kidney failure
General disorders and administration site conditions	Not known	Reaction in the injection site

The most common adverse reactions following colistimethate sodium nebulization are cough and bronchospasm (chest tightness detectable by decrease in FEV1) approximately in 10% patients (see section 4.4)

MedDRA System Organ Classification.	Frequency	Reported adverse reaction
Immune system disorders	Not known	Hypersensitivity reactions such as skin rashes
Respiratory, thoracic and mediastinal disorders	Very common	Coughing, chest tightness, bronchoconstriction or bronchospasm

General disorders and administration site conditions	Not known	Sore throat and mouth irritation

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

Overdose may lead to apnoea, muscle weakness and renal impairment. No antidote is available.

Management of overdose is by means of supportive treatment and measures designed to increase clearance of colistimethate sodium such as inducing an osmotic diuresis with mannitol, peritoneal dialysis or prolonged haemodialysis.

8. Pharmacological properties

8.1 Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemic use, other antibacterials, polymyxins
ATC Code: J01XB01

Mechanism of action

Colistin is a cyclic polypeptide antibacterial agent belonging to the polymyxin group. Polymyxins work by damaging cell membrane and the resulting physiological effects are lethal to the bacterium. Polymyxins are selective for aerobic Gram-negative bacteria that have a hydrophobic outer membrane.

Resistance

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

Cross-resistance

Cross-resistance between colistin (polymyxin E) and polymyxin B can be expected. Since polymyxins' the mechanism of action is different from that of other antibacterial agents, resistance to colistin and polymyxin by the above mechanism alone would not be expected to result in resistance to other drugs classes.

PK/PD relationship

Polymyxins have been reported to show a concentration-dependent bactericidal effect on susceptible bacteria. The fAUC/ MIC ratio is considered to be correlated with clinical efficacy.

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

Haemophilus influenzae

Klebsiella species

Pseudomonas aeruginosa

Species for which acquired resistance may be a problem

Stenotrophomonas maltophilia

*Achromobacter xylosoxidans (*formerly *Alcaligenes xylosoxidans)*

Inherently resistant organisms

Burkholderia cepacia and related species

Proteus spp

Providencia spp

Serratia spp

Cross resistance

The resistance to polymyxins is not crossed with other antibiotic families

11.1 Pharmacokinetic properties

Absorption

Indications that the pharmacokinetics in critically ill patients differ from those in patients with less severe physiological derangement and from those in healthy volunteers. The following data are based on studies using HPLC to determine CMS and colistin plasma concentrations. After infusion of colistimethate sodium the inactive pro-drug is converted to the active colistin. Peak plasma concentrations of colistin have been shown to occur with a delay of up to 7 hours after administration of colistimethate sodium in critically ill patients.

Distribution

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

Both CMS and colistin display linear PK in the clinically relevant dose range.

Elimination

No information is available upon elimination of colistimethate sodium after nebulization. It is estimated that approximately 30% of colistimethate sodium is converted to colistin in healthy subjects, its clearance is dependent on creatinine clearance and as renal function decreases, a greater portion of CMS is converted to colistin. In patients with very poor renal function (creatinine clearance <30ml/min) the extent of conversion could be as high as 60% to 70%. CMS is eliminated predominantly by the kidneys via glomerular filtration. In healthy subjects, 60% to 70% of CMS is excreted unchanged in the urine within 24 hours.

The elimination of active colistin is incompletely characterised. Colistin undergoes extensive renal tubular reabsorption and may either be cleared non-renally or undergo renal metabolism with the potential for renal accumulation. Colistin clearance is decreased in renal impairment, possibly due to increased conversion of CMS.

Half-life of colistin in healthy subjects and those with cystic fibrosis is reported to be around 3 h and 4 h, respectively, with a total clearance of about 3 L/h. In critically ill patients, half-life has been reported to be prolonged to around 9 h to 18 h.

Kinetics of colistimethate sodium appears to be similar in all age groups, provided kidney function is normal.

14.1 Preclinical safety data

No mutagenicity or carcinogenicity studies have been performed.

