New Zealand Data Sheet

COLISTIN-LINK®

Colistimethate sodium equivalent to colistin 150mg

powder for injection

For intramuscular and intravenous use.

Description

Colistimethate sodium for injection, USP

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_{6}O_{26}S_{6}.

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\begin{array}{cccccc}
  N^\gamma & N^\gamma & N^\gamma & N^\gamma & N^\gamma & N^\gamma & N^\gamma & N^\gamma & N^\gamma & N^\gamma & N^\gamma & N^\gamma & N^\gamma & N^\gamma & N^\gamma & N^\gamma & N^\gamma & N^\gamma & N^\gamma \\
  CH_2 & CH_2 & CH_2 & CH_2 & CH_2 & CH_2 & CH_2 & CH_2 & CH_2 & CH_2 & CH_2 & CH_2 & CH_2 & CH_2 & CH_2 & CH_2 & CH_2 & CH_2 & CH_2 \\
  O=\text{S}\equiv\text{O} & O=\text{S}\equiv\text{O} & O=\text{S}\equiv\text{O} & O=\text{S}\equiv\text{O} & O=\text{S}\equiv\text{O} & O=\text{S}\equiv\text{O} & O=\text{S}\equiv\text{O} & O=\text{S}\equiv\text{O} \\
  \text{ON}_a & \text{ON}_a & \text{ON}_a & \text{ON}_a & \text{ON}_a & \text{ON}_a & \text{ON}_a & \text{ON}_a \\
\end{array}
\]

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

CAS No. 8068-28-8

Colistin Link is supplied in vials containing colistimethate sodium (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.

Clinical Pharmacology

Microbiology

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

Human Pharmacology

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.

Clinical Trials

Clinically, colistimethate sodium 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.

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.

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.
**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 formation 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 medicines, 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.

**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.

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.

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.

**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.

**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.
Dosage and 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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Normal</th>
<th>Mild</th>
<th>Moderate</th>
<th>Considerable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma Creatine, mg/100 mL</td>
<td>0.7-1.2</td>
<td>1.3-1.5</td>
<td>1.6-2.5</td>
<td>2.6-4.0</td>
</tr>
<tr>
<td>Urea clearance % of normal</td>
<td>80-100</td>
<td>40-70</td>
<td>25-40</td>
<td>10-25</td>
</tr>
<tr>
<td>Dosage - Unit Dose of Colistin Link, mg</td>
<td>100-150</td>
<td>75-115</td>
<td>66-150</td>
<td>100-150</td>
</tr>
<tr>
<td>Frequency, times per day</td>
<td>3 or 2</td>
<td>2</td>
<td>2 or 1</td>
<td>every 36 hrs</td>
</tr>
<tr>
<td>Total daily dose, mg</td>
<td>300</td>
<td>150-230</td>
<td>133-150</td>
<td>100</td>
</tr>
<tr>
<td>Approx dose level, mg/kg/day</td>
<td>5.0</td>
<td>2.5-3.8</td>
<td>2.5</td>
<td>1.5</td>
</tr>
</tbody>
</table>

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.

**Overdosage**

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia) or 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.

**Presentation and Storage Conditions**

Injection: 150 mg colistin (as colistimethate sodium); powder

Colistin Link 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 colistin in 2 mL equivalent to 4,500,000 IU.

**Storage Conditions**

Store below 25°C

**Storage Conditions - Reconstituted Solution**

Store 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.
Medicine Schedule

Prescription medicine.

Package Quantities

Injection, 150 mg, 1s.

Sponsor Details

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AUST R 14667

Date of Preparation

18 September 2015