PRODUCT INFORMATION

Colistin Link

Colistin 150 mg/2 mL (as colistimethate sodium) powder for injection vial

For Intramuscular and Intravenous use.

NAME OF THE MEDICINE

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}.

CAS Number: 8068-28-8

DESCRIPTION

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.

PHARMACOLOGY

Microbiology

Colistimethate sodium 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 colistimethate sodium 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.

**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**

Colistimethate sodium 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 sodium has proven clinically effective in the 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, colistimethate sodium may be used to initiate therapy in serious infections that are suspected to be due to gram-negative organisms.

**CONTRAINDICATIONS**

The use of colistimethate sodium 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 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. 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 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 advanced age should be considered.

When actual renal impairment is present, colistimethate sodium 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 colistimethate sodium 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 colistimethate sodium 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 drug in women of child-bearing potential.

**INTERACTIONS WITH OTHER MEDICINES**
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 colistimethate sodium 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 colistimethate sodium.

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 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 been generally due to failure to follow recommended guidelines, usually overdosage, 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-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 colistimethate sodium at dose levels of 1.6-5 mg/kg per day. The BUN values returned to normal following cessation of colistimethate sodium administration.

Paresthesia, tingling of the extremities or tingling of the tongue and generalised itching or urticaria have been reported by patients who received colistimethate sodium 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 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 colistin in 2 mL.

During reconstitution swirl gently to avoid frothing.

Dosage-Adults and children-intravenous or intramuscular administration
Colistin Link 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 for Adults with Impaired Renal Function

<table>
<thead>
<tr>
<th>Renal Function</th>
<th>Degree of Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>Plasma Creatinine, mg/100 mL</td>
<td>0.7-1.2</td>
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<tr>
<td>Urea clearance % of normal</td>
<td>80-100</td>
</tr>
<tr>
<td>Dosage Unit Dose of Colistin Link, mg</td>
<td>100-150</td>
</tr>
<tr>
<td>Frequency, times/day</td>
<td>4 to 2</td>
</tr>
<tr>
<td>Total daily dose, mg</td>
<td>300</td>
</tr>
<tr>
<td>Approximate daily dose, mg/kg/day</td>
<td>5.0</td>
</tr>
</tbody>
</table>

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 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 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.

**OVERDOSAGE**

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

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

**PRESENTATION AND STORAGE CONDITIONS**

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.

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).

**NAME AND ADDRESS OF THE SPONSOR:**

Link Medical Products Pty. Ltd.
5 Apollo Street
Warriewood, NSW 2102
Australia
AUST R 14667

**POISON SCHEDULE OF THE MEDICINE:**
Schedule 4

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS:**
20 September 1991

**DATE OF MOST RECENT AMENDMENT:**
SRN: 17 May 2013