Colistim INJECTION

(Colistimethate Sodium)

کولی سسٹم انجیکشن

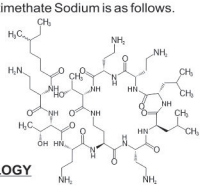
(کولسٹی میتھیٹ سوڈیم)

COMPOSITION:

Colistim Injection 1MIU
Each vial contains:
Colistimethate sodium (1MIU) eq. to Colistin base activity.....34mg
(USP specifications)
Colistim Injection 2MIU
Each vial contains:
Colistimethate sodium 2MIU eq. to 68mg
Colistin base activity (approximately) corresponds to 160mg Colistimethate sodium (base)
(USP specifications)
Colistim Injection 3MIU
Each vial contains:
Colistimethate sodium 3MIU eq. to 100mg Colistin base activity (approximately) corresponds to 240mg Colistimethate sodium (base)
(USP specifications)
Colistim Injection 4.5MIU
Each vial contains:
Colistimethate sodium 4.5MIU eq. to 150mg Colistin base activity (approximately) corresponds to 360mg Colistimethate sodium (base)
(USP specifications)

DESCRIPTION

COLISTIM for injection (colistimethate sodium) is a sterile parenteral antibiotic product which, when reconstituted is suitable for intravenous administration.
The sodium content is approximately 0.099 mg (0.0043 mEq) of sodium per milligram of COLISTIM. Colistimethate sodium is a polypeptide antibiotic with an approximate molecular weight of 1750.
Molecular formula of Colistimethate Sodium is as follows
$C_{58}H_{105}N_{16}Na_5O_{28}S_5$
Structural formula of Colistimethate Sodium is as follows.



CLINICAL PHARMACOLOGY
MODE OF ACTION

COLISTIM is a cyclic polypeptide antibacterial agent belonging to the polymyxin group. Polymyxins work by damaging the cell membrane and the resulting physiological effects are lethal to the bacterium. Polymyxins are selective for aerobic Gram-negative bacteria that have a hydrophobic outer membrane.

DOSAGE & ADMINISTRATION

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 recommended.

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

•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.

•Pediatric population

The data supporting the dose regimen in pediatric 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.

•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.
Patients with a totally implantable venous access device (TIVAD) in place may tolerate a bolus injection of upto 2 million units in 10ml given over a minimum of 5 minutes.
Colistimethate sodiumcan also be breathed into the lungs as a fine spray made using a machine called a nebuliser. The droplets of the spray produced by the nebuliser are small enough to enter the lungs so that Colistimethate sodium can reach the site of the bacterial infection.

DILUTION:

•For bolus injection:

Reconstitute the contents of the vial with not more than 7ml sterile water for injection or 0.9% sodium chloride.
For infusion:
The contents of the reconstituted vial may be diluted, usually with 50ml 0.9% sodium chloride
During reconstitution swirl gently to avoid frothing. The reconstituted Colistimethate sodium is a clear solution.

•For use in a nebulizer:

Dose

• When Colistimethate sodium is to be given by inhalation using a nebuliser, the usual dose for children under two years of age is 500,000 to one million units given twice a day.
• In older children and adults, the dose is one or two million units twice a day, with a maximum of two million units three times a day.

Method of administration

If you are treating yourself at home, your doctor or nurse will show you how to use Colistimethate sodium in your nebulizer when you first start the treatment. The following are general instructions.
The plastic cap is flipped open and the foil seal carefully ripped from around the top of the vial to remove it completely. The rubber bung is taken out carefully and sterile water or sterile salt water (saline) is added to each vial to dissolve the powder as follows:

1 million unit vial:	2ml sterile water / saline
2 million unit vial:	4ml sterile water / saline

IMPORTANT: Do not mix Colistimethate sodium with any other product for nebulisation at the same time

INDICATIONS

COLISTIM for injection is indicated for the treatment of acute or chronic infections due to sensitive strains of certain gram-negative

bacilli. It is particularly indicated when the infection is caused by sensitive strains of Pseudomonas aeruginosa.
This antibiotic is not indicated for infections due to Proteus or Neisseria. Colistimethate for injection has proven clinically effective in treatment of infections due to the following gram-negative organisms: Enterobacter aerogenes, Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa. Colistimethate for injection may be used to initiate therapy in serious infections that are suspected to be due to gram-negative organisms and in the treatment of infections due to susceptible
gram-negative pathogenic bacilli. To reduce the development of drug-resistant bacteria and maintain the effectiveness of COLISTIM for injection and other antibacterial drugs, COLISTIM for injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

