Colistimethate for Injection, USP

To reduce the development of drug-resistant bacteria and maintain the effectiveness of colistimethate and other antibacterial drugs, colistimethate should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

**INDICATIONS AND USAGE**

Colistimethate for Injection, USP is indicated for the treatment of acute or chronic infections due to susceptible aerobic gram-negative microorganisms in the following sites:

- Pneumonia
- Urinary tract infections
- Peritonitis
- Abdominal infections
- Septicemia
- Skin and skin structure infections
- Bloodstream infections

**CONTRAINDICATIONS**

The use of Colistimethate for Injection, USP should be avoided.

**WARNINGS**

- Maximum daily dose calculated from colistin base activity should not exceed 5 mg/kg/day with normal renal function.
- Transient neurological disturbances may occur. These disturbances are usually self-limited and cease or subside with or without discontinuation of the antibiotic. If nausea, vomiting, or diarrhea occurs, the drug should be discontinued. Appropriate fluid and electrolyte therapy should be instituted as clinically indicated.
- Carcinogenesis, mutagenesis, or impairment of reproductive capacity have not been studied for this agent.
- Hyperkalemia can occur and is probably a dose-related phenomenon. It should be observed with particular care.

**PRECAUTIONS**

- Since Colistimethate for Injection, USP is eliminated mainly by renal excretion, it should be used with caution in patients with impaired renal function. However, if it is necessary to remeasure the drug, dosing should be reduced proportionally to the extent of the impairment.

**OVERDOSAGE**

Nephrotoxicity can occur and is probably a dose-related phenomenon. Therapy need not be discontinued, but such patients should be observed with particular care.

- Respiratory arrest has been reported following intramuscular administration of colistimethate sodium. Therefore, it should be used with caution in patients with impaired renal function.

**PREGNANCY**

- Colistimethate for Injection, USP is a sterile parenteral product and should be used with caution in pregnant women. There are no adequate and well-controlled studies in pregnant women, and it should be used only if clearly necessary.

**NURSING MOTHERS**

- Colistimethate for Injection, USP is excreted in the breast milk of lactating women. Therefore, it should be used with caution in nursing women.

**DRUG INTERACTIONS**

- Colistimethate for Injection, USP does not appear to interact with other antibiotics.

**ADVERSE REACTIONS**

- Transient neurological disturbances may occur. These disturbances are usually self-limited and cease or subside with or without discontinuation of the antibiotic. If nausea, vomiting, or diarrhea occurs, the drug should be discontinued. Appropriate fluid and electrolyte therapy should be instituted as clinically indicated.

**ADDITIONAL INFORMATION**

- Colistimethate for Injection, USP is a sterile aqueous solution of a highly purified, water-soluble derivative of colistin base activity.

**REFERENCES**

- The empirical formula is C\textsubscript{58}H\textsubscript{105}N\textsubscript{16}Na\textsubscript{5}O\textsubscript{28}S\textsubscript{5} and the approximate molecular weight of 1750.
- Each vial contains colistimethate sodium or colistin base activity.
- The use of Colistimethate for Injection, USP is intended for patients with a history of sensitivity to the drug or any of its components.

**CLINICAL PHARMACOLOGY**

- Enterobacter aerogenes, Escherichia coli, Klebsiella pneumoniae.
- Enterococcus, and Pseudomonas aeruginosa.
- Its bactericidal action against these organisms is dose-related, and it is probably a dose-related phenomenon. Therapy need not be discontinued, but such patients should be observed with particular care.

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Colistimethate sodium given intramuscularly during organ transplantation in rabbits at an intramuscular colistimethate sodium concentration of 65 mg/kg resulted in talipes varus in 2.6% and 2.9% of fetuses, respectively. These doses are 36 and 51 times the maximum daily human dose based on mg/m². In addition, colistimethate sodium was teratogenic in rats at an intramuscular concentration of 42 mg/kg. These doses are 25 and 38 times the maximum daily human dose based on mg/m². These observations indicate that colistimethate sodium should be used with caution in patients of all ages, including pregnant and lactating women. Pregnancy Category C. Colistimethate sodium is transferred across the placental barrier in humans, it is secreted in human milk, and it may be excreted in human breast milk. Therefore, colistimethate sodium should be used in pregnant women and mothers of breast-feeding infants with caution. No r e s e a r c h i n p e d i a t r i c p a t i e n t s is recommended.

Geriatric Use
Clinical studies of colistimethate sodium did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection in the elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other therapy. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Pediatric Use
In clinical studies, colistimethate sodium was administered to the pediatric population (infants, children and adolescents). Although adverse reactions to the drug were similar in the adult and pediatric populations, subjective symptoms of toxicity may not be reported by pediatric patients. Therefore, careful monitoring of pediatric patients is recommended.

Information for Patients
Patients should be counseled that antibiotic drugs including Colistimethate for Injection, USP should only be used to treat bacterial infections. They should be advised that treatment with any antibiotic drug does not prevent the spread of viral infections (e.g., the common cold). When Colistimethate for Injection, USP is administered to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Stopping doses of colistimethate sodium before the full course of therapy may (1) decrease the effectiveness of the treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by colistimethate sodium for the same or other antibiotic drugs in the future. Decreased effectiveness of the antibiotic which usually ends when the antibotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop diarrhea (possibly caused by antibiotics that usually end when the antibiotic is discontinued. If this occurs, patients should contact their physicians as soon as possible.

ADVERSE REACTIONS
The following adverse reactions have been reported:

Gastrointestinal: gastritis (gastritis gastrinorrhoea), nausea, vomiting, abdominal pain, diarrhea, anorexia, dyspepsia, constipation, flatulence, colitis (including pseudomembranous colitis), ileus, jaundice, hemolytic anemia, and pancreatitis.

