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

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Colistimethate Sodium for Injection IP

Koolistin® 1MIU/ 2MIU / 3MIU / 4.5MIU कुलिस्टिन १ एम आई यू / २ एम आई यू / ३ एम आई यू / ४.५ एम आई यू

COMPOSITION:
Koolistin® 1MIU
Each Vial Contains:
Colistimethate Sodium IP 10,00,000 IU
(IU: International Units)

Koolistin®2MIU
Each Vial Contains:
Colistimethate Sodium IP 20,00,000 IU
(IU: International Units)

Koolistin® 3MIU
Each Vial Contains:
Colistimethate Sodium IP 30,00,000 IU
(IU: International Units)

Koolistin® 4.5MIU
Each Vial Contains:
Colistimethate Sodium IP 45,00,000 IU
(IU: International Units)

PHARMACEUTICAL FORM
Lyophilized powder for solution for intravenous injection and infusion only.

ATC code: J01XB01

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
Pharmacotherapeutic group: other antibacterials for systemic use; polymyxins

Mechanism of Action
Colistimethate sodium is a cyclic polypeptide antibiotic derived from *Bacillus polymyxa var. colistinus* and belongs to the polymyxin group. The polymyxin antibiotics are cationic surface-active agents that work by damaging the cell membrane. The resulting physiological effects are lethal to the bacterium. Polymyxins are selective for Gram-negative bacteria that have a hydrophobic outer membrane.

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 aerobic Gram-negative microorganisms: *Enterobacter aerogenes, Escherichia coli, Klebsiella pneumoniae*, and *Pseudomonas aeruginosa.*

Commonly susceptible species
Acinetobacter species*, *Citrobacter* species, *E.coli, Haemophilus influenza, Paeruginosa.*

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
In vitro results may not correlate with clinical responses in the case of *Acinetobacter species*.
When necessary, expert advice should be sought in case of local prevalence of resistance when utility of the agent in at least some types of infections is questionable.

Resistance
Resistant bacteria are characterized by the modification of the phosphate groups of lipopolysaccharide 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
Cross resistance between colistimethate sodium and polymyxin B is expected. Since the mechanism of action of the polymyxin is different from that of other antibiotics, resistance to colistimethate sodium and polymixin by the mechanism alone would not be expected to result in resistance to other drug classes.

Pharmacokinetic Properties
Absorption
Absorption from the gastrointestinal tract does not occur to any appreciable extent in the normal individual. The drugs are not absorbed through mucous membranes, or intact or denuded skin. In healthy volunteers, given a bolus injection of 150 mg (2 million units approx.), peak serum levels of 18 mg/L were observed 10 minutes after intravenous injection.

Distribution
Protein binding of colistimethate sodium is low. Polymyxins persist in the liver, kidney, brain, heart and muscle.

Biotransformation
Colistimethate sodium undergoes conversion to polymyxin E1 and polymyxin E2 (colistin) *in vivo*. It has been estimated that approximately 30% of the colistimethate sodium is converted to colistin. 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
The main route of elimination of colistimethate sodium after intravenous administration is by renal excretion. About 80% of administered dose excreted in urine in 24 hours. Because it is largely excreted in the urine, dosage reduction is required in renal impairment to prevent accumulation. After IV administration to healthy adults the elimination half-life is around 1.5 hrs. Colistimethate sodium kinetics appears to be similar in children and adults, including the elderly, provided renal function is normal. Limited data are available on use in neonates which suggest kinetics 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.

CLINICAL PARTICULARS
Therapeutic Indications
Colistimethate sodium is used to initiate therapy in serious infections that are suspected to be due to Gram-negative organisms.
It is used for the treatment of some serious infections caused by multiple-drug resistant Gram-negative bacteria, such as those in the lower respiratory tract and urinary tract. It is used only when the causative agent is susceptible and other more effective and less toxic anti-infectives are contraindicated or ineffective.

Posology and Method of Administration
IM Injection: Reconstitute the content with 3mL of sterile water for injections. Administer by deep intramusular injection into a large muscle mass (such as gluteal muscles or lateral part of thigh)
IV Injection: The normal adult dose should be dissolved in 10mL sterile water for injections to form a clear solution and given over a minimum of 5 minutes.
IV Infusion: Colistimethate sodium can be given as a 50 mL IV intravenous infusion over a period of 30 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. For reconstitution and dilution see **Reconstitution for Injection/Infusion** section.

