



Colistimethate

COLATE

160 mg (equivalent to 2,000,000 IU)
Lyophilized Powder for Injection (I.V.)

Antibacterial



FORMULATION:

Each vial contains:

Colistimethate Sodium, BP.....160 mg (equivalent to 2,000,000 IU)
Lyophilized Powder for Injection (I.V.)

PRODUCT DESCRIPTION:

Colistimethate sodium is a white or almost white, hygroscopic powder sterile parenteral antibiotic product which when reconstituted (see Reconstitution), is suitable for intravenous administration. Each vial contains Colistimethate sodium which is a polypeptide antibiotic with an approximate molecular weight of 1750. The empirical formula is $C_{58}H_{105}N_{16}Na_5O_{28}S_5$.

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 agents that work by damaging the cell membrane, the resulting physiological affects are lethal to the bacterium. Polymyxins are selective for Gram-negative bacteria that have a hydrophobic outer membrane.

Resistance:

Resistant bacteria are characterized by modification of the phosphate groups of lipopolysaccharide that 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: 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 polymixin by the above mechanism alone would not be expected to result in resistance to other drug classes.

Breakpoints:

The suggested general MIC breakpoint to identify bacteria susceptible to colistimethate sodium is <4mg/1. Bacteria for which the MIC of colistimethate sodium is >8mg/1 should be considered resistant.

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. 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.

PHARMACOKINETICS:

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.

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.

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.

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.

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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.

INDICATIONS:

Colistimethate Sodium is indicated in the treatment of the following infections where sensitivity testing suggests that they are caused by susceptible bacteria: **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 contra-indicated or may be ineffective because of bacterial resistance.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

DOSAGE AND MODE 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 too. 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:

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. The most appropriate time interval to the first maintenance dose has not been established. Modelling suggests that loading and maintenance doses of up to 12 MIU may be required in patients with good renal function in some cases. Clinical experience with such doses is however 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. The following dose adjustments are suggested as guidance.

Dose reductions are recommended for patients with creatinine clearance < 50 ml/min: Twice daily dosing is recommend.

Creatinine clearance (ml/min)	Daily dose
< 50-30	5.5-7.5 MIU
<30-10	4.5-5.5 MIU
<10	3.5 MIU

MIU = million IU

Haemodialysis and continuous haemo(dia) filtration Colistin appears to be dialyzable through conventional haemodialysis and continuous venovenous haemo(dia)filtration (CVVHF, CVVHDF). There are extremely limited data from population PK studies from very small numbers of patients on renal replacement therapy. Firm dose recommendations cannot be made. The following regimes could be considered.

Haemodialysis

No-HD days: 2.25 MIU/day (2.2-2.3 MIU/day). HD days: 3 MIU/day on haemodialysis days, to be given after the HD session. Twice daily dosing is recommended.

CVVHF/ CVVHDF

As in patients with normal renal function. 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. Children ≤ 40kg 75,000-150,000 IU/kg/day divided into 3 doses. For children with a body weight 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. No dose recommendations have been established in children with impaired renal function.

Intrathecal and intraventricular administration

Based on limited data, the following dose is recommended in adults:

Intraventricular route

125,000 IU/day 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.

Reconstitution:

The 160 mg (equivalent to 2,000,000 IU) vial should be reconstituted with 25 mL Sterile Water for Injection, USP. The reconstituted solution provides colistimethate sodium at a concentration equivalent to 6.4 mg/mL (80,000 IU/mL) colistin base activity.

During reconstitution, swirl gently to avoid frothing.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If these conditions are observed, the product should not be used.

CONTRAINDICATION

Hypersensitivity to colistimethate sodium (colistin) or to Polymyxin B.

SPECIAL WARNINGS & PRECAUTIONS:

This product should not be administered directly. Please refer to instructions for reconstitution.

Consideration should be given to co-administering intravenous colistimethate sodium with another antibacterial agent whenever this is possible, taking into account the remaining susceptibilities of the pathogen(s) under treatment. 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.

There are limited clinical data on the efficacy and safety of intravenous colistimethate sodium. The recommended doses in all subpopulations are equally based on limited data (clinical and pharmacokinetic/ pharmacodynamics data). In particular there are limited safety data for the use of high doses (> 6MIU/day) and the use of a loading dose, and for special populations (patients with renal impairment and the paediatric population). Colistimethate sodium should only be used when other, more commonly prescribed antibiotics are not effective or not appropriate.

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. Patients who are hypovolaemic or those receiving other potentially nephrotoxic drugs are at increased risk of nephrotoxicity from colistin. 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 over dosage 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.

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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.

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 antibacterial agents and may occur with colistimethate sodium. They may range from mild to lifethreatening in severity. It is important to consider this diagnosis in patients who develop diarrhoea during or after the use of colistimethate sodium. Discontinuation of therapy and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Intravenous colistimethate sodium does not cross the blood brain barrier to a clinically relevant extent. The use of intrathecal or intraventricular administration of colistimethate sodium in the treatment of meningitis was not systematically investigated in clinical trials and is supported by case reports only. Data supporting the posology are very limited. The most commonly observed adverse effect of CMS administration was aseptic meningitis.

PREGNANCY AND LACTATION

Pregnancy:

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.

Lactation:

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

INTERACTION:

Concomitant use of intravenous colistimethate sodium with other medications that are potentially nephrotoxic or neurotoxic should be undertaken with great caution. 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 P450 (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 coadministered with drugs known to inhibit or induce drug metabolising enzymes or drugs 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.

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.

ADVERSE DRUG REACTION:

The likelihood of adverse drug events may be related to various factors such as age, renal function and condition of the patient.

Cystic Fibrosis Patients

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%).

System Organ Class	Frequency	Undesirable effects
Nervous System	27%	Apnoea, transient sensory disturbances (such as facial paraesthesia and vertigo) and, rarely, vasomotor instability, slurred speech, visual disturbances, confusion or psychosis.
Renal System	>1%	Renal impairment and nephrotoxicity

Seriously Ill Hospitalized Non-Cystic Fibrosis Patients

In seriously ill hospitalised 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.

System Organ Class	Frequency	Undesirable effects
Integumentary System	-	Hypersensitivity reactions including skin rash and drug fever
Renal System	20% (approx.)	

(-) Data not available

The probability of occurrence of adverse drug reaction associated with the use of colistimethate sodium to infants <1 year of age is expected. This is due to underdeveloped renal function for this age group. Furthermore, the effect of immature renal and metabolic function on the conversion of colistimethate sodium to colistin is not known, hence caution is advised.

OVERDOSE AND TREATMENT

Overdose can result in neuromuscular blockade that can lead to muscular weakness, apnea 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.

STORAGE CONDITION:

Store at temperatures not exceeding 30°C. Protect from light.

DOSAGE FORM AND PACKAGING AVAILABLE

Dosage Form: Lyophilized Powder for Injection (I.V.)

Packaging: USP Type I Glass Vial with grey bromobutyl rubber stopper and aluminum flip-off seal x 10 mL (Box of 1's)

CAUTION:

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

ADR REPORTING:

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph and BIOCare: pv@biocarelifesciences.com. Seek medical attention immediately at the first sign of any adverse drug reaction.

Marketing Authorization Holder:

biocare
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Registration Number: DRP-13944

Date of First Authorization: 24 May 2023

Date of Revision of Package Insert: 21 June 2023