

Vaxcel®

POLYMYXIN E 1M IU

POWDER FOR INJECTION, INFUSION OR INHALATION

COMPOSITION:

Each vial contains
Colistimethate Sodium 1 Million IU

PRESENTATION:

A white or almost white powder, hygroscopic. A clear solution is obtained after reconstitution, as well as after further dilution.

INDICATIONS:

Vaxcel Polymyxin E 1M IU Powder for Injection, Infusion or Inhalation is indicated in the treatment of the following infections where sensitivity testing suggests that they are caused by susceptible bacteria:

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

-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.

PHARMACODYNAMICS:

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 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.

Resistance:

Resistant bacteria are characterised 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 polymyxin 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 $\leq 4\text{mg/l}$. Bacteria for which the MIC of colistimethate sodium is $\geq 8\text{mg/l}$ 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.

Commonly susceptible species
<i>Acinetobacter</i> species* <i>Citrobacter</i> species <i>Escherichia coli</i> <i>Haemophilus influenzae</i> <i>Pseudomonas aeruginosa</i>
Species for which acquired resistance may be a problem
<i>Enterobacter</i> species <i>Klebsiella</i> species
Inherently resistant organisms
<i>Brucella</i> species <i>Burkholderia cepacia</i> and related species <i>Neisseria</i> species <i>Proteus</i> species <i>Providencia</i> species <i>Serratia</i> species Anaerobes All Gram positive organisms

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

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 4mg/l or more. Therefore, the possibility of systemic absorption should always be borne in mind when treating patients by inhalation.

Distribution:

After the administration to patients with cystic fibrosis of 75mg/kg/day in divided doses given as 30 min intravenous infusions to steady state the C_{max} was determined to be $23 \pm 6\text{mg/l}$ and C_{min} at 8 hours was $4.5 \pm 4\text{mg/l}$. In another study in similar patients given 2 million units every 8 hours for 12 days the C_{max} was 12.9mg/l ($5.7\text{--}29.6\text{mg/l}$) and the C_{min}

was 2.76mg/l ($1.0\text{--}6.2\text{mg/l}$). In healthy volunteers given a bolus injection of 150mg (2 million units approx.) peak serum levels of 18mg/l were observed 10 minutes after injection. Protein binding is low. Polymyxins persist in the liver, kidney, brain, heart and muscle. One study in cystic fibrosis patients gives the steady-state volume of distribution as 0.09L/kg .

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:

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. After intravenous administration to healthy adults the elimination half-life is around 1.5 hrs. In a study in cystic fibrosis patients given a single 30-minute intravenous infusion the elimination half-life was 3.4 ± 1.4 hrs. The elimination of colistimethate sodium following inhalation has not been studied. A study in cystic fibrosis patients failed to detect any colistimethate sodium in the urine after 1 million units were inhaled twice daily for 3 months. 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.

DOSAGE AND ADMINISTRATION:

Parenteral administration: intravenous infusion
Inhalation: nebuliser

Systemic Treatment:

Vaxcel Polymyxin E 1M IU Powder for Injection, Infusion or Inhalation can be given as a 50ml 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 10ml given over a minimum of 5 minutes. 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. Serum level estimations are recommended especially in renal impairment, neonates and cystic fibrosis patients. Levels of $10\text{--}15\text{mg/l}$ (approximately $125\text{--}200$ units/ml) colistimethate sodium should be adequate for most infections. A minimum of 5 days treatment is generally recommended. For the treatment of respiratory exacerbations in cystic fibrosis patients, treatment should be continued up to 12 days.

Children and Adults (Including 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 60kg bodyweight or greater. It is emphasised that further adjustments may have to be made based on blood levels and evidence of toxicity.

Suggested Dosage Adjustment in Renal Impairment

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

Aerosol Inhalation:

For local treatment of lower respiratory tract infections Vaxcel Polymyxin E 1M IU Powder for Injection, Infusion or Inhalation is dissolved in 2-4ml of water for injections or 0.9% sodium chloride intravenous for use in a nebuliser attached to an air/oxygen supply. 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.

Incompatibilities:

Mixed infusions, injections and nebuliser solutions involving colistimethate sodium should be avoided.

DIRECTION FOR USE:

Parenteral Administration:

The normal adult dose of 2 million units should be dissolved in $10\text{--}50\text{ml}$ 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.

Inhalation:

The required amount of powder is dissolved preferably in 2-4 ml 0.9% sodium chloride solution and poured into the nebuliser. Alternatively, water for injections may be used. The solution will be slightly hazy and may froth if shaken. Usually jet or ultrasonic nebulisers are preferred for antibiotic delivery. These should produce the majority of their output in the respirable particle diameter range of $0.5\text{--}5.0$ microns when used with a suitable compressor. The instructions of the manufacturers should be followed for the operation and care of the nebuliser and compressor. The

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output from the nebuliser 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:

Hypersensitivity to colistimethate sodium or to polymyxin B. Patients with myasthenia gravis.

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. It is advisable to assess baseline renal function and to monitor during treatment. Serum colistimethate sodium concentrations should be monitored. Few cases of pseudo-Bartter syndrome have been reported in children and adults with the intravenous use of colistimethate sodium. Monitoring of serum electrolytes should be started in suspected cases and appropriate management should be implemented, however, normalisation of electrolyte imbalance might not be achieved without discontinuation of colistimethate sodium. Brochospasm may occur on inhalation of antibiotics. This may be prevented or treated with appropriate use of beta2-agonists. If troublesome, treatment should be withdrawn.

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 disturbances. Patients should be warned not to drive or operate machinery if these effects occur.

Use in Pregnancy and Lactation:

There are no adequate data from the use of colistimethatesodium in pregnant women. Single dose studies in human pregnancy show that colistimethate sodium crosses the placental barrier and there may be a risk of fetal toxicity if repeated doses are given to pregnant patients. Animal studies are insufficient with respect to the effect of colistimethate sodium on reproduction and development. Colistimethate sodium should be used in pregnancy only if the benefit to the mother outweighs the potential risks to the fetus. Colistimethate sodium is secreted in breast milk. Colistimethate sodium should be administered to breastfeeding women only when clearly needed.

SIDE 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. Pseudo-Bartter syndrome has been reported after intravenous administration of colistimethate sodium with unknown frequency (see Warnings and Precautions). In cystic fibrosis patients treated within the recommended dosage limits, nephrotoxicity appears to be rare (less than 1%). In seriously ill hospitalised non-CF 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.

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.

OVERDOSAGE AND TREATMENT:

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. Measures to increase the rate of elimination of Colistimethate sodium e.g. mannitol diuresis, prolonged haemodialysis or peritoneal dialysis may be tried, but effectiveness is unknown.

STORAGE:

Store below 30°C. Protect from light. Reconstituted solution can be stored for 6 hours at below 30°C, or 24 hours at 2-8°C. From microbiological point of view, the product should be used immediately.

PACK QUANTITIES:

Single vial per box and 10 vials per box.
Not all pack sizes may be marketed.

Further information can be obtained from pharmacist, physician or the manufacturer.

Product Registration Holder & Manufactured By :



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