Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Colistimethate sodium 2 million IU Powder for solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 2 million IU colistimethate sodium.

3 PHARMACEUTICAL FORM

Powder for solution for injection/infusion.

White to off white powder.
pH of 1 vial Colistimethate sodium 2 million IU powder in 10 ml: 6.5 - 8.5

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

Posology

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.

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

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 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.

Special populations

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

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.

Dose reductions are recommended for patients with creatinine clearance < 50 ml/min:
Twice daily dosing is recommended.

Creatinine clearance(ml/min)	**Daily dose**
< 50-30	5.5 - 7.5 million IU
< 30-10	4.5 - 5.5 million IU
< 10	3.5 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 PK studies from very small numbers of patients on renal replacement therapy. Firm dose recommendations cannot be made. The following regimes could be considered.

Haemodialysis
No-HD days: 2.25 million IU/day (2.2-2.3 million IU/day).
HD days: 3 million IU/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.

Hepatic impairment
There are no data in patients with hepatic impairment. Caution is advised when administering colistimethate sodium in these patients.

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

Children ≤ 40kg
75,000-150,000 IU/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 intracerebroventricular administration
Based on limited data, the following dose is recommended in adults:

Intracerebroventricular route
125,000 IU/day

Intrathecally administered doses should not exceed those recommended for intracerebroventricular use.

No specific dosing recommendation can be made in children for intrathecal and intracerebroventricular routes of administration.

Method of administration

Intravenous, intrathecal or intracerebroventricular use.
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 10 ml 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.

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

Dose conversion table:
In the EU, the dose of colistimethate sodium (CMS) must be prescribed and administered only as 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 active substance = 12,500 IU/mg

4.3 Contraindications

Hypersensitivity to colistimethate sodium, colistin or to 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 (> 6 million IU/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.

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.

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 medicinal products 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 *Clostridioides 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 intracerebroventricular 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 aseptic meningitis (see section 4.8).

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say 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 is co-administered with medicinal products known to inhibit or induce drug metabolising enzymes or medicinal products 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 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of colistimethate sodium in pregnant women. 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. Animal studies are insufficient with respect to the effect of colistimethate sodium on reproduction and development *(see section 5.3, Preclinical safety data)*. Colistimethate sodium should be used in pregnancy only if the benefit to the mother outweighs the potential risk to the foetus.

Breastfeeding
Colistimethate sodium is secreted in human milk, hence, breastfeeding is not recommended.

Fertility
Data on the possible impact of colistimethate sodium on human fertility are not available.

4.7 Effects on ability to drive and use machines

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

In cystic fibrosis patients neurological events have been reported in up to 27% of patients. These are generally mild and resolve during or shortly after treatment.

Neurotoxicity may be associated with overdose, failure to reduce the dose in patients with renal insufficiency and concomitant use of either curariform agents or other medicinal products 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.

Pseudo-Bartter syndrome has been reported after intravenous administration of colistimethate sodium with unknown frequency (see section 4.4).

Adverse effects on renal function have been reported, usually following use of higher than recommended doses in patients with normal renal function, or failure to reduce the dosage in patients with renal impairment or during concomitant use of other nephrotoxic medicinal products. The effects are usually reversible on discontinuation of therapy.

In cystic fibrosis patients treated within the recommended dosage limits, nephrotoxicity appears to be rare (less than 1%). In seriously ill hospitalised non-CF patients, signs of nephrotoxicity have been reported in approximately 20% of patients.

Hypersensitivity reactions including skin rash and drug fever have been reported. If these occur treatment should be withdrawn.

Local irritation at the site of injection may occur.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

Overdose can result in neuromuscular blockade that can lead to muscular weakness, apnoea and possible respiratory arrest. Overdose can also cause acute renal failure characterised by decreased urine output and increased serum concentrations of BUN and creatinine.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemic use, other antibacterials, 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 aerobic 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 medicinal product 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.

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

[a] Breakpoints apply to dosage of 4.5 million IU x 2. A loading dose (9 million IU) may be needed.
[b] Colistin MIC determination should be performed with broth microdilution. Quality control must be performed with both a susceptible QC strain (*E. coli* ATCC 25922 or *P. aeruginosa* ATCC 27853) and the colistin resistant *E. coli* NCTC 13846 (*mcr-1* positive)

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 baumannii
Haemophilus influenzae
Pseudomonas aeruginosa
Klebsiella spp.
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 species
Providencia species
Serratia species

5.2 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 <30 ml/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.

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 mg/kg 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.

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

Mixed infusions and injections solutions involving colistimethate sodium should be avoided.

6.3 Shelf life

3 years.

Reconstituted / diluted solution:
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:

- 2 million IU for 3 hours at 2-8°C when dissolved in 10 ml of sodium chloride 9 mg/ml (0.9 %) solution for injection or water for injection.

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

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 solutions for intrathecal and intracerebroventricular administration, the reconstituted medicinal product should be used immediately.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

For 2 million IU: Clear type I glass vials with capacity >10 ml closed with type I bromobutyl rubber stoppers 20mm and sealed with 20mm orange pull-off plastic caps and aluminum discs.

Pack sizes: 1, 10 and 30 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for preparation of the solution for injection / infusion

For bolus injection:
Reconstitute the contents of the vial with not more than 10 ml water for injection or sodium chloride 9 mg/ml (0.9 %) solution for injection.

For infusion:
The contents of the reconstituted vial may be diluted, usually with 50 ml sodium chloride 9 mg/ml (0.9 %) solution for injection.

When the intrathecal and intracerebroventricular routes of administration are used, the volume administered should not exceed 1 ml (reconstituted concentration 125,000 IU/ml).

After reconstitution, the solution is clear and colorless or not more intensively colored than Y6 solution free from visible particles.

Solutions are for single use only and any remaining solution should be discarded.

The medicinal product is to be visually inspected prior to use (also after dilution). Only clear solutions practically free from particles should be used.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA1122/031/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9th June 2023

10 DATE OF REVISION OF THE TEXT

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