Colistimethate for Injection, USP

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

FOR INTRAMUSCULAR AND INTRAVENOUS USE

DESCRIPTION

Colistimethate for Injection, USP is a sterile parenteral antibiotic product which, when reconstituted (see Reconstitution), is suitable for intramuscular or intravenous administration.

Each vial contains colistimethate sodium or pentasodium colistimethanesulfonate (150 mg colistin base activity). The sodium content is approximately 0.099 mg (0.0043 mEq) of sodium per milligram of colistin.

Colistimethate Sodium, USP is pentasodium [[4-[[3-hydroxy-1-[[1-[[3-(1-hydroxyethyl)-12,15-bis(2-methylpropyl)-2,5,8,11,14,17,20-heptaoxo-6,9,18-tris[2-(sulfonatomethylamino)ethyl]-1,4,7,10,13,16,19-heptazacyclotricos-21-yl]amino]-1-oo-4-sulfonatobenzenamido]butan-2-yl]amino]-1-oxobutan-2-yl]amino]-3-(6-methylfocanoxyamino)-4-oxobuty]methanesulfonate.

Colistimethate Sodium, USP is a polypeptide antibiotic with an approximate molecular weight of 1750. The molecular formula is C₉₅H₁₃₁Na₅O₇₅S₁₀ and the structural formula is represented below:

\[
\text{R} = \text{C} - \text{L-Dba-L-Thr-L-Dba-L-Dbu-L-Dbu-L-Dbu-L-Dbu-L-Dbu-L-Thr-Na}
\]

\[
\text{Dba} = 2,4-diaminobutionic acid; \text{R} = 5-	ext{methylhexyl in colistin A}
\]

Colistimethate for Injection, USP is a white to slightly yellow lyophilized cake. The color of the reconstituted solution is clear colorless to pale yellow and essentially free from particulates.

CLINICAL PHARMACOLOGY

Typical serum and urine levels following a single 150 mg dose of colistimethate for injection IM or IV in normal adult subjects are shown in Figure 1.

![Figure 1](image_url)

Higher serum levels were obtained at 10 minutes following IV administration. Serum concentration declined with a half-life of 2 to 3 hours following either intravenous or intramuscular administration in adults and in the pediatric population, including premature infants.

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.

Microbiology

Colistimethate sodium is a surface active agent which penetrates into and disrupts the bacterial cell membrane. It has been shown to have bactericidal activity against most strains of the following microorganisms, both in vitro and in clinical infections as described in the INDICATIONS AND USAGE section:

- Enterobacter aerogenes, Escherichia coli, Klebsiella pneumonie and Pseudomonas aeroginosa.
- Pseudomonas aeruginosa.
- Proteus morganii.
- Neisseria gonorrhoeae.

Susceptibility Tests

Colistimethate sodium is no longer listed as an antimicrobial for routine testing and reporting by clinical microbiology laboratories.

INDICATIONS AND USAGE

Colistimethate for injection 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 for injection has proven clinically effective in treatment of infections due to the following gram-negative organisms: Enterobacter aerogenes, Escherichia coli, Klebsiella pneumonie and Pseudomonas aeroginosa.

Colistimethate for injection may be used to initiate therapy in serious infections that are suspected to be due to gram-negative organisms and in the treatment of infections due to susceptible gram-negative bacilli.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of colistimethate for injection and other antibacterial drugs, colistimethate for injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

The use of colistimethate for injection is contraindicated for patients with a history of sensitivity to the drug or any of its components.

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 include circulatory paresthesia or numbness, tingling or formation of the extremities, generalized 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.

Nephrotoxicity can occur and is probably a dose-dependent effect of colistimethate sodium. These manifestations of nephrotoxicity are reversible following discontinuation of the antibiotic.

Overdosage can result in renal insufficiency, muscle weakness, and apnea (see OVERDOSAGE section). See PRECAUTIONS, Drug Interactions subsection for use concomitantly with other antibiotics and curariform drugs.

Respiratory arrest has been reported following intramuscular administration of colistimethate sodium. Impaired renal function increases the possibility of apnea and neuromuscular blockade following administration of colistimethate sodium. Therefore, it is important to follow recommended dosing guidelines. See DOSAGE AND ADMINISTRATION section for use in renal impairment.

Colistin sulfate associated diarreae (CDAD) has been reported with use of nearly all antibacterial agents, including colistimethate for injection, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued. Appropriately fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS

General

Since colistimethate for injection 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 for injection 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 for injection 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 recognized, 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 apnea (see OVERDOSAGE section).

Signs indicating the development of impaired renal function include: diminishing urine output, rising BUN and serum creatinine. Treatment with colistimethate for injection should be discontinued immediately if signs of impaired renal function occur. However, if it is necessary to reinstate the drug, dosing should be adjusted accordingly after drug plasma levels have fallen (see DOSAGE AND ADMINISTRATION section).

Prescribing colistimethate for injection in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Drug Interactions

Certain other antibiotics (aminoglycosides and polymyxin) 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 for injection except with the greatest caution.

