COLISTIN®

Colistimethate Sodium Powder For Solution For Injection, Infusion or Inhalation 1 Million IU 1 MIU

Colistimethate sodium for injection and inhalation

COLISTIN

COMPOSITION

COLISTIN 1 MIU
Each vial contains:
1 Million International Units (1 MIU) Colistimethate Sodium

DOSAGE FORM/S
Powder for solution for injection, infusion and inhalation

PHARMACOLOGY

Pharmacodynamics

Mode 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

Commonly susceptible species

Acinetobacter species*

Citrobacter species

Escherichia coli

Haemophilus influenzae

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

**In vitro* results may not correlate with clinical responses in the case of *Acinetobacter* species.

When 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.

Cross-resistance

Cross-resistance between colistimethate sodium and polymyxin B would be expected. Since the mechanism of action of the polymyxins is different from that of other antibiotics, resistance to colistin and polymyxin by the above mechanism alone would not be expected to result in resistance to other drug classes.

Pharmacokinetics

Absorption

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, nebuliser system and lung status. 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.

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.

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).

Distribution

Protein binding is low. Polymyxins persist in the liver, kidneys, brain, heart, and muscle. The steady-state volume of distribution in cystic fibrosis patients is 0.09 L/kg.

Biotransformation

Colistimethate sodium undergoes conversion to its base *in vivo*. Approximately 80% of the dose is recoverable unchanged in the urine. There is no biliary excretion and any remaining drug is believed to be inactivated in the tissues.

Elimination

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, dose reduction is required in renal impairment to prevent accumulation (refer under **DOSAGE AND METHOD OF ADMINISTRATION**).

After intravenous administration to healthy adults, the elimination half-life is around 1.5 hours. In a study in cystic fibrosis patients given a single 30-minute intravenous infusion, the elimination half-life was 3.4±1.4 hours.

The elimination of colistimethate sodium following inhalation has not been studied.

Colistimethate sodium kinetics appear 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.

INDICATIONS

COLISTIN is indicated in the treatment of the following infections, where sensitivity testing suggests that they are caused by susceptible bacteria:

i) Intravenous administration for the treatment of some serious infections caused by Gram-negative bacteria, including those of the lower respiratory tract and urinary tract, when more commonly used systemic antibacterial agents may be contraindicated or may be ineffective because of bacterial resistance.

ii) Treatment by inhalation of *Pseudomonas aeruginosa* lung infection in patients with cystic fibrosis.

DOSAGE AND METHOD OF ADMINISTRATION

Systemic Treatment

COLISTIN can be given as a 50 mL 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 (see ***Reconstitution for Parenetral Administration***).

The dose is determined by the severity and type of infection and the age, weight and renal function of the patient. Should clinical or bacteriological response be slow the dose may be increased as indicated by the patient's condition.

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.

Children and Adults (Including the Elderly)

Up to 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.

Anomalous distribution in patients with cystic fibrosis may require higher doses in order to maintain therapeutic serum levels.

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. The table below is a guide to dose regimen modifications in patients of 60 kg bodyweight 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 60 kg Bodyweight
Mild	20-50	1-2 million units every 8 hours
Moderate	10-20	1 million units every 12-18 hours
Severe	<10	1 million units every 18-24 hours

Serum level estimations are recommended especially in renal impairment, neonates and cystic fibrosis patients. Levels of 10-15 mg/L (approximately 125-200 units/mL) colistimethate sodium should be adequate for most infections.

Reconstitution for Parenteral Administration
The normal adult dose of 2 million units should be dissolved in 10-50 mL of 0.9% sodium chloride intravenous infusion or water for injections to form a clear solution. The solution is for single use only and any remaining solution should be discarded.

Aerosol Inhalation

For local treatment of lower respiratory tract infections, **COLISTIN** powder is dissolved in 2-4 mL of water for injections or 0.9% sodium chloride intravenous infusion for use in a nebulizer attached to an air/oxygen supply (see ***Reconstitution for Inhalation***).

In small, uncontrolled clinical trials, doses of from 500,000 units twice daily up to 2 million units three times daily have been found to be safe and effective in patients with cystic fibrosis.

The following recommended doses are for guidance only and should be adjusted according to clinical response:

Children <2 years: 500,000-1 million units twice daily
Children>2 years and Adults: 1-2 million units twice daily

Reconstitution for Inhalation
The required amount of powder is dissolved, preferably, in 2-4 mL of 0.9% sodium chloride solution and poured into the nebulizer. Alternatively, 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.

CONTRAINDICATIONS

COLISTIN is contraindicated in patients with known hypersensitivity to colistimethate sodium (colistin) or to polymyxin B and in patients with myasthenia gravis.

WARNINGS AND PRECAUTIONS

Use with extreme caution in patients with porphyria.

Nephrotoxicity or neurotoxicity may occur if the recommended parenteral dose is exceeded.

Use with caution in renal impairment (see **DOSAGE AND METHOD OF ADMINISTRATION**) as colistimethate sodium is renally excreted. It is advisable to assess baseline renal function and to monitor during treatment. Serum colistimethate sodium 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

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.

Neuromuscular blocking drugs and ether should be used with extreme caution in patients receiving colistimethate sodium.

Renal Impairment

Use with caution in renal impairment as colistimethate sodium is renally excreted and please refer under **DOSAGE AND METHOD OF ADMINISTRATION**.

Hepatic Impairment

No data available.

Pregnancy
There are no adequate data on the use of colistimethate sodium in pregnant women. Single dose studies in human pregnancy show that colistimethate sodium crosses the placental barrier and hence should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Lactation
Colistimethate sodium is secreted in breast milk. Colistimethate sodium should be administered to breastfeeding women only when clearly needed.

Paediatric Use
Please refer under **PHARMACOKINETICS** AND **DOSAGE AND METHOD OF ADMINISTRATION**.

Geriatric Use
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.

UNDESIRABLE EFFECTS

Systemic Treatment
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 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.

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 drugs. 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, hospitalized, non-cystic fibrosis 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.

Inhalation Treatment
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.

OVERDOSAGE

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

There is no specific antidote, so overdose should be managed 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.

INCOMPATIBILITIES

Mixing drugs in infusions, injections and nebulizer solutions involving colistimethate sodium should be avoided.

The addition of other antibiotics such as erythromycin, tetracycline, and cephalothin to solutions of **COLISTIN** may lead to precipitation.

STORAGE AND HANDLING INSTRUCTIONS

Before opening:

Do not store above 25°C. Keep the vials in the outer carton.

Reconstituted solutions:

Solutions for infusion or injection
Chemical and physical in-use stability for 28 days at 4oC has been demonstrated.
From a microbiological point of view, solutions should be used immediately. If not used immediately in-use storage times and conditions prior to use are the responsibility of the user. They would normally be no longer than 24 hours at 2 to 8°C, unless reconstituted and diluted under controlled and validated aseptic conditions.

Solutions for nebulization
Solutions for nebulization have similar in-use stability and should be treated as above. Patients self-treating with nebulized antibiotic should be advised to use solutions immediately after preparation. If this is not possible, solutions should not be stored for longer than 24hrs in a refrigerator.

PACKAGING INFORMATION

COLISTIN 1 MIU is available in vial of 10 mL

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[TAJ GROUP]

TAJ PHARMACEUTICALS LIMITED

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U.S.- F.D.A. Standards

cGMP & W.H.O Certified

"Working for healthier India"

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