Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Colistimethate sodium, 1 million International Units (IU), powder for solution for injection or infusion

2. Qualitative and quantitative composition

Each vial contains 1 million International Units (IU) which is approximately equivalent to 80 mg of colistimethate sodium.
Excipients with known effect: None
For the full list of excipients, see section 6.1

3. Pharmaceutical form

Powder for solution for injection or infusion
The powder is white to off white

4. Clinical particulars

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

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

The following dose recommendations are made based on limited population-pharmacokinetic data in critically ill patients (see also section 4.4):

Adults and adolescents

Maintenance dose 9 MIU/day in 2- 3 divided doses.

In patients who are critically ill, a loading dose of 9 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 MIU may be required in patients with good renal function in some cases. Clinical experience with such doses is however extremely limited, and 1 safety has not been established.

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

Older people

Dose adjustment is not considered necessary.

Renal impairment

Dose adjustment is not considered necessary; however, caution is advised in patients with renal impairment (see sections 4.4 and 5.2).

Hepatic impairment

Dose adjustment is not considered necessary

Method of administration

Colistimethate sodium is administered intravenously as a slow infusion over 30 – 60 minutes. Patients with a totally implantable venous access device (TIVAD) in place may tolerate a bolus injection of up to 2 million units in 10ml given over a minimum of 5 minutes (see section 6.6). 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) **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 because of the different expressions of 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 the values must be considered nominal and approximate only.

CMS conversion table

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 colistimethate sodium or other polymyxins.

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, co- 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 (> 6MIU/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.

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 mature in this age group. Further, the effect of immature renal and metabolic function on the conversion of colistimethate sodium to colistin is not known.

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

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 paraesthesia, muscle weakness, vertigo, slurred speech, vasomotor instability, visual disturbances, confusion, psychosis and apnoea. Monitoring should be performed for perioral paraesthesia and paraesthesia in the extremities, which are signs of overdose (see section 4.9).

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

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

Antibiotic-associated colitis and pseudomembranous colitis have been reported with nearly all anti-bacterial 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.

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 in the treatment of meningitis was not systematically investigated in clinical trials and is supported by case reports only. Data supporting the posology are very limited. The most commonly observed adverse effect of CMS administration was 4 aseptic meningitis (see section 4.8).

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, nondepolarising 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

The commonest undesirable effects following nebulisation of colistimethate sodium are coughing and bronchospasm (indicated by chest tightness which may be detected by a decrease in FEV_1) in approximately 10% of patients. (See also Section 4.4)

Adverse reactions are tabulated below by system organ class and frequency. 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)

Body System	Frequency	Reported adverse reaction
Immune system disorders	Not known	Hypersensitivity reactions such as skin rash
Respiratory, thoracic and mediastinal disorders	Very common	Cough, chest tightness, bronchoconstriction or bronchospasm
General disorders and administration site conditions	Not known	Sore throat and sore mouth.

Should hypersensitivity reactions such as skin rash occur treatment with colistimethate sodium should be withdrawn.

Cases of sore throat or sore mouth may be due to hypersensitivity or superinfection with *Candida* species

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 can result in neuromuscular blockade that can lead to muscular weakness, apnoea and possible respiratory arrest. Overdose can also cause renal insufficiency or acute renal failure characterised by decreased urine output and increased serum concentration of BUN and creatinine. Overdose may cause vertigo, slurred speech, vasomotor instability, visual disturbances, confusion and psychosis.

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, but the effectiveness in unknown.

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 the cell membrane and the resulting physiological effects are lethal to the bacterium.

Polymyxins are selective for aerobe Gram-negative bacteria that have a hydrophobic outer membrane.

Resistance

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

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

PK/PD relationship Polymyxins have been reported to have a concentration-dependent bactericidal effect on susceptible bacteria. fAUC/ MIC 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

The information on the pharmacokinetics of colistimethate sodium (CMS) and colistin is limited. There are indications that 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/ 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.

Absorption from the gastrointestinal tract does not occur to any appreciable extent in the normal individual.

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

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 the 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 3h and 4h, respectively, with a total clearance of

around 3L/h. In critically ill patients, half-life has been reported to be prolonged to around 9-18h

14.1 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 a potential for teratogenicity. However, in the rabbit, colistimethate sodium given intramuscularly during organogenesis 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 occurred at 9.3 mg/kg. No effects were seen on mouse or rat fertility at intravenous doses of up to 25 mg/kg/day.

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

18. Pharmaceutical Particulars

18.1 List of Excipients

None

18.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

18.3 Shelf-Life

Unopened:

2 years

After reconstitution

Hydrolysis of colistimethate is significantly increased when reconstituted and diluted below its critical micelle concentration of about 80,000 IU per ml. Solutions below this concentration should be used immediately.

For solutions for bolus injection, the chemical and physical in-use stability of reconstituted solution in the original vial, with a concentration ≥ 80,000 IU/mL, has been demonstrated for 24 hours at 2 to 8°C.

From a 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 user.

For solutions for infusion, which have been diluted beyond the original vial volume and / or with a concentration < 80,000 IU/mL, should be used immediately. For the intrathecal and intraventricular routes of administration, the reconstituted product should be used immediately.

18.4 Special Precautions for storage

This medicinal product does not require any special storage conditions. For storage conditions after reconstitution/dilution of the medical product see section 6.3.

18.5 Nature and Content of container

The product is supplied in clear type I glass vials, 10 ml, sealed with a siliconised chlorobutyl type I rubber stopper and protected by a 20 mm aluminium tear-off cap incorporating a red flip-up central plastic top. The product is supplied in pack sizes of 10 vials.

18.6 Special precautions for disposal and other handling

For single use only and any remaining solution should be discarded. For bolus injection, Colistimethate sodium must be reconstituted, under aseptic conditions, with not more than 10 ml of sodium chloride solution 9 mg/ml (0.9%) or water for injection, to produce a clear colourless to pale yellow solution. During reconstitution swirl gently to avoid frothing. If used for infusion, following reconstitution, the solution should be diluted to a suitable volume for infusion over 30 minutes with sodium chloride solution 9 mg/ml (0.9%) for infusion (usually 50 ml of 0.9% sodium chloride). The solution should be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.

For the intrathecal and intraventricular routes of administration, the volume administered should not exceed 1 ml (reconstituted concentration 125,000 IU/ml). The reconstituted product should be used immediately.

Solutions should be used immediately after reconstitution (see section 4.2). For information related to stability of the reconstituted product see section 6.3.

Discard any unused solution. Waste material should be disposed of in accordance with local requirements.

19. Marketing Authorization Holder

Pharaon Healthcare Africa FZ-LLC

20. Marketing Authorization Number

CTD11176/23898

21. Date of first authorization/renewal of the authorization

15/09/2024

22. Date of revision of the text

13/05/2025