Curare-like muscle relaxants (e.g., tubocurarine) and other drugs, including ether, suxamethonium, gallamine, decamethonium and sodium citrate, potentiate the neuromuscular blocking effect and should be used with extreme caution in patients being treated with colistimethate for injection.

Sodium cephalothin may enhance the nephrotoxicity of colistimethate for injection. The concomitant use of sodium cephalothin and colistimethate for injection should be avoided.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal carcinogenicity studies and genetic toxicology studies have not been performed with colistimethate sodium. There were no adverse effects on fertility or reproduction in rats at doses of 9.3 mg/kg/day (0.30 times the maximum daily human dose when based on mg/m²).

Pregnancy

Teratogenic Effects- Pregnancy Category C

Colistimethate sodium given intramuscularly during organogenesis to rabbits at 4.15 and 9.3 mg/kg resulted in tailpinus varus in 2.6% and 2.9% of fetuses, respectively. These doses are 0.25 and 0.55 times the maximum daily human dose based on mg/m². In addition, increased resorption occurred at 9.3 mg/kg. Colistimethate sodium was not teratogenic in rats at 4.15 or 9.3 mg/kg. These doses are 0.13 and 0.30 times the maximum daily human dose based on mg/m². There are no adequate and well-controlled studies in pregnant women. Since colistimethate sodium is transferred across the placental barrier in humans, it should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether colistimethate sodium is excreted in human breast milk. However, colistin sulfate is excreted in human breast milk. Therefore, caution should be exercised when colistimethate sodium is administered to nursing women.
Dosage Schedule for Patients with Renal Impairment

<table>
<thead>
<tr>
<th>Degree of Renal Impairment</th>
<th>Normal</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance (mL/min)</td>
<td>120</td>
<td>50-79</td>
<td>30-49</td>
<td>10-29</td>
</tr>
<tr>
<td>Dosage Schedule</td>
<td>2.5 - 5 mg/kg, divided into 2 to 4 doses per day</td>
<td>2.5 - 3.8 mg/kg, divided into 2 doses per day</td>
<td>2.5 mg/kg, once daily or divided into 2 doses per day</td>
<td>1.5 mg/kg every 36 hours</td>
</tr>
</tbody>
</table>

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

### Dosage and Administration

**For 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 colistimethate for injection to one of the following:
   - 0.9% NaCl
   - 5% dextrose in 0.9% NaCl
   - 5% dextrose in water
   - 5% dextrose in 0.45% NaCl
   - 5% dextrose in 0.225% NaCl
   - Lactated Ringer’s solution
   - 10% invert sugar solution

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

Administer the second half of the total daily dose by slow intravenous infusion, starting 1 to 2 hours after the initial dose, over the next 22 to 23 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 final intravenous infusion solution containing colistimethate sodium should be freshly prepared and used for no longer than 4 hours.

**For Intramuscular 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 8°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 follows:

- NDC 25021-159-10
  - 150 mg per vial
  - 1 vial per carton

Colistimethate for Injection, USP is a sterile, pyrogen-free, non-pyrogenic, non-animal-derived, non-sterile, non-pyrogenic product. The container closure is not made with natural rubber latex.

**Storage Conditions**

- Store dry powder at 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F). [See USP Controlled Room Temperature.]

Store reconstituted solution in refrigerator at 2° to 8°C (36° to 46°F) or between 20° to 25°C (68° to 77°F) and use within 7 days.

Sterile, Nonpyrogenic, Preservative-free.

**Mfd.: SAGENT Pharmaceuticals Schaumburg, IL 60195 (USA) Made in India ©2013 SAGENT Pharmaceuticals, Inc. December 2013**

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

### Phlebitis Prevention

- Allow the entire dose to infuse. Do not continue the infusion if phlebitis is observed.
- Avoid extravasation. If extravasation occurs, discontinue the infusion, and apply local cold compresses. If signs of tissue necrosis occur, consult a physician.

### Other Considerations

- A decrease in the glomerular filtration rate of renal function adjusted dose may be needed for 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.

### Patient Information

- In obese individuals, dosage should be based on ideal body weight.
- The daily dose and frequency should be reduced for the patients with renal impairment. Suggested modifications of dosage schedule for patients with renal impairment are presented in Table 1.

### Dosage Schedule

<table>
<thead>
<tr>
<th>Degree of Renal Impairment</th>
<th>Normal</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance (mL/min)</td>
<td>120</td>
<td>50-79</td>
<td>30-49</td>
<td>10-29</td>
</tr>
<tr>
<td>Dosage Schedule</td>
<td>2.5 - 5 mg/kg, divided into 2 to 4 doses per day</td>
<td>2.5 - 3.8 mg/kg, divided into 2 doses per day</td>
<td>2.5 mg/kg, once daily or divided into 2 doses per day</td>
<td>1.5 mg/kg every 36 hours</td>
</tr>
</tbody>
</table>

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