Nervous System: tingling of extremities and tongue, slurred speech, dizziness, vertigo, paresthesia and seizures.

Integumentary: generalized itching, urticaria and rash.

Bone and Joint: Fibula Fracture and pin site irritation.

Laboratory Deviations: increased blood urea nitrogen (BUN), increased creatinine and decreased creatinine clearance.

Respiratory System: respiratory distress and apnea.

Renal System: nephrotoxicity and decreased urine output.

For medical advice about adverse reactions contact your medical professional.

To report SUSPECTED ADVERSE REACTIONS, contact Xellia Pharmaceuticals USA, LLC at 1-855-422-3296 or FDA at 1-800-FDA-1234 or http://www.fda.gov/medwatch.

OVERDOSE
Overdoses with such colistimethate sodium can cause neuromuscular blockade characterized by paresthesia, lethargy, confusion, dizziness, hallucinations, somnolence, slurred speech and disorientation. Respiratory muscle paralysis may lead to apnea, respiratory arrest and death. Overdosage with the drug may also cause acute renal failure due to tubular necrosis, which may require dialysis and increases in serum concentrations of BUN and creatinine, respectively. Adverse Reactions: In any case of overdose, colistimethate sodium therapy should be discontinued and general supportive measures should be utilized. It is unknown whether colistimethate sodium can be removed by hemodialysis or peritoneal dialysis in overdose cases.

DOSEAGE AND ADMINISTRATION
Intramuscular Administration: Prior to injection, USP is supplied in vials containing colistimethate sodium equivalent to 150 mg colistin base activity per vial.

Reconstitution for Intravenous or Intramuscular Administration
The 150 mg vial should be reconstituted with 3 mL Sterile Water for Injection, USP. The reconstituted solution provides colistimethate sodium at a concentration equivalent to 75 mg/mL. colistin base activity.

During reconstitution gently to avoid foaming. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration and use. Because the solutions are clean and clear, if these conditions are observed, the product should not be used.

DOSAGE

Adults

Parenteral Patients - Intravenous or Intramuscular Administration
The dose of Colistimethate for Injection, USP should be 2.5 to 5 mg per kg of body weight in 2 to 4 divided doses every 6 to 8 hours with normal renal function, depending on the severity of the infection. In clinical studies, overdosage should be given on ideal body weight.

To report SUSPECTED ADVERSE REACTIONS, contact Xellia Pharmaceuticals USA, LLC at 1-855-422-3296 or FDA at 1-800-FDA-1234 or http://www.fda.gov/medwatch.

Table 1: Suggested Modification of Dosage Schedule

<table>
<thead>
<tr>
<th>Renal Function</th>
<th>Normal</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily Dose</td>
<td>2.5 mg/kg, given as a single dose</td>
<td>2.5 mg/kg, given as one-half dose over 30 minutes every 12 hours</td>
<td>2.5 mg/kg, given as one-half dose over a period of 3 to 5 minutes every 12 hours</td>
<td>1.5 mg/kg, given as one-half dose every 12 hours</td>
</tr>
</tbody>
</table>

Note: The suggested total daily dose is calculated from colistin base activity.

INTRAABDOMINAL ADMINISTRATION

1. For Intramuscular Injection, administer by deep intramuscular injection into a large muscle mass (such as the gluteal muscles or lateral part of the thigh).

Store reconstituted solution for intramuscular injection in a refrigerator 2° to 6°C (36° to 46°F) or between 20° to 25°C (68° to 77°F), and use within 7 days.

HOW SUPPLIED
Colistimethate for Injection, USP is supplied in vials containing colistimethate sodium equivalent, to 150 mg colistin base activity per vial as a white to slightly yellow lyophilized powder. NDC-7054-023-01: one individual vial. NDC-7054-022-02: six vials per carton. NDC-7054-022-25: two vials per carton. NDC-7054-022-12: three vials per carton.

Store between 20° to 25°C (68° to 77°F). (See USP chapter “Sterile And Sterile-Prepared Products.”) Manufactured by: Xellia Pharmaceuticals USA, LLC

Raleigh, NC 27616

Made in Denmark

Intravenous Administration

For Adults with Impaired Renal Function

Suggested modifications of dosage schedule for patients with renal impairment are presented in Table 1:

<table>
<thead>
<tr>
<th>Renal Function</th>
<th>Normal</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance Value</td>
<td>&gt;80</td>
<td>50-79</td>
<td>30-49</td>
<td>10-29</td>
</tr>
<tr>
<td>Dosage Schedule</td>
<td>2.5 mg/kg, given as a single dose</td>
<td>2.5 mg/kg, given as one-half dose over 30 minutes every 12 hours</td>
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Note: The suggested total daily dose is calculated from colistin base activity.

INTRAABDOMINAL ADMINISTRATION

1. Direct Intraperitoneal Administration - Slowly inject one-half of the total daily dose over a period of 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 Colistimethate for Injection, USP to one of the following: 0.9% NaCl 5% dextrose in 0.5 NaCI 5% dextrose in water 0.5% dextrose in 0.45% NaCI 0.5% dextrose in 0.225% NaCl lactated Ringer's solution 10% inert sugar solution

There are no sufficient data to recommend usage of colistimethate sodium for injection with other drug products other than the above listed infusion solutions.

In a study, the second half of the total daily dose was given slow intravenous infusion, starting 1 to 2 hours after the initial dose, over the next 23 to 24 hours. 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 fluid volume solution infusion containing colistimethate sodium should be freshly prepared and used no longer than 24 hours.