NOT TO BE USED IN FOOD PRODUCING ANIMALS, POULTRY, AQUA FARMING AND ANIMAL FEED SUPPLEMENTS

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

R_x

COLISTIMETHATE SODIUM FOR INJECTION IP

EUDOMONAS®-1/2/3/4.5 MIU

COMPOSITION

Eudomonas 1 miu
Each Vial contains:
Colistimethate Sodium IP 10,00,000 IU

Eudomonas 2 miu
Each Vial contains:
Colistimethate Sodium IP 20,00,000 IU

Eudomonas 3 miu
Each Vial contains:
Colistimethate Sodium IP 30,00,000 IU

Eudomonas 4.5 miu
Each Vial contains:
Colistimethate Sodium IP 45,00,000 IU

DOSAGE FORM
Sterile powder for solution for Injection, Infusion and Inhalation

INDICATIONS[1,2]
Colistimethate sodium for injection may be used to initiate therapy in serious infections that are suspected to be due to gram-negative organisms.

- Intravenous administration for the treatment of some serious infections caused by multiple-drug resistant gram-negative bacteria, such as lower respiratory tract and urinary tract.Used only when the causative agent is susceptible and other more effective and less toxic anti-infectives are contraindicated or ineffective

- In patients with cystic fibrosis, inhaled colistimethate sodium may be used to treat serious bacterial lung infections caused by *Pseudomonas aeruginosa*.

Dose conversion table:
The following table demonstrates the equivalencies between Colistimethate sodium IU , Colistimethate sodium mg & Colistin-base activity (CBA) mg.

Colistimethate sodium (IU)	Colistimethate sodium (mg)	Colistin-base activity (CBA) (mg)
12 500	1	0.4
150 000	12	5
1 000 000	80	34
4 500 000	360	150
9 000 000	720	300

DOSAGE AND ADMINISTRATION[1,3,4]
Recommended Dosage
The dosage is determined by the severity and type of infection, the sensitivity of the causative bacteria and the age, weight and renal function of the patient.
Estimation of serum levels is particularly recommended for patients with renal impairment, neonates and patients with cystic fibrosis. Serum levels of 10 - 15 mg/l (approximately 125-200 units/ml) should be adequate for most infections.

Administration and Preparation Instructions
INJECTION
The normal adult dose should be dissolved in 10 ml of sterile water for injections to form a clear solution and given over a minimum of 5 minutes.
The solution is for single use only and any remaining solution should be discarded.
Swirl gently during reconstitution to avoid frothing.

INFUSION
Colistimethate Sodium can be given as a 50 ml intravenous infusion in 0.9% sodium chloride solution or sterile water for injections.
A minimum of 5 days treatment is generally recommended. For the treatment of respiratory exacerbations in cystic fibrosis patients, treatment should be continued for up to 12 days.

NEBULIZER
The required amount of powder is dissolved, preferably, in 2-4 mL of 0.9% sodium chloride solution and poured into the nebulizer. Alternatively, sterile water for injections may be used. The solution will be slightly hazy and may froth if shaken. Usually jet or ultrasonic nebulizers are preferred for antibiotic delivery. These should produce the majority of their output in the respirable particle diameter range of 0.5-5.0 microns when used with a suitable compressor. The instructions of the manufacturers should be followed for the operation and care of the nebulizer and compressor. The output from the nebulizer may be vented to the open air or a filter may be fitted. Nebulisation should take place in a well-ventilated room. The solution is for single use only and any remaining solution should be discarded.

Children and adults (including the elderly)

Children < 2 years: 500,000 – 1,000,000 units, twice daily.

Upto 60kg: 50,000 units/kg/day, to a maximum of 75,000 units/kg/day. The total daily dose should be

divided into three doses given at approximately 8-hour intervals.
Over 60kg: 1-2 million units three times a day. The maximum dose is 6 million units in 24 hours.
Renal Impairment: In moderate or severe renal impairment, excretion of Colistimethate is delayed. Therefore, the dose and the dose interval should be adjusted in order to prevent accumulation. The table below is a guide to dose regimen modifications in patients of 60kg body weight or greater. It is stressed that adjustments may still have to be made on evaluation of the individual patient based on blood levels and evidence of toxicity.

Suggested Dose Adjustment in Renal Impairment

Grade	Creatinine clearance (ml/min)	Over 60kg body weight
Mild	20-50	1-2 million units every 8hr
Moderate	10-20	1 million units every 12-18 hr
Severe	<10	1 million units every 18-24 hr

USE IN SPECIAL POPULATION[5,6]

Pregnancy
Pregnancy Category C
There are no adequate and well-controlled studies in pregnant women. Since colistimethate sodium is transferred across the placental barrier in humans, it should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether colistimethate sodium is excreted in human breast milk. However, colistin sulphate is excreted in human breast milk. Therefore, caution should be exercised when colistimethate sodium is administered to nursing women.