If clinical or bacteriological response is slow then the dose may be increased as indicated by the patient's condition.

Children and Adults (Including the Elderly)
Up to 60Kg: The usual recommended dose is 50,000 international units/Kg per day to a maximum of 75,000 international units/Kg per day. The total daily dose should be divided into three doses given at approximately 8 hour intervals.
Over 60Kg: The usual dose is 1 to 2 million international units three times a day. The maximum dose is 6 million units in 24 hours.
Children *<2 years*
The recommended dose is 500,000 to 1,000,000 international units, twice daily.

Adult Loading Dose:

Body weight	Loading Dose	Notes
Over 50Kg	9 million international units (MIU)	• In obese patients(BMI>30) dosing should be based on ideal Body weight. Use of actual body weight in these patients is associated with increased incidence of nephrotoxicity. • In critically ill patients a dose of 9MIU should be used. The loading dose is unaffected by renal impairment
Below 50Kg	6 million international units (MIU)	

Adult Maintenance Dose:

Creatinine Clearance (mL/min)	Dose & Frequency (based on SPCs)	starting time after loading dose
>50	4.5MIU 12 hourly	12 hours
30-50	3MIU 12 hourly	24 hours
10-30	2.5MIU 12 hourly	24 hours
<10	3MIU 8 hourly	24 hours
Patient undergoing continuous venovenous haemodiafiltration (CVVHDF)	3MIU 8 hourly	8 hours

SPCs: Summary of Product characteristics
NOTE: Increasing maintenance dose to 6 MIU 12 hourly may in critically ill depending on patient response and MIC (Minimum Inhibitory Concentration) - discuss with an Physician and review daily.

Special Populations
Renal Impairment
In moderate to severe renal impairment, excretion of colistimethate sodium is delayed. Therefore, the dose and dose interval should be adjusted in order to prevent accumulation. Table 1 is a guide to dose regimen modifications in patients of 60 Kg body weight or greater. It is emphasized that further adjustments may have to be made based on blood levels and evidence of toxicity.

Table 1: Suggested Dosage Adjustment in Renal Impairment

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

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Pediatrics
Serum concentrations decline more rapidly than in adults. Close clinical monitoring of pediatric patients is recommended.
Hepatic Impairment
It is not known whether the dose of colistimethate requires adjustment in patients with hepatic impairment and therefore caution is advised.

Geriatrics
Elderly patients are more likely to have decreased renal function, hence care should be taken in dose selection and it may be useful to monitor renal function.

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

Special Warnings and Precautions for Use
Nephrotoxicity
Impairment of renal function has been reported, usually following the use of higher than recommended IV doses in patients with normal renal function, or failure to reduce the IV dosage in patients with renal impairment or when used concomitantly with other nephrotoxic drugs. The effect is usually reversible on discontinuation of therapy.

Neurotoxicity
High serum concentrations of colistimethate sodium after IV administration may be associated with overdosage or failure to reduce the dosage in patients with renal impairment, and this may lead to neurotoxicity. Concomitant use with either non-depolarising muscle relaxants or antibiotics with similar neurotoxic effects can also lead to neurotoxicity. Dose reduction of colistimethate sodium may relieve symptoms.
Porphyria
Use with extreme caution in patients with porphyria.

Neuromuscular Blockade
Neuromuscular blockade (which may result in respiratory arrest) can occur, especially when used in patients who have neuromuscular disease such as myasthenia gravis or are receiving neuromuscular blocking agents, general anaesthetics, or other drugs with neuromuscular blocking potential (see **Drug Interactions** section)
Apnea and neuromuscular blockade are reported most frequently when dosage was not reduced in proportion to the degree of renal impairment.
If apnea occurs, respiration should be assisted, and calcium chloride injections and oxygen to be administered if appropriate. Neuromuscular blockade induced by colistimethate is non-competitive and is not reversed by neostigmine.

