For the use of registered medical practitioner or a hospital or a laboratory only.

AMERICAN
COLISTICAN

Colistimethate Sodium For Injection IP 1 Million IU 2 Million IU / 3 Million IU and 4.5 Million IU

1. Name of the medicinal product
Colistimethate Sodium for Injection IP 1 Million IU, 2 Million IU, 3 Million IU and 4.5 Million IU.

2.Qualitative and quantitative composition
Composition: Each Vial contains:
Colistimethate Sodium IP 10,00,000 IU / 20,00,000 IU / 30,00,000 IU and 45,00,000 IU
(As Sterile Lyophilized Powder) (IU: International Units)

3. Pharmaceutical form
Powder for Injection

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 section 4.4):

Adults and adolescents
Maintenance dose 9MIU/day in 2-3 divided doses. In patients who are critically ill, a loading dose of 9 MIU should be administered.
Loading and maintenance doses of up to 12 MIU may be required in patients with good renal function in some cases, however clinical data is 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, Dose reductions are recommended for patients with creatinine clearance <50 ml/min: Twice daily dosing is recommended. Patients with creatinine clearance <50 – 30 ml/min, <30 – 10 ml/min and <10 ml/min are advised daily dose of 5.5 – 7.5 MIU, 4.5 – 5.5 MIU and 3.5 MIU respectively, (MIU = million IU).
Haemodialysis (HD) and continuous hemo (dia) filtration (CHDF): Colistin appears to be dialyzable through conventional haemodialysis and Continuous Veno-Venous Hemofiltration (CVVHF), Continuous Veno-Venous Hemodiafiltration (CVVHDF). The recommended regimen is for No-HD days: 2.25 MIU/day (2.2-2.3 MIU/day) and HD days: 3 MIU/day on haemodialysis days, to be given after the HD session. Twice daily dosing is recommended.
For patients undergoing CVVHF/CVVHDF, 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.
Older people No dose adjustments 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 consideration when selecting the dose. The dose should be based on lean body weight. For children weighing ≤ 40kg, 75,000-150,000 IU/kg/day divided into 3 doses and for those 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 and in children with impaired renal function.
Intrathecal and intraventricular administration Based on limited data, the following dose is recommended in adults: For Intraventricular route, 125,000 IU/day and Intrathecally administered doses should not exceed those recommended for intraventricular use. No specific dosing recommendation can be made in children for intrathecal and intraventricular routes of administration.

Method of administration
Colistimethate Sodium is administered intravenously as a 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).

Dose conversion table
The following conversion table is prepared for information and the values must be considered nominal and approximate only.

CMS conversion table

Potency IU	≈ mg CBA	≈ mass of CMS (mg)*
12.5000	0.4	1
150.000	5	12
1.000.000	34	80
4.5000.000	150	360
9.000.000	300	720

* Nominal potency of the drug substance = 12.500 IU/mg

4.3 Contraindications
Hypersensitivity to Colistimethate sodium (also known as colistin) or to polymyxin B.

4.4 Special warnings and precautions for use
There is limited safety data for the use of high doses (> 6MIU/day) and the use of a loading dose, and for special populations, especially patients with renal impairment and the paediatric population.
4.4.1 Development of resistance: 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.
4.4.2 Renal Function impairment: Colistimethate sodium should only be used when other, more commonly prescribed antibiotics are not effective or not appropriate. Kindly refer to the dosage recommendation as per creatinine clearance for patients with renal function impairment. Renal function monitoring should be performed at the start of treatment and regularly during treatment in all patients. 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.
4.4.3: Pediatrics: 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.
4.4.4 Patients with 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.
4.4.5 Respiratory arrest has been reported following intramuscular administration of colistimethate sodium and should be specially considered in patients with impaired renal function neuromuscular blockade following administration of colistimethate sodium.
4.4.6 Porphyria
4.4.7 Antibiotic-associated colitis and pseudomembranous colitis
4.4.8 Development of aseptic meningitis following intraventricular administration of colistimethate sodium.

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. Included are the aminoglycoside antibiotics such as amikacin, gentamycin, netilimicin and tobramycin. Concomitant use with cephalosporin antibiotics may increase risk of nephrotoxicity.
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.
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. 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).

4.6 Pregnancy and lactation
There are no adequate data from the use of Colistimethate sodium in pregnant women. Animal studies in rats and mice do not indicate teratogenic properties. However, single dose studies in human pregnancy show that Colistimethate crosses the placental barrier and there may be a risk of foetal toxicity if repeated doses are given to pregnant patients.
Colistimethate should be used in pregnancy only if the benefit to the mother outweighs the potential risk to the foetus.
Colistimethate is secreted in breast milk, and should be administered to breastfeeding women only when clearly needed.

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, condition of the patient; co administered medication with nephrotoxicity and neurotoxicity and associated comorbid conditions such as myasthenia gravis and cystic fibrosis.
Dose related neurotoxicity and in cases of overdosing (refer to section 4.9)
Hypersensitivity reactions including skin rash have been reported. If these occur treatment should be withdrawn.
Local irritation at the site of injection may occur.

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 and measures to increase the rate of elimination of colistimethate e.g. mannitol diuresis, prolonged haemodialysis or peritoneal dialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties
5.1.1 *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.
5.1.2 *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.
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.
Commonly susceptible species include *Acinetobacter baumannii, Haemophilus influenzae, Klebsiella* spp, and *Pseudomonas aeruginosa*
Species for which acquired resistance may be a problem include *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans (*formerly *Alcaligenes xylosoxidans)*
Inherently resistant organisms include *Burkholderia cepacia* and related species, *Proteus* spp, *Providencia* spp, *Serratia* spp

5.2 Pharmacokinetic properties
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. 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
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. However, colistimethate sodium given intramuscularly during organogenesis to rabbits at 4.15 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 reabsorption occurred at 9.3mg/kg.

6. Pharmaceutical particulars

6.1 List of excipients
No excipients has been used in manufacturing of Colistimethate sodium for Injection IP.

6.2 Incompatibilitie
Colistimethate sodium for Injection IP is found visually compatible with single concentrations of 9 other antimicrobial products during the simulated Y-site injection at 26°C without ligh protection for at least 1 hour.

6.3 Shelf life
Not exceeding 24 months from the date of Manufacture.
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. 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.

6.4 Special precautions for storage
Do not store above 25°C. Store the vial in the outer carton in order to protect from light and moisture. Do not freeze. Reconstituted Colistimethate sodium solution may be kept for up to 8 hours when not stored above 25°C or for up to 24 hours stored in a refrigerator.

6.5 Nature and contents of container
Colistimethate Sodium for Injection IP 1 Million IU, 2 Million IU, 3 Million IU and 4.5 Million IU in Glass Vial.

6.6 Special precautions for disposal and other handling
For bolus injection: Reconstitute the contents of the vial with not more than 7ml water for injection or 0.9% Sodium Chloride Intravenous Infusion IP.
For infusion: The contents of the reconstituted vial may be diluted, usually with 50ml 0.9% Sodium Chloride Intravenous Infusion IP. During reconstitution swirl gently to avoid frothing. The reconstituted Colistimethate sodium is a clear solution.
The outer surface of the primary container is non-sterile. For single use only. Any unused solution should be disposed of in accordance with local requirements.
Does not contain preservatives.

Shelf Life: 24 Months

Presentation : 1 Glass vial in a carton along with package insert.

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