Paediatric Use
In clinical studies, colistimethate sodium was administered to the pediatric population (neonates, infants, children and adolescents). Although adverse reactions appear to be similar in the adult and pediatric populations, subjective symptoms of toxicity may not be reported by pediatric patients. Close clinical monitoring of pediatric patients is recommended.

Geriatric Use
Proper care should be taken while selecting the dose as elderly patients are more likely to have diminished renal functions, and renal functions should be monitored.

Gender
No gender-related difference in the safety profile of colistimethate sodium is reported. Hepatic Impairment No data has shown difference in the safety profile of colistimethate sodium in hepatic impaired patients.

CONTRAINDICATIONS[7]
The use of colistimethate sodium for injection is contraindicated for patients with a history of sensitivity to the drug, any of its components or polymixin B and in patients with myasthenia gravis.

WARNINGS AND PRECAUTIONS[8]
Use with extreme caution in patients with porphyria.
Nephrotoxicity can occur and is probably a dose-dependent effect of colistimethate sodium. These manifestations of nephrotoxicity are reversible following discontinuation of the antibiotic.
Use with caution in renal impairment. It is advisable to assess baseline renal function and to monitor during treatment. Serum colistimethate concentrations should be monitored.
Bronchospasm may occur on inhalation of antibiotics. This may be prevented or treated with appropriate use of beta2-agonists. If troublesome, treatment should be withdrawn.

DRUG INTERACTIONS
Antibiotics (aminoglycosides and polymyxin) have also been reported to interfere with the nerve transmission at the neuromuscular junction. Based on this reported activity, they should not be given concomitantly with colistimethate sodium for injection except with the greatest caution.
Curariform muscle relaxants (e.g., tubocurarine) and other drugs, including ether, succinylcholine, gallamine, decamethonium and sodium citrate, potentiate the neuromuscular blocking effect and should be used with extreme caution in patients being treated with colistimethate sodium for injection.
Sodium cephalothin may enhance the nephrotoxicity of colistimethate for injection. The concomitant use of sodium cephalothin and colistimethate sodium for injection should be avoided.

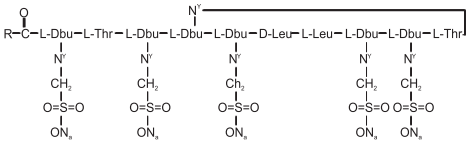
UNDESIRABLE EFFECTS[8]
Adverse events may be related to the age, renal function and condition of the patient.
Patients suffering from cystic fibrosis, neurological events like tingling of extremities and tongue, slurred speech, dizziness, vertigo and paresthesia have been reported in up to 27% of patients. These are generally mild and resolve during or shortly after treatment.
Renal system is affected by the adverse events like nephrotoxicity and decreased urine output, usually following use of higher than recommended doses in patients with normal renal function, or failure to reduce the dose in patients with renal impairment or during concomitant use of other nephrotoxic antibiotics. The effects are usually reversible on discontinuation of therapy.
Patients suffering from cystic fibrosis treated within the recommended dosage limits, nephrotoxicity appear to be rare (less than 1%). In seriously ill hospitalised non-CF patients, signs of nephrotoxicity have been reported in approximately 20% of patients.
Overdose is reported to cause Nephrotoxicity, failure to reduce dose in patients with renal insufficiency and concomitant use of either neuromuscular blocking drugs or other drugs 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.
Hypersensitivity reactions like skin rash have been reported. If these occur treatment should be withdrawn.
Local irritation at the site of injection may occur.

Ability to Drive
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.

OVERDOSE
Overdosage with colistimethate sodium can cause neuromuscular blockade characterized by paresthesia, lethargy, confusion, dizziness, ataxia, nystagmus, disorders of speech and apnea. Respiratory muscle paralysis may lead to apnea, respiratory arrest and death. Overdosage with the drug can also cause acute renal failure, manifested as decreased urine output and increases in serum concentrations of BUN and creatinine.
As in any case of overdose, colistimethate sodium therapy should be discontinued and general

supportive measures should be utilized. There is no specific antidote is available.
It is unknown whether colistimethate sodium can be removed by hemodialysis or peritoneal dialysis in overdose cases.

