NEW ZEALAND DATA SHEET

1. COLISTIN-LINK® 150 mg/2 mL powder for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains colistimethate sodium (equivalent to colistin 150 mg).

Once reconstituted, each mL of solution contains 75 mg of colistin.

3. PHARMACEUTICAL FORM

Powder for injection.

Colistin Link is supplied in vials containing colistimethate sodium for injection, USP (equivalent to 150 mg colistin per vial) as a white to slightly yellow lyophilized cake containing the equivalent of 4,500,000 IU antibiotic activity.

4. CLINICAL PARTICULARS

4.1. Therapeutic 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*.

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

4.2. Dose and method of administration

Important

Colistin Link is supplied in vials containing colistimethate sodium.

Reconstitution

The vial should be reconstituted with 2.0 mL sterile water for injections. The reconstituted solution provides 150 mg colistin in 2 mL.

During reconstitution swirl gently to avoid frothing.

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 1.

Table 1. Colistin Link:

Suggested modification of dosage schedules 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, 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%.

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

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.

4.3. 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 medicine.

4.4. Special warnings and precautions for use
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 **Section 4.5 Interactions with other medicines and other forms of interactions** for use concomitantly with curariform medicines, and **Section 4.2 Dose and method of administration** 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.

Use in renal impairment
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.

If apnoea occurs, it may be treated with assisted respiration, oxygen and calcium chloride injections.

4.5 Interaction with other medicines and other forms of interaction
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.

4.6. Fertility, pregnancy and lactation

Pregnancy
Category B2.
The safety of colistimethate sodium during human pregnancy has not been established.

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 medicine in women of childbearing potential, colistimethate sodium should be used only if deemed essential for the treatment of the indicated conditions.

Breast-feeding
No data available.

Fertility
No data available.

4.7. Effect on ability to drive and use machines
Patients should be warned not to drive vehicles or use hazardous machinery while on therapy as transient neurological disturbances may occur. See **Section 4.4 Special warnings and precautions for use**.

4.8. Undesirable 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9. Overdose
For advice on the management of overdose, please contact the Poison Information Centre on 13 11 26 (Australia) or the National Poisons Centre on 0800 764 766 (New Zealand).

Overdose can result in renal insufficiency, muscle weakness and apnoea. As in any case of overdose, colistimethate sodium therapy should be discontinued and general supportive measures should be utilised.

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 dot (10 mg/kg/day dose group) and in both 20 mg/kg/day dose groups.

5. PHARMACOLOGICAL PROPERTIES

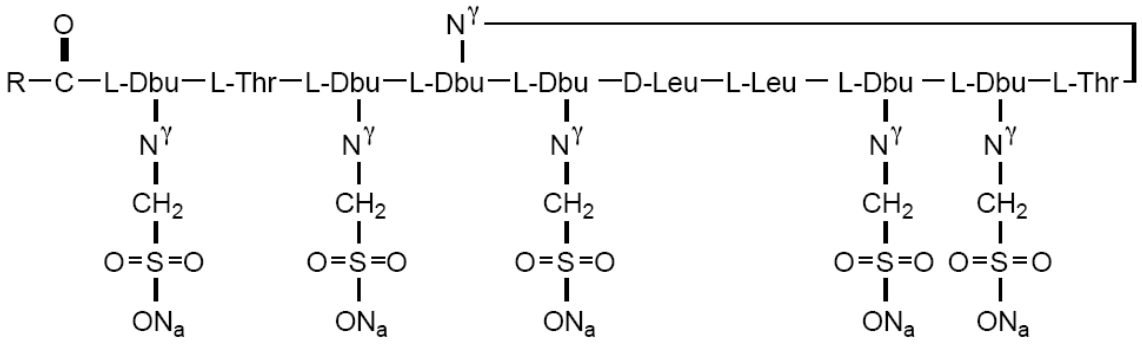
5.1. Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemic use, other antibacterials, polymyxins.

ATC Code: J01XB01

Colistin Link contains the sodium salt of colistimethate, a polypeptide antibiotic with an approximate molecular weight of 1750; the empirical formula is $C_{56}H_{106}N_{16}Na_6O_{26}S_6$. CAS: number 8068-28-8.

Chemical structure



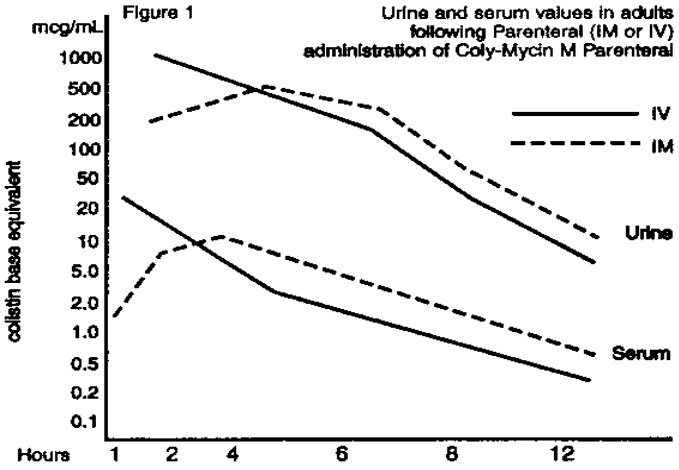
Dbu is 2,4-diaminobutanoic acid; R is 5-methylheptyl in colistin A and 5-methylhexyl in colistin B

Mechanism of action
Colistimethate sodium has bactericidal activity against the following Gram-negative bacilli: *Enterobacter aerogenes*, Escherichia coli, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*.

Clinical efficacy and safety

Clinically, colistimethate sodium has been of particular therapeutic value in acute and chronic urinary tract infections cause 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.

5.2. Pharmacokinetic properties
Typical serum and urine levels following a single 150 mg dose of Colistin-Link 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 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.

5.3. Preclinical safety data
No data available.

6. PHARMACEUTICAL PARTICULARS
6.1. List of excipients
None.

6.2. Incompatibilities
In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3. Shelf life
36 months.

Once reconstituted, store the solution at 2°C to 8°C (Refrigerate. Do not freeze).

Contains no additional antimicrobial agent, use in one patient on one occasion only, as soon as practicable after reconstitution. Reconstituted solution must be used within 24 hours.

6.4. Special precautions for storage
Store below 25°C

For storage conditions after reconstitution of the medicine, see **section 6.3 Shelf-life.**

6.5. Nature and contents of container
Colistin Link is supplied in a vial (glass) 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 colistin in 2 mL equivalent to 4,500,000 IU.

6.6. Special precautions for disposal
Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE
Prescription medicine.

8. SPONSOR
Link Pharmaceuticals Ltd
Level 31 Vero Centre
48 Shortland Street
Auckland 1140New Zealand

Tel: +64 9 358 7146

Link Medical Products Pty. Ltd.
5 Apollo Street
Warriewood, NSW 2102
Australia

AUST R 14667

9. DATE OF FIRST APPROVAL
15 March 1973

10. DATE OF REVISION OF THE TEXT
23 January 2019

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
N/A	DS reformatted to align with new requirement.