**INDICATIONS AND USAGE**

Colistimethate for injection is indicated for the treatment of acute or chronic infections due to susceptible gram-negative bacilli. It is particularly indicated when the infection is caused by sensitive strains of certain gram-negative bacilli. It is particularly indicated when the infection is caused by sensitive strains of *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*.

**DOSAGE AND ADMINISTRATION**

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.

**FOR INTRAMUSCULAR AND INTRAOPERATIVE 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).

Colistimethate sodium is a polypeptide antibiotic with an approximate molecular weight of 1750. The empirical formula is C₁₅₈H₂₁₅N₃₆Na₅O₃₈S₅ and the structural formula is represented below:

\[
\text{CH}_2 \text{ONa} \quad \text{CH}_2 \quad \text{ONa} \quad \text{CH}_2 \quad \text{ONa} \quad \text{CH}_2 \quad \text{ONa} \quad \text{CH}_2 \quad \text{ONa}
\]

Typical serum and urine levels following a single 150 mg dose of colistimethate for injection IM were 0.1 to 2.0 mcg/mL and 0.2 to 6.0 mcg/mL, respectively. The highest serum and urine levels following IM administration in adults and in the pediatric population, including premature infants, were 2.0 mcg/mL and 6.0 mcg/mL, respectively.

Average urine levels ranged from about 270 mcg/mL at 2 hours to about 15 mcg/mL at 8 hours after intramuscular administration and from 200 to about 25 mcg/mL during a similar period following intravenous 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:

- Aerobic gram-negative microorganisms: Enterobacter aerogenes, Escherichia coli, Klebsiella pneumoniae and *Pseudomonas aeruginosa*.

**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 the treatment of infections due to the following gram-negative organisms:

- *Escherichia coli*,
- *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*.

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 pathogenic bacilli.

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 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.

Transplant neurological disturbances may occur. These include circulatory paresthesia or numbness, tingling or formation of the extraneurites, 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 OVERDOSE 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 colistimethane sulfonate and colistimethane sodium. Colistimethate for injection should be used with caution in all patients who present 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. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

**PRECAUTIONS**

General

Since colistimethate 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 OVERDOSE section). Signs indicating the development of impaired renal function include: diminishing urine output, rising BUN and serum creatinine and decreased creatinine clearance. Therapy 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 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 colistimethate for injection. Based on this reported activity, they should not be given concomitantly with colistimethate for injection except with the greatest caution.

Curariform muscle relaxants (e.g., succinylcholine), curare-like drugs, including ether, curare-like drugs, and certain other antibiotics (aminoglycosides and polymyxin) have also been reported to interfere with colistimethate for injection. Based on this reported activity, they should not be given concomitantly with colistimethate for injection except with the greatest caution.

Certain other antibiotics (aminoglycosides and polymyxin) have also been reported to interfere with colistimethate for injection. Based on this reported activity, they should not be given concomitantly with colistimethate for injection except with the greatest caution.

Certain other antibiotics (aminoglycosides and polymyxin) have also been reported to interfere with colistimethate for injection. Based on this reported activity, they should not be given concomitantly with colistimethate for injection except with the greatest caution.

**Sodium cephalothin may enhance the nephrotoxicity of colistimethate for injection. The interference of nerve transmission at neuromuscular junctions may occur and result in muscle weakness and apnea (see OVERDOSE section).**

**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 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 talipes 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 doses of 9.3 mg/kg/day. These doses are 0.3 and 0.3 times the maximum daily human dose based on mg/m². There are no adequate and well-controlled studies in pregnant women. 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).

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

**Nursing Mothers**

It is not known whether colistimethate sodium is excreted in human breast milk. However, colistin sulphate is excreted in human breast milk. Therefore, caution should be exercised when colistimethate sodium is administered to nursing women.
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. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dosage selection for an 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 drug 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 (neonates, infants, children and adolescents). Although adverse reactions appear to be similar in the adult and pediatric populations, subjective symptoms of toxicity may not be reported by pediatric patients. Close clinical monitoring of pediatric patients is recommended.

Patients should be counseled that antibacterial drugs including colistimethate should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When colistimethate is prescribed 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. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by colistimethate or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery andbloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

ADVERSE REACTIONS
The following adverse reactions have been reported:

Gastrointestinal: gastrointestinal upset
Nervous System: tingling of extremities and tongue, slurred speech, dizziness, vertigo and paresthesia
Integumentary: generalized itching, urticaria and rash
Body as a Whole: fever
Laboratory Deviations: increased blood urea nitrogen (BUN), elevated creatinine and decreased creatinine clearance
Respiratory System: respiratory distress and apnea
Renal System: nephrotxicity and decreased urine output

For medical advice about adverse reactions contact your medical professional. To report SUSPECTED ADVERSE REACTIONS, contact JHP at 1-866-923-2547 or MEDWATCH at 1-888-FDA-1088 (1-800-332-1088) or http://www.fda.gov/medwatch/.

OVERDOSAGE
Overdosage with colistimethate sodium can cause neuromuscular blockade characterized by paresthesia, lethargy, confusion, dizziness, ataxia, nystagmus, disorders of speech and apnea. Respiratory muscle paralysis may lead to apnea, respiratory arrest and death. Overdosage with the drug can also cause acute renal failure, manifested as decreased urine output and increases in serum concentrations of BUN and creatinine.

As 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

Important: Colistimethate for injection 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 2 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 swirl gently to avoid frothing.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Whenever solution and container permit. If these conditions are observed, the product should not be used.

Dosage

Adults and Pediatric Patients—Intravenous or Intramuscular Administration: The dose of Colistimethate for injection should be 2.5 to 5 mg/kg per day of colistin base in 2 to 4 divided doses for patients with normal renal function, depending on the severity of the infection.

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.