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTY[2,9-11]
DESCRIPTION:
Colistimethate sodium is a *N*-(4-amino-1-(1-(4-amino-1-oxo-1-(3,12,23-tris(2-aminoethyl)- 20-(1-hydroxyethyl) -6,9- diisobutyl -2,5,8,11,14,19,22 –heptaoxo - 1,4,7,10,13,18- hexaazacyclotricosan-15-ylamino) butan-2-ylamino) - 3-hydroxybutan-2-ylamino)-1-oxobutan-2-yl) -*N*, 5-dimethylheptanamide. Its empirical formula is $C_{58}H_{105}N_{16}Na_3O_{28}S_3$, with a molecular weight of 1749.82. The structural formula is:



Dbu is 2,4- diaminobutanoic acid; R is 5-methylheptyl in colistin A and 5-methylhexyl in colistin B

Pharmacotherapeutic group: Polymyxin Antibiotic
ATC code: J01XB01

PHARMACOLOGY:
Pharmacodynamics
Mechanism of Action
Colistimethate (also known as colistin) is a cyclic polypeptide antibiotic derived from *Bacillus polymyxa var. colistinus* and belongs to the polymyxin group. The polymyxin antibiotics are cationic agents that work by damaging the cell membrane. Polymyxins are selective for Gram negative bacteria that have a hydrophobic outer membrane. The resulting physiological effects are lethal to the bacterium.

Microbiology:
Colistimethate sodium is a surface active agent which penetrates into and disrupts the bacterial cell membrane. It has been shown to have bactericidal activity against most strains of the following microorganisms:
Aerobic gram-negative microorganisms: *Enterobacter aerogenes, Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa*.

Resistance
Resistant bacteria are characterised by modification of the phosphate groups of lipopolysaccharides due to substitution with ethanolamine or aminoarabinose. Naturally resistant Gram-negative bacteria, such as *Proteus rnirabilis* and *Burkholderia cepacia*, show complete substitution of their lipid phosphate by ethanolamine or aminoarabinose.

Susceptibility
The prevalence of 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*, *Citrobacter* species, *Escherichia coli, Haemophilus influenza, Pseudomonas aeruginosa.*

Species for which acquired resistance may be a problem
Enterobacter species, *Klebsiella* species,

Inherently resistant organisms
Brucella species, *Burkholderia cepacia* and related species, *Neisseria* species, *Proteus* species, *Providencia* species, *Serratia* species

Anaerobes
All Gram positive organisms
*Note that the *in-vitro* demonstration of susceptibility may not reliably predict clinical efficacy for *Acinetobacter* species.

Pharmacokinetics
Absorption
Absorption from the gastrointestinal tract does not occur to any appreciable extent in the normal individual.
Studies in healthy volunteers and patients with various infections have reported serum levels from nil to potentially therapeutic concentrations of 4 mg/L or more. Therefore, the possibility of systemic absorption should always be borne in mind when treating patients by inhalation. When given by nebulisation, variable absorption has been reported that may depend on the aerosol particle size, nebuliser system and lung status.
In patients with cystic fibrosis, after administration of 7.5 mg/kg/day in divided doses given as 30-minute intravenous infusions to steady-state, the Cmax was determined to be 23 ± 6 mg/L and the Cmin at 8 hours was 4.5 ± 4 mg/L. 2 million units, when administered every 8 hours in similar patients for 12 days, the Cmax achieved was 12.9 mg/L (5.7 – 29.6 mg/L) and the Cmin was 2.76 mg/L (1.0 – 6.2 mg/L).In healthy volunteers given a bolus injection of 150 mg (2 million units approximately), peak serum levels of 18 mg/L are observed 10 minutes after injection.

Distribution
Protein binding of colistimethate sodium is low. Polymyxins persist in the liver, kidney, brain, heart and muscle. One study in CF patients estimated the steady-state volume of distribution as 0.09L/Kg.
In healthy volunteers given a bolus injection of 150 mg (approximately 2 million units) peak serum levels of 18mg/L were observed 10 minutes after injection. After administration to cystic fibrosis (CF) patients of 7.5 mg/kg/day given as 30 minute intravenous infusions to steady state the Cmax was determined to be 23 (±6) mg/L and Cmin at 8 hr was 4.5 (±4) mg/L. In another study in CF patients given 2 million units every 8 hours for 12 days the Cmax was 12.9 mg/L (5.7 – 29.6 mg/L) and the Cmin was 2.76 mg/L (1.0 – 6.2 mg/L).