Clostridium difficile-associated diarrhea (CDAD) and Colitis
Clostridium difficile-associated diarrhea (CDAD) has been reported with the use of nearly all antibacterial agents, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to the overgrowth of *C.difficile.* Therefore, it is important to consider this diagnosis in patients who present with diarrhea during or subsequent to the administration of colistimethate sodium.
Discontinuation of therapy with colistimethate sodium and the administration of specific treatment for *C. difficile* associated diarrhea should be considered. Medicinal products that inhibit peristalsis should not be given.

Selection and Use of Anti-infectives
To reduce the development of drug-resistant bacteria and maintain effectiveness of colistimethate and other antibacterials, use only for treatment or prevention of infections proven or strongly suspected to be caused by susceptible bacteria. When selecting or modifying anti-infective therapy, use results of culture and *in vitro* susceptibility testing. In the absence of such data, consider local epidemiology and susceptibility patterns when selecting anti-infectives for empiric therapy.

Drug Interactions
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, cephalothin sodium, aminoglycosides and non-depolarizing muscle relaxants
Neuromuscular blocking drugs like tubocurarine succinylcholine, gallamine, decamethonium sodium citrate and ether should be used with extreme caution in patients receiving colistimethate sodium.
The potential of colistimethate sodium to affect the pharmacokinetics of other medicinal products has not been evaluated. Caution is recommended if colistimethate sodium is combined with medicinal products with a narrow therapeutic index.

Pregnancy and Lactation
Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Since colistimethate sodium is found to be 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. Colistimethate sodium is secreted in breast milk. It should be administered to breast feeding women only when clearly needed

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.

Undesirable Effects
Adverse events may be related to the age, renal function and condition of the patient.

Neurological Events
About 27% of patients suffering from cystic fibrosis were reported with neurological events like tingling of extremities and tongue, slurred speech, dizziness, vertigo and paresthesia. These are generally mild and resolve during or shortly after treatment.

Nephrological Events
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-cystic fibrosis 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 (see **Special Warnings and Precautions for Use** section). 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
Hypersensitivity reactions like skin rash, pruritis have been reported. If these occur treatment should be withdrawn. Local irritation at the site of injection may 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 (blood urea nitrogen) and creatinine. As in any case of overdose, colistimethate sodium therapy should be discontinued and general supportive measures should be utilized. No specific antidote is available. It is unknown whether colistimethate sodium can be removed by hemodialysis or peritoneal dialysis in overdose cases.

PHARMACEUTICAL PARTICULARS
Incompatibilities
This medicinal product must not be mixed with any other medicinal products except those mentioned in **Special Precautions for Disposal and Other Handling** section.

Shelf Life: Please refer to carton/label.

Reconstituted solution for injection/infusion: Reconstituted solution of Colistimethate sodium for injection may be stored for up to 24 hours in a refrigerator at 2°C to 8°C.

Storage and Precautions
Store below 25°C. Protect from light & moisture.
For storage conditions of reconstituted solution for injection/infusion (see **Reconstituted solution for injection/infusion** section).
Keep out of reach of children.

Reconstitution for Injection/Infusion
The normal adult dose should be dissolved in 3 mL (for IM injection), 10 mL (for IV injection) of sterile water for injections to form a clear solution. 50 mL (for infusion) of 0.9 % sodium chloride intravenous infusion or sterile water for injections to form a clear solution.
The solution is for single-use only and any remaining solution should be discarded. Swirl gently during reconstitution to avoid frothing.

Special Precautions for Disposal and Other Handling
Any unused medicinal product should be disposed off in accordance with the local requirements.

Nature and Contents of Container
Koolistin® 1MIU and Koolistin® 2MIU are supplied as a Lyophilized powder for reconstitution in a 10 mL USP Type I glass vial with a rubber stopper and flip off seal, packed in a carton along with package insert.
Koolistin® 3MIU and Koolistin® 4.5MIU is supplied as a Lyophilized powder for reconstitution in a 10 mL USP Type I glass vial with a rubber stopper and flip off seal, packed in a carton along with package insert.

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

Marketed by:
Biocon Biologics India Limited
Biocon House, Semicon Park,
Electronics City, Phase - II,
Bengaluru - 560 100, India.

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To report adverse events and/or product complaints visit our website **www.biocon.com** or call toll free number: **1800 102 9465** or e-mail us at **drugsafety@biocon.com**

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