

Higher serum levels were obtained at 10 minutes following IV administration. Serum concentration declined with a half-life of 2-3 hours following either intravenous or intramuscular administration in adults and children including premature infants.

Colistimethate sodium is transferred across placental barrier, and blood levels of about 1 mcg/mL are obtained in the foetus following intravenous administration to the mother.

Average urine levels ranged from about 270 mcg/mL at 2 hours to about 15 mcg/mL at 8 hours after intravenous administration and from 200 to about 25 mcg/mL during a similar period following intramuscular administration.

Indications

The treatment of acute or chronic infections due to sensitive strains of certain Gram-negative bacilli; particularly when the infection is caused by sensitive strains of *Pseudomonas aeruginosa*, and the following Gram-negative organisms; *Aerobacter aerogenes*, *Escherichia coli*, *Klebsiella pneumoniae*.

Contraindications

This antibiotic is not indicated for infections due to *Proteus* or *Neisseria* spp. The use of this antibiotic is contraindicated in patients with a history of sensitivity to the drug.

Warnings

Maximum daily dose should not exceed 5 mg/kg/day with normal renal function. Transient neurological disturbances may occur. These include circumoral paraesthesias or numbness, tingling or formication of the extremities, generalised 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. Overdose can result in renal insufficiency, muscle weakness and apnoea. See **Precautions** for use concomitantly with curariform drugs, and **Dosage and Administration** section for use in renal impairment.

A case of fatal lung and airway toxicity in a cystic fibrosis patient has been reported following off-label use of colistimethate, inhaled via nebuliser, for the treatment of *Pseudomonas aeruginosa* infection.

When reconstituted, colistimethate undergoes hydrolysis to colistin, which has the potential to cause lung toxicity.

Colistimethate is approved only for injection into a vein or a muscle; it is not approved for use as a liquid to be inhaled via nebuliser.

In light of this reported patient death, it is recommended that:

- If using the liquid form in a nebuliser, it should be used immediately after being mixed.
- Patients should discard any unused pre-mixed liquid form of colistimethate.
- Healthcare professionals who use colistimethate to treat patients with CF should be aware of the potential for serious and life threatening side effects from inhalation of pre-mixed, ready-to-use liquid forms of colistimethate. The side effects are a result of local toxicity to the lung and airway.
- Healthcare professionals who treat patients with CF should work out a treatment plan with their patients that best meets their needs.
- Patients and/or their caregivers with questions or concerns about this advisory should contact their healthcare provider to determine how best to continue treating their infection.

Precautions

Since colistimethate sodium is eliminated mainly by renal excretion, it should be used with caution when the possibility of impaired renal function exists. The decline in renal function with advance age should be considered.

When actual renal impairment is present, the greatest caution should be exercised and the dosage should be reduced in proportion to the extent of the impairment. Dosage in excess of renal excretory capacity will lead to high serum levels and can result in further impairment of renal function, initiating a cycle which, if not recognised, can lead to acute renal insufficiencies, renal shutdown and further concentration of the antibiotic to toxic levels in the body. At this point, interference of nerve transmission at neuromuscular junctions may occur and result in muscle weakness and apnoea.

Easily recognised signs indicating the development of impaired renal function are diminishing urine output, rising BUN and serum creatinine. If present, therapy should be discontinued immediately.

If a life-threatening situation exists, therapy may be reinstated at a lower dosage after blood levels have fallen.

Use in Pregnancy

Great caution should be exercised in use of this drug in women of childbearing potential, COLISTIN LINK Parenteral should be used only if deemed essential for the treatment of the indicated conditions. Category B2.

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 Gram-positive antimicrobial spectrum eg penicillin, tetracycline, have not been reported to interfere with nerve transmission and accordingly would not be expected to potentiate this effect.

Other drugs 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 COLISTIN LINK Parenteral.

If apnoea occurs it may be treated with assisted respiration, oxygen and calcium chloride injections. Cephalothin should not be used concurrently owing to increase in renal problems.

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 drugs 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 drug 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 drug by intravenous or intramuscular injection. In addition, the following adverse reactions have been reported for colistimethate sodium: drug 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.

Dosage and Administration

Reconstitute the vial (150 mg) with 2 mL of Sterile Water for Injection.

Adults and Children: Intravenous or intramuscular administration given in two to four divided doses at dose levels of 2.5 to 5 mg/kg/day for patients with normal renal function depending on the severity of the infection.

Intramuscular administration: Should be given by deep intramuscular injection in two to four divided doses.

Intravenous administration: Should be given by intravenous injection in two divided doses. Administer half the total daily dose slowly over 3 to 5 minutes. The remaining half of the total daily dose may be administered by intravenous drip starting one to two hours after the initial loading dose at a rate of 5 to 6 mg per hour in the presence of normal renal function.

The daily dose should be reduced in the presence of any renal impairment which can often be anticipated from the history. Modifications of dosage in the presence of renal impairment are presented in the following Table I.

Table I COLISTIN LINK Parenteral:

Suggested modification of dosage schedule for adults with impaired renal function

	Normal	Mild	Moderate	Considerable
Plasma creatine (mg/100 mL)	0.7 - 1.2	1.3 - 1.5	1.6 - 2.5	2.6 - 4.0
Urea clearance % of normal	80 - 100	40 - 70	25 - 40	10 - 25
Dosage - Unit dose of COLISTIN LINK M, mg	100.150	75 - 115	66 - 150	100 - 150
Frequency, times per day	3 or 2	2	2 or 1	every 36 hrs
Total daily dose, mg	300	150 - 230	133 - 150	100
Approx dose level mg/kg/day	5.0	2.5 - 3.8	2.5	1.5

Note: The suggested unit dose is 2.5 to 5 mg/kg. However, the time interval between injections should be increased in the presence of impaired renal function.

Compatibility: The following intravenous fluids are compatible with colistimethate sodium; Normal Saline, 5% Dextrose in Water, 5% Dextrose in Normal Saline, 5% Dextrose with 0.45% Sodium Chloride, 5% Dextrose with 0.225% Sodium Chloride. Lactated Ringer's solution or invert sugar solution 10%. Unused portions of IV fluids containing colistimethate sodium should be discarded after 24 hours and fresh material prepared. The physical admixture in the same vial of colistimethate sodium with other antibiotics or medications is not recommended.

Presentation

Injection: 150 mg colistin base; powder

Medicine Classification

Prescription medicine.

Package Quantities

Injection, 150 mg, Is.

Name and Address of Sponsor

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