Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Colistimethate sodium 2 million IU Powder for nebuliser solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 2 million IU colistimethate sodium.

3 PHARMACEUTICAL FORM

Powder for nebuliser solution.

White to off-white powder.

pH of 1 vial Colistimethate sodium 2 million IU powder in 4 ml: 6.5 - 8.5

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Colistimethate sodium by inhalation is indicated for the management of adult and paediatric chronic pulmonary infections due to *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

It is recommended that colistimethate sodium (CMS) should be administered under the supervision of physicians with appropriate experience in its use.

Posology
The dosage can be adjusted depending on the severity of the condition and clinical response.

Recommended dose range:

Administration via inhalation

Adults, adolescents and children ≥ 2 years
1-2 million IU two to three times per day (max 6 million IU/day)

Children < 2 years
0.5-1 million IU twice daily (max 2 million IU/ day)

Relevant clinical guidance on treatment regimens, including duration of treatment, periodicity and co-administration of other antibacterial agents should be adhered to.

Special populations

Elderly
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

For inhalation use.

Suitable nebulisers are the reusable jet nebulisers including the PARI LC PLUS or the PARI LC SPRINT, which are used with a suitable compressor (PARI TurboBOY SX), or the membrane nebuliser namely eFlow rapid.
Both types of compressors are on/off switch and user friendly.

Colistimethate sodium 2 million IU is intended for administration by nebulisation using a suitable nebuliser as mentioned above.

Drug delivery characteristics from *in vitro* studies with the different nebuliser systems are detailed in the table below:

	Nebuliser System		
Parameter	*PARI LC Sprint*	*PARI LC plus*	eFlow rapid
Total Drug Delivered from Nebuliser mouthpiece (million IU)	1.256	1.319	1.207
Drug delivery rate (million IU/minute)	0.119	0.124	0.183
Fine Particle Fraction (% <5 µm)	65.3	53.7	50.0
Droplet Size Distribution.Mass Median Aerodynamic Diameter (MMAD) (µm)	3.7	4.4	4.8
Geometric Standard Deviation (GSD)	2.4	2.1	1.8
Measured using Colistimethate sodium 2 million IU reconstituted with 4 ml of 0.9% sodium chloride solution			

Colistimethate sodium is very soluble in the reconstitution medium. The recommended technique for dissolving the medicinal product is the addition of 4 ml isotonic sodium chloride solution (0.9% w/w), to the vial containing Colistimethate sodium 2 million IU by gentle shaking.

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

Due to potential foaming, vigorous shaking should be avoided. The resulting solution for nebulisation should be clear and carefully transferred into the medication reservoir of the nebuliser.

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

The nebuliser must be kept according to the instructions of the corresponding nebuliser during operation.

The patient should sit in an upright position and breathing normally during inhalation. Inhalation should be performed without any interruption to normal breathing.

The nebuliser must be cleaned and disinfected after use as described in the 'instruction of use' of the corresponding nebuliser.

Colistimethate sodium undergoes hydrolysis to the active substance colistin in aqueous solution. For special precautions for disposal and handling of reconstituted solutions, see section 6.6.

If other treatments are being taken, they should be taken in the order recommended by the physician.

Drug conversion
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

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.

Bronchospasm may occur on inhalation of antibiotics. This may be prevented or treated with appropriate use of beta$_2$-agonists. If troublesome, treatment should be withdrawn.

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

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 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

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

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.

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

Inhalation may induce coughing or bronchospasm.

Sore throat or mouth has been reported and may be due to *Candida albicans* infection or hypersensitivity. Skin rash may also indicate hypersensitivity, if this occurs treatment should be withdrawn.

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]
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)*.

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.

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

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

Distribution
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
The elimination of colistimethate sodium following nebulisation has not been studied.

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 foetuses 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 nebuliser solutions involving colistimethate sodium should be avoided.

6.3 Shelf life

3 years.

Reconstituted 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.

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 4 ml of sodium chloride (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.

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 20 mm and sealed with 20 mm mm aluminum cap (orange pull-off or lilac tear-off).

Pack sizes of 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 nebulizer solution
The content of the vial should be reconstituted with either water for injections or with sodium chloride 9 mg/mL (0.9 %) solution for injection.

Colistimethate sodium is very soluble in the reconstitution medium. The recommended technique for dissolving the medicinal product is the addition of 4 ml isotonic sodium chloride solution (0.9% w/w), to the vial containing Colistimethate sodium 2 million IU by gentle shaking.
The output from the nebuliser may be vented to the open air or a filter may be fitted. Nebulisation should take place in a well ventilated room.

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.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA1122/030/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

July 2023