No adverse effects on fertility or reproduction were observed in rats with 9.3 mg/kg/day doses (0.30 times the maximum daily human dose expressed as mg/mm2). However, animal studies are insufficient to evaluate the effects on reproduction.

Colistimethate sodium given intramuscularly during organogenesis to rabbits at doses of 4.15 and 9.3 mg/kg resulted in talipes varus in 2.6% and 2.9% of foetuses respectively. These doses are 0.25- and 0.55 times the maximum daily human dose expressed as mg/mm2. In addition, increased reabsorption occurred at 9.3 mg/kg. Colistimethate sodium was not teratogenic in rats at 4.15 or 9.3 mg/kg. These doses are 0.13- and 0.30 times the maximum daily human dose expressed as mg/mm2.

18. Pharmaceutical Particulars

18.1 List of Excipients

None

18.2 Incompatibilities

Mixing solutions containing colistimethate sodium with other infusions, solutions for injection or solutions for nebulization should be avoided. The addition of other antibiotics such as erythromycin, tetracycline or cephalothin to solutions of colistimethate sodium may lead to precipitation

18.3 Shelf-Life

Colistimethate sodium 1 MIU: 3 years.

Hydrolysis of colistimethate increases significantly after reconstitution and dilution below its critical micellar concentration of 80,000 IU per ml. Solutions below this concentration should be used immediately.

Reconstituted solutions for nebulisation, with a concentration of ≥ 80,000 IU/ml, are chemically and physically stable in the original vial for 24 h at 2°C - 8°C.

From the microbiological point of view, unless the method of opening / reconstitution / dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Solutions for injection which have been diluted beyond the original volume of the vial and/or with a concentration < 80,000 IU/ml should be used immediately.

The administered volume of solution for intrathecal or intraventricular administration should not exceed 1 ml (reconstituted concentration of 125,000 IU/ml). The reconstituted solution should be administered immediately.

18.4 Special Precautions for storage

Colistimethate sodium 1 MIU: Store below 30oC.

For storage conditions after reconstitution / dilution of the medicinal product, see section 6.3.

18.5 Nature and Content of container

It is presented in packs containing 10 vials of type I glass vials with bromobutyl stopper and flip-off aluminium cap.

18.6 Special precautions for disposal and other handling

***For bolus injection*:**

Reconstitute the contents of the vial with not more than 10 ml water for injections or 0.9% sodium chloride.

The maximum dose that can be administered as an intravenous injection is 2 MIU, diluted in 10 ml administered within a minimum of 5 minutes.

For infusion:

The contents of the reconstituted vial may be diluted, usually with 50 ml of 9 mg/ml sodium chloride and be administered in 30 minutes approximately.

The solution after reconstitution should be a clear solution free of particulate matter. If particles are observed in suspension the solution should be discarded.

For inhalation by nebulizer

This medicinal product may be administered by inhalation using a suitable nebulizer.

Reconstitute vial content either with water for injections to produce a hypotonic solution or with a 50:50 mixture of water for injections and 0.9% sodium chloride to produce an isotonic solution or with 0.9% sodium chloride to produce a hypertonic solution.

Reconstitution volume will depend on the instructions for use of the nebulizer device; normally, it does not exceed 4 ml.

Conventional nebulizers operate on a continuous flow basis; therefore, probably part of nebulized medication is released into the environment. When used with conventional nebulizer, colistimethate sodium Altan Pharma should be administered in a well-ventilated room, especially in hospitals where several patients may be using nebulizers at the same time. Tubes or filters must be used so as to prevent release of discarded aerosol into the environment.

For intrathecal and intraventricular route

The volume administered should not exceed 1 ml (reconstituted concentration 125,000 IU/ml). The reconstituted product should be administered immediately.

During reconstitution shake gently to avoid the appearance of foam. The solution is for single use only. Discard any unused solution. Waste must be disposed of in accordance with local regulations.

19. Marketing Authorization Holder

Martindale Pharma

20. Marketing Authorization Number

CTD10431/22238

21. Date of first authorization/renewal of the authorization

30/07/2024

22. Date of revision of the text

13/05/2025