

PRODUCT INFORMATION

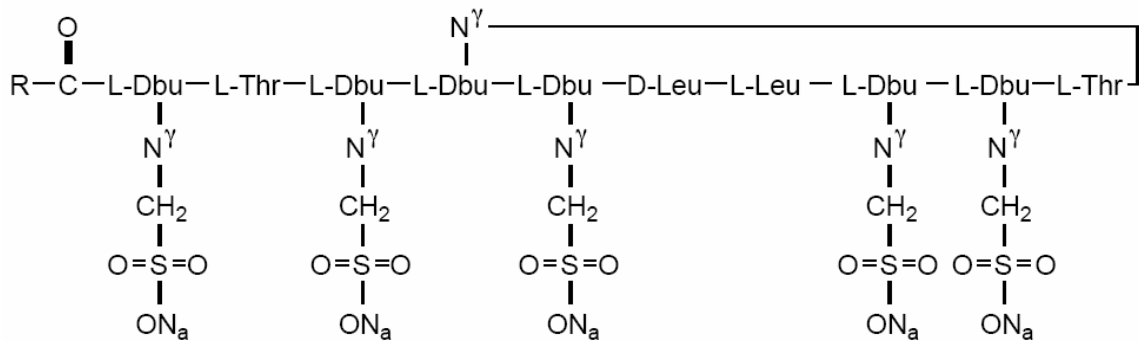
COLISTIN LINK PARENTERAL

(Colistimethate sodium for injection, USP)

For Intramuscular and intravenous use.

DESCRIPTION

Colistin Link Parenteral contains the sodium salt of colistimethate, a polypeptide antibiotic with an approximate molecular weight of 1750; the empirical formula is $C_{56} H_{106} N_{16} Na_6 O_{26} S_6$.

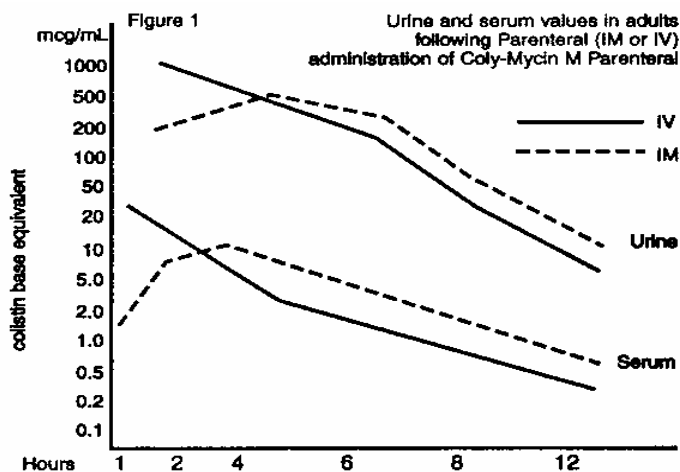


Dbu is 2,4-diaminobutanoic acid; R is 5-methylheptyl in colistin A and 5-methylhexyl in colistin B

CLINICAL PHARMACOLOGY

Microbiology Colistin Link Parenteral has bactericidal activity against the following gram-negative bacilli: *Enterobacter*, *aerogenes*, *Escherichia coli*, *Klebsiella pneumonia* and *Pseudomonas aeruginosa*.

Human Pharmacology Typical serum and urine levels following a single 150 mg dose of Colistin Link Parenteral IM or IV in normal adult subjects are shown in Figure 1.



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 the 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 AND USAGE

Colistin Link Parenteral 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*. Colistin Link Parenteral has proven clinically effective in treatment of infections due to the following gram-negative organisms: *Enterobacter aerogenes*, *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*.

Pending results of appropriate bacteriologic cultures and sensitivity tests, Colistin Link Parenteral may be used to initiate therapy in serious infections that are suspected to be due to gram-negative organisms.

CONTRAINDICATIONS

The use of Colistin Link Parenteral is contraindicated for patients with a history of sensitivity to the drug.

WARNING

Maximum daily dose should not exceed 5 mg/kg/day with normal renal function.

Transient neurological disturbances may occur. These include circumoral paresthesias 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. Overdosage 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.

PRECAUTIONS

Since Colistin Link Parenteral 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 advanced age should be considered.

When actual renal impairment is present, Colistin Link Parenteral may be used, but the greatest caution should be exercised and the dosage should be reduced in proportion to the extent of the impairment. Administration of amounts of Colistin Link Parenteral 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 insufficiency, 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 with Colistin Link Parenteral should be discontinued immediately.

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

Certain other antibiotics (kanamycin, streptomycin, dihydrostreptomycin, polymyxin, neomycin) have also been reported to interfere with the nerve transmission at the neuromuscular junction. Based on this reported activity, they should not be given concomitantly with Colistin Link Parenteral except with the greatest caution. The antibiotics with a gram-positive antimicrobial spectrum, eg. penicillin, tetracycline, cephalothin sodium, have not been reported to interfere with the nerve transmission and, accordingly, would not be expected to potentiate this activity of Colistin Link Parenteral.

Other drugs, including curariform muscle relaxants (ether, 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.