Biotransformation
Colistimethate sodium is converted to the base *in-vivo*. As 80% of the dose can be recovered unchanged in the urine, and there is no biliary excretion, it can be assumed that the remaining drug is inactivated in the tissues. The mechanism is unknown.
Excretion

Colistimethate sodium pharmacokinetics appears to be similar in children and adults, including the elderly, provided renal function is normal. Limited data are available on use in neonates that suggest that pharmacokinetics are similar to children and adults but the possibility of higher peak serum levels and prolonged half-life in these patients should be considered and serum levels monitored.
The main route of elimination after parenteral administration is by renal excretion with 40% of a parenteral dose recovered in the urine within 8 hours and around 80% in 24 hours. Because Colistimethate sodium is largely excreted in the urine, dosage reduction is required in renal impairment to prevent accumulation.
After intravenous administration to healthy adults the elimination half-life is around 1.5 hrs. In a study in CF patients given a single intravenous infusion over 30 minutes the elimination half-life was 3.4 $\pm$ 1.4 hrs.

STORAGE
Store below 25°C Protect from light and moisture.
Keep all medicines out of reach of children.

Reconstituted solution
Solutions for Infusion or Injection
Reconstituted Colistimethate sodium solution may be kept up to 24 hours stored in a refrigerator I.e 2-8°C.

Solutions for Nebulization
Solutions for nebulization have similar in-use stability and may be kept for up to 24 hours stored in a refrigerator i.e 2-8°C. Patients self-treating with nebulized antibiotic should be advised to use solutions immediately after preparation.

Does not contain any preservatives.

SHELF LIFE
Please see manufacturing date and Expiry date printed on pack. Do not use the product after the expiry date which is stated on the packaging. The expiry date refers to the last day of that month.

PACKAGING
10 ml USP Type III glass vial with a rubber stopper and aluminium cap, Packed in a single mono carton along with Patient information Leaflet.

REFERENCES:
1. Sabuda DM, Laupland K, Pitout J, Dalton B, Rabin H, Louie T, et al. Utilization of colistin for treatment of multidrug-resistant Pseudomonas aeruginosa. Can J Infect Dis Med Microbiol 2008;19(6):413-8.

2. Young DC, Zobell JT, Waters CD, Ampofo K, Stockmann C, Sherwin CM, et al. Optimization of anti-pseudomonal antibiotics for cystic fibrosis pulmonary exacerbations: IV. colistimethate sodium. Pediatr Pulmonol 2012.

3. Falagas ME, Kasiakou SK, Kofteridis DP, Roditakis G, Samonis G. Effectiveness and nephrotoxicity of intravenous colistin for treatment of patients with infections due to polymyxin-only-susceptible (POS) gram-negative bacteria. Eur J Clin Microbiol Infect Dis 2006;25(9):596-9.

4. Healan AM, Gray W, Fuchs EJ, Griffiss JM, Salata RA, Blumer J. Stability of colistimethate sodium in aqueous solution. Antimicrob Agents Chemother 2012;56(12):6432-3.

5. Celebi S, Hacimustafaoglu M, Koksal N, Ozkan H, Cetinkaya M. Colistimethate sodium therapy for multidrug-resistant isolates in pediatric patients. Pediatr Int 2010;52(3):410-4.

6. Garonzik SM, Li J, Thamlikitkul V, Paterson DL, Shoham S, Jacob J, et al. Population pharmacokinetics of colistin methanesulfonate and formed colistin in critically ill patients from a multicenter study provide dosing suggestions for various categories of patients. Antimicrob Agents Chemother 2011;55(7):3284-94.

7. Decker DA, Fincham RW. Respiratory arrest in myasthenia gravis with colistimethate therapy. Arch Neurol 1971;25(2):141-4.

8. Hartzell JD, Neff R, Ake J, Howard R, Olson S, Paolino K, et al. Nephrotoxicity associated with intravenous colistin (colistimethate sodium) treatment at a tertiary care medical center. Clin Infect Dis 2009;48(12):1724-8.

9. Landman D, Georgescu C, Martin DA, Quale J. Polymyxins revisited. Clin Microbiol Rev 2008;21(3):449-65.

10. Athanassa ZE, Markantonis SL, Fousteri MZ, Myrianthefs PM, Boutzouka EG, Tsakris A, et al. Pharmacokinetics of inhaled colistimethate sodium (CMS) in mechanically ventilated critically ill patients. Intensive Care Med 2012;38(11):1779-86.

11. Couet W, Gregoire N, Gobin P, Saulnier PJ, Frasca D, Marchand S, et al. Pharmacokinetics of colistin and colistimethate sodium after a single 80-mg intravenous dose of CMS in young healthy volunteers. Clin Pharmacol Ther 2011;89(6):875-9.

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Varenyam Healthcare Pvt. Ltd.
FF/SF, Sun Welkin Tower-H, Harni-Halol Road,
Vadodara-390022, Gujarat, India.

Mfd. by:
Bharat Parenterals Limited
At : GUT NO. 444/1, Khadki, Koshimba Road,
Lakhmapur, Nashik, Pin code - 422202,
Maharashtra, India.