PRESCRIBING INFORMATION

[Pr]Colistimethate for Injection, USP

(colistimethate sodium)

Powder for Solution

(equivalent to 150 mg colistin base)

Antibacterial Antibiotic

SteriMax Inc.
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March 22, 2016

Colistimethate for Injection U.S.P. contains the sodium salt of colistimethate which is a polypeptide antibiotic with an approximate molecular weight of 1750. The empirical formula is $C_{58}H_{105}N_{16}O_{28}Na_5S_5$. Colistimethate for Injection U.S.P. has bacterial activity against many gram-negative bacilli.

INDICATIONS

Colistimethate for Injection U.S.P. 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 U.S.P. 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 U.S.P. 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 modification of dose in cases of renal impairment are given in the following table:

SUGGESTED MODIFICATION OF DOSAGE SCHEDULES OF COLISTIMETHATE FOR INJECTION U.S.P. FOR ADULTS WITH IMPAIRED RENAL FUNCTION

RENAL FUNCTION	**DEGREE OF IMPAIRMENT**			
	Normal	**Mild**	**Moderate**	**Considerable**
Plasma creatine (mg/100 mL)	0.7-1.2	1.3-1.5	1.6-2.5	2.6-4.0
Urea clearance % of normal	80-100	40-70	25-40	10-25
DOSAGE	**DEGREE OF IMPAIRMENT**			
	Normal	**Mild**	**Moderate**	**Considerable**
Unit dose of Colistimethate for Injection U.S.P.	100-150	75-115	66-150	100-150
Frequency times per day	4 or 2	2	2 or 1	Every 36 hrs
Total daily dose, mg	300	150-230	133-150	100
Approximate dose level mg/kg	5.0	2.5-3.8	2.5	1.5

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

After reconstitution, Colistimethate for Injection U.S.P. 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 U.S.P. 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, or 10% invert sugar solution. There are not sufficient data to recommend usage of Colistimethate for Injection U.S.P. 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 requirement 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 U.S.P. is contraindicated for patients with a history of sensitivity to colistin.

PRECAUTIONS

Colistimethate for Injection U.S.P. 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 U.S.P. 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 U.S.P. 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 creatine, therapy with Colistimethate for Injection U.S.P. should be discontinued immediately. Depending on the clinical situation, therapy may be instituted later at a lower dosage level.

The following antibiotics have been reported to produce several potentially serious toxic effects in common with Colistimethate for Injection U.S.P. and should not be used concomitantly except with great caution: Kanamycin, streptomycin, dihydrostreptomycin, neomycin and polymyxin B sulphate.

WARNINGS

Colistimethate for Injection U.S.P. 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 U.S.P. during human pregnancy has not been established.

ADVERSE REACTIONS

Respiratory arrest has been reported following intramuscular administration of sodium colistimethate. Impaired renal function increases the possibility of apnea and neuromuscular blockade following administration of sodium colistimethate. 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 U.S.P. 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 U.S.P. at dose levels of 1.6-5.0 mg/kg per day. The BUN value returned to normal following cessation of Colistimethate for Injection U.S.P. 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 U.S.P. by intravenous or intramuscular injection. In addition, the

following adverse reactions have been reported for Colistimethate for Injection U.S.P.: 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.

HOW SUPPLIED

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

How to store

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