Use In pregnancy (Category B2)

The safety of colistimethate sodium during human pregnancy has not been established.

ADVERSE REACTIONS

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 been generally due to failure to follow recommended guidelines, usually overdose, failure to reduce dose commensurate with degree 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 creatinine can be interpreted as signs of nephrotoxicity, which is probably a dose-dependant 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 Colistin Link Parenteral at dose levels of 1.6-5 mg/kg per day. The BUN values returned to normal following cessation of Colistin Link Parenteral administration.

Paresthesia, tingling of the extremities or tingling of the tongue and generalised itching or urticaria have been reported by patients who received Colistin Link Parenteral 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

Important Colistin Link Parenteral is supplied in vials containing colistimethate sodium.

Reconstitution The vial should be reconstituted with **2.0 mL** water for injections. The reconstituted solution provides 150 mg of antibiotic in 2 mL.

During reconstitution swirl **gently** to avoid frothing.

Dosage-Adults and children-intravenous or intramuscular administration-Colistin Link Parenteral should be given in 2 to 4 divided doses at dose levels of 2.5 to 5 mg/kg per day for patients with normal renal function, depending on the severity of the infection.

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 Table 1.

Table 1. Suggested modification of Dosage Schedules of Colistin Link Parenteral for Adults with Impaired Renal Function

| Renal Function | Degree of Impairment | | | |
|--------------------------------------|----------------------|-------------|-----------------|---------------------|
| | <i>Normal</i> | <i>Mild</i> | <i>Moderate</i> | <i>Considerable</i> |
| Plasma Creatinine, 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 Coly-Mycin M, mg | 100-150 | 75-115 | 66-150 | 100-150 |
| Frequency, times/day | 4 to 2 | 2 | 2 or 1 | every 36 hr |
| Total daily dose, mg | 300 | 150-230 | 133-150 | 100 |
| Approximate daily dose, mg/kg/day | 5.0 | 2.5-3.8 | 2.5 | 1.5 |

NOTE: The suggested unit dose is 2.5-5 mg/kg; however, the time INTERVAL between injections should be increased in the presence of impaired renal function.

INTRAVENOUS ADMINISTRATION

1. Direct intermittent Administration - slowly inject one-half of the total daily dose over a period of 3 to 5 minutes every 12 hours.
2. Continuous infusion - slowly inject one-half of the total daily dose over 3 to 5 minutes. Add the remaining half of the total daily dose of Colistin Link Parenteral to one of the following:

0.9% NaCl

5% glucose in 0.9% NaCl

5% glucose in water

5% glucose in 0.45% NaCl

5% glucose in 0.225% NaCl

lactated Ringer's solution

10% invert sugar solution

There are not sufficient data to recommend usage of Colistin Link Parenteral with other drugs or other than the above listed infusion solutions.

Administer by slow intravenous infusion starting 1 to 2 hours after the initial dose at a rate of 5-6 mg/hr in the presence of normal renal function. In the presence of impaired renal function, reduce the infusion rate depending on the degree of renal impairment.

The choice of intravenous solution and the volume to be employed are dictated by the requirements of fluid and electrolyte management.

Any infusion solution containing colistimethate sodium should be freshly prepared and used for no longer than 24 hours.

HOW SUPPLIED

Colistin Link Parenteral is supplied in vials containing colistimethate sodium as a white to slightly yellow lyophilized cake and is available as one vial per carton. On reconstitution each vial provides 150 mg of antibiotic in 2 mL.

Store below 25C.

Contains no additional antimicrobial agent. Use in one patient on one occasion only, as soon as practicable after reconstitution. Store reconstituted solution at 2°C to 8°C (Refrigerate. Do not freeze).

TOXICOLOGY AND ANIMAL PHARMACOLOGY

Acute Toxicity The intravenous LD₈₀ was 41.5 mg/kg in the dog and 739 mg/kg in the mouse, intramuscular toxicity was 42 mg/kg in the dog and 267 mg/kg in the mouse.

Subacute Toxicity In albino rabbits and beagle dogs, IV doses of 5, 10 and 20 mg/kg/day for 28 days resulted in elevated blood urea nitrogen in the dog (10 mg/kg/day dose group) and in both 20 mg/kg dose groups.

CLINICAL STUDIES

Clinically, Colistin Link Parenteral has been of particular therapeutic value in acute and chronic urinary tract Infections caused by sensitive strains of *Pseudomonas aeruginosa*. Colistimethate sodium is clinically effective in the treatment of infections due to other sensitive gram-negative pathogenic bacilli which have become resistant to broad spectrum antibiotics.

Colistimethate sodium has been used to treat bacteriuria and overt urinary infections in pregnant women during the third trimester. However, in view of the evidence of possible embryotoxic and teratogenic effects of colistimethate sodium in pregnant rabbits, caution should be exercised in use of this drug in women of child-bearing potential.

NAME AND ADDRESS OF SPONSOR:

Link Medical Products Pty. Ltd.
Level 1 Bridgepoint Centre
3 Brady Street, Mosman NSW 2088
Australia

AUST R 14667

DATE OF MOST RECENT AMENDMENT:

August 15th, 2006