PRECAUTIONS
Maximum daily dose should not exceed 5 mg/kg/day (2.3 mg/lb) with normal renal function.
Transient neurological disturbances may occur. These include circumoral paresthesia or numbness, tingling or formication of the extremities, generalized pruritus, vertigo, dizziness, and slurring of speech. For these reasons, patients should be warned not to drive vehicles or use hazardous machinery while on therapy. Reduction of dosage may alleviate symptoms. Therapy need not be discontinued, but such patients should be observed with particular care.
Nephrotoxicity can occur and is probably a dose-dependent effect of colistimethate sodium. These manifestations of nephrotoxicity are reversible following discontinuation of the antibiotic.
Overdosage can result in renal insufficiency, muscle weakness, and apnea.

PHARMACOKINETICS
The information on the pharmacokinetics of colistimethate sodium (CMS) and COLISTIM 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/COLISTIM. plasma concentrations.
After infusion of colistimethate sodium the inactive pro-drug is converted to the active COLISTIM. Peak plasma concentrations of COLISTIM 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 COLISTIM 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 COLISTIM display linear PK in the clinically relevant dose range.
Elimination
It is estimated that approximately 30% of colistimethate sodium is converted to COLISTIM. in healthy subjects, its clearance is dependent on creatinine clearance and as renal function decreases, a greater portion of CMS is converted to COLISTIM.. 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.
The elimination of the active COLISTIM is incompletely characterized .COLISTIM undergoes extensive renal tubular reabsorption and may either be cleared non-renally or undergo renal metabolism with the potential for renal accumulation. COLISTIM clearance is decreased in renal impairment, possibly due to increased conversion of CMS.
Half-life of COLISTIM 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.

ADVERSE EFFECTS
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. This has generally been due to failure to follow recommended guidelines, usually over dosage in the presence of renal impairment and/or concomitant use of other antibiotics or medicines with neuromuscular blocking potential.
A decrease in urine output or increase in blood urea nitrogen or serum creatine can be interpreted as signs of nephrotoxicity which is probably a dose-dependent effect of colistimethate sodium. These manifestations of nephrotoxicity are reversible following discontinuation of the antibiotic.
Increases of blood urea nitrogen have been reported for patients receiving the medicine at dose levels of 1.6 to 5 mg/kg/day. The BUN values returned to normal following cessation of administration. Paraesthesia, tingling of the extremities or tingling of the tongue and generalised itching or urticaria have been reported by patients who received the medicine by intravenous or intramuscular injection. In addition, the following adverse reactions have been reported for colistimethate sodium: medicine fever and gastrointestinal upset, vertigo and slurring of speech. The subjective symptoms reported by the adult may not be manifest in infants or young children thus requiring close attention to renal function

DRUG INTERACTIONS
Certain other antibiotics (kanamycin, streptomycin, dihydrostreptomycin, polymyxin, neomycin) have also been reported to interfere with the nerve transmission at the neuromuscular junction. Based on the reported activity they should not be given concomitantly except with the greatest caution. The antibiotics with a Gram-positive antimicrobial spectrum e.g., penicillin, tetracycline, cephalothin sodium, have not been reported to interfere with nerve transmission and accordingly would not be expected to potentiate this effect.
Other medicines including curariform muscle relaxants (either tubocurarine, 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.

CONTRAINDICATIONS
The use of COLISTIM for injection is contraindicated for patients with a history of sensitivity to the drug or any of its components.

STORAGE & INSTRUCTIONS:
Store between 15-25°C. Protect from heat, sunlight & moisture. Keep away from the reach of children. Do not freeze.
To be sold on the prescription of a registered medical practitioner only.

HOW SUPPLIED:
Colistim Injection 1MIU
1 vial + 2ml sterile water for injection
Colistim Injection 2MIU
1 vial + 5ml sterile water for injection
Colistim Injection 3MIU
1 vial + 10ml sterile water for injection
Colistim Injection 4.5MIU
1 vial + 10ml sterile water for injection

خوراک وطریقہ استعمال:
ڈاکٹر کی ہدایت کے مطابق استعمال کریں

ہدایات:
دوا کو ۱۵-۲۵ ڈگری سینٹی گریڈ درجہ حرارت کے درمیان رکھیں۔
دھوپ، گرمی، نمی اور منجمد ہونے سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

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