Colistimethate for Injection, USP contains the sodium salt of colistimethate which is a polypeptide antibiotic with an approximate molecular weight of 1750. The empirical formula is C_{58}H_{105}N_{16}O_{28}Na_{5}S_{5}. Colistimethate for Injection, USP has bactericidal activity against many gram-negative bacilli.

INDICATIONS
Colistimethate for Injection, USP should be considered for the treatment of severe acute or resistant chronic infections due to colistin sensitive strains of gram-negative pathogenic bacilli. It is particularly indicated when the infection is caused by sensitive strains of *Pseudomonas aeruginosa*. Colistimethate for Injection, USP has been clinically effective in the treatment of some infections due to the following gram-negative organisms: *Aerobacter aerogenes, Escherichia coli, Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. This antibiotic is not indicated for infections due to Proteus or Neisseria organisms.

DOSAGE AND ADMINISTRATION
Colistimethate for Injection, USP should be given intravenously or intramuscularly in 2 to 4 divided doses at dose levels of 2.5 to 5.0 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 patient history. Suggested modifications of dose in cases of renal impairment are given in the following table:

<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 creatine (mg/100 mL)</td>
<td>0.7 – 1.2</td>
</tr>
<tr>
<td>Urea clearance % of normal</td>
<td>80 - 100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DOSAGE</th>
<th>DEGREE OF IMPAIRMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>Unit dose of Colistimethate for Injection, USP</td>
<td>100 – 150</td>
</tr>
<tr>
<td>Frequency times per day</td>
<td>4 or 2</td>
</tr>
<tr>
<td>Total daily dose, mg</td>
<td>300</td>
</tr>
<tr>
<td>---------------------</td>
<td>-----</td>
</tr>
<tr>
<td>Approximate dose level, mg/kg</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Note:
The suggested unit dose is 2.5 – 5.0 mg/kg. However, the time INTERVAL between injections should be increased in the presence of impaired renal function.

PREPARATION
The Colistimethate for Injection, USP vial should be reconstituted with 2 mL Sterile Water for Injection, USP. The reconstituted solution provides colistimethate sodium equivalent to 75 mg colistin base per mL. During reconstitution swirl gently to avoid frothing.

After reconstitution, Colistimethate for Injection, USP should be kept in a cool place and should be used within 24 hours.

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, USP to one of the following: 0.9% NaCl Injection; 5% Dextrose and 0.9% NaCl Injection; 5% Dextrose Injection; 5% Dextrose and 0.45% NaCl Injection; 5% Dextrose and 0.225% NaCl Injection; Lactated Ringer’s Injection, or 10% Invert Sugar Injection. There are not sufficient data to recommend usage of Colistimethate for Injection, USP with other drugs or with 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.
CONTRAINDICATIONS
The use of Colistimethate for Injection, USP is contraindicated for patients with a history of sensitivity to colistin.

PRECAUTIONS
Colistimethate for injection is eliminated from the body chiefly via the kidney. It should be used with caution where there is a possibility of impaired renal function. For example, the decline in renal function with advanced age should be considered.

When actual renal impairment is present, Colistimethate for Injection, USP 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 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 and anuria. If the development of impaired renal function is indicated by diminishing urine output, rising BUN and/or rising serum creatinine, therapy with Colistimethate for Injection, USP should be discontinued immediately. Depending on the clinical situation, therapy may be instituted later at a lower dosage level.

The following antibiotic have been reported to produce several potentially serious toxic effects in common with colistimethate for injection and should not be used concomitantly except with great caution; kanamycin, streptomycin, dihydrostreptomycin, neomycin and polymyxin B sulphate.

WARNING
Colistimethate for Injection, USP should be administered to patients under close supervision by a physician, or to hospitalized patients where medically qualified personnel are on duty at all times. The safety of colistimethate for injection during human pregnancy has not been established.

ADVERSE REACTIONS
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. This has been generally due to failure to follow recommended guidelines, usually over-dosage, 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 for injection. These manifestations of nephrotoxicity are reversible if the drug is discontinued.
Increases in blood urea nitrogen have been reported for patients receiving colistimethate for injection at dose levels of 1.6 – 5.0 mg/kg per day. The BUN value returned to normal following cessation of colistimethate for injection administration.

Paraesthesia, tingling of the extremities or of the tongue and generalized itching or urticaria have been reported by patients who received colistimethate for injection by intravenous or intramuscular injection. In addition, the following adverse reactions have been reported for colistimethate for injection: drug fever and gastrointestinal upset, vertigo, and slurring of speech. The subjective symptoms reported by adults may not be manifest in infants or young children, thus requiring close attention to the renal function.

**REPORTING SUSPECTED SIDE EFFECTS**

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

**NOTE**: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

**AVAILABILITY OF DOSAGE FORMS**

Colistimethate for Injection, USP is supplied in vials containing colistimethate sodium equivalent to 150 mg colistin base activity per vial.

**STABILITY AND STORAGE RECOMMENDATIONS**

Colistimethate for Injection, USP in powder form should be stored at controlled room temperature (15 - 30°C).

**PHARMACEUTICAL PARTNERS OF CANADA INC.**

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