Colistin Hikma®

Colistimethate Sodium

ACTION

Colistimethate sodium is a cyclic polypeptide antibiotic derived from Bacillus polymyxa var. colistinus and belongs to the polymyxin group. The polymyxin antibiotics are cationic agents that work by damaging the cell membrane. The resulting physiological effects are lethal to the bacterium. Polymyxins are selective for Gram-negative bacteria that have a hydrophobic outer membrane.

INDICATIONS

Colistin Hikma is indicated in the treatment of the following infections where sensitivity testing suggests that they are caused by susceptible bacteria:

- Treatment by intravenous administration of some serious infections caused by Gram-negative bacteria, including those of the lower respiratory tract and urinary tract, when more commonly used systemic antibacterial agents may be contra-indicated or may be ineffective because of bacterial resistance (nosocomial infections).
- Treatment by inhalation of lung infection, caused by Pseudomonas aeruginosa, in patients with cystic fibrosis (CF).

DOSAGE AND ADMINISTRATION

Posology

Systemic Treatment:

Colistin Hikma can be given as a 50ml intravenous infusion over a period of 30 minutes. Patients with a totally implantable venous access device (TIVAD) in place may tolerate a bolus injection of up to 2 million units in 10ml given over a minimum of 5 minutes.

The dose is determined by the severity and type of infection and the age, weight and renal function of the patient. Should clinical or bacteriological response be slow the dose may be increased as indicated by the patient's condition. Serum level estimations are recommended especially in renal impairment, neonates and cystic fibrosis patients. Levels of 10–15 mg/l (approximately 125-200 units/ml) colistimethate sodium should be adequate for most infections.

A minimum of 5 days treatment is generally recommended. For the treatment of respiratory exacerbations in cystic fibrosis patients, treatment should be continued for up to 12 days.

Children and adults (including the elderly):

Up to 60 kg: 50,000 units/kg/day to a maximum of 75,000 units/kg/day. The total daily dose should be divided into three doses given at approximately 8-hour intervals.

Over 60 kg: 1-2 million units three times a day. The maximum dose is 6 million units in 24 hours.

Anomalous distribution in patients with cystic fibrosis may require higher doses in order to maintain therapeutic serum levels.

Renal impairment:

In moderate to severe renal impairment, excretion of colistimethate sodium is delayed. Therefore, the dose and dose interval should be adjusted in order to prevent accumulation. The table below is a guide to dose regimen modifications in patients of 60kg bodyweight or greater. It is emphasized that further adjustments may have to be made based on blood levels and evidence of toxicity.

Suggested Dosage Adjustment in Renal Impairment

Grade	Creatinine clearance (ml/min)	Over 60kg body weight
Mild	20-50	1-2 million units every 8hr
Moderate	10-20	1 million units every 12-18 hr
Severe	<10	1 million units every 18-24 hr

Aerosol Inhalation:

For local treatment of lower respiratory tract infections Colistin Hikma powder is dissolved in 2-4 ml of water for injections or 0.9% sodium chloride intravenous infusion for use in a nebuliser attached to an air/oxygen supply.

In small, uncontrolled clinical trials, doses of from 500,000 units twice daily up to 2 million units three times daily have been found to be safe and effective in patients with cystic fibrosis.

The following recommended doses are for guidance only and should be adjusted according to clinical response:

Children <2 years: 500,000-1 million units twice daily

Children >2 years and adults: 1-2 million units twice daily

The solution should be used immediately after reconstitution. Reconstituted solution could be slightly cloudy and foamy if stirred.

Method of administration

For instructions on reconstitution and/or dilution of the medicinal product before administration.

CONTRAINDICATIONS

- Hypersensitivity to colistimethate sodium (colistin) or to polymyxin B.
- Patients with myasthenia gravis, since colistimethate sodium reduces the amount of acetylcholine released at the neuromuscular presynaptic junction.

WARNINGS AND PRECAUTIONS

Use with extreme caution in patients with porphyria.

Nephrotoxicity or neurotoxicity may occur if the recommended parenteral dose is exceeded.

Use with caution in renal impairment. It is advisable to assess baseline renal function and to monitor during treatment. Serum colistimethate sodium concentrations should be monitored.

Bronchospasm may occur on inhalation of antibiotics. This may be prevented or treated with appropriate use of beta2-agonists. If troublesome, treatment should be withdrawn.

Drug Interactions

- Concomitant use of colistimethate sodium with other medicinal products of neurotoxic and/or nephrotoxic potential should be avoided. These include the aminoglycoside antibiotics such as gentamicin, amikacin, netilmicin and tobramycin. There may be an increased risk of nephrotoxicity if given concomitantly with cephalosporin antibiotics.
- Neuromuscular blocking drugs and ether should be used with extreme caution in patients receiving colistimethate sodium.

Fertility, Pregnancy and Lactation

Pregnancy category C.

There are no adequate data from the use of colistimethate sodium in pregnant women. Single dose studies in human pregnancy show that colistimethate sodium crosses the placental barrier and there may be a risk of foetal toxicity if repeated doses are given to pregnant patients.

Animal studies are insufficient with respect to the effect of colistimethate sodium on reproduction and development. Colistimethate sodium should be used in pregnancy only if the benefit to the mother outweighs the potential risk to the fetus.

Colistimethate sodium is secreted in breast milk. Colistimethate sodium should be administered to breastfeeding women only when clearly needed.

Effects on Ability to Drive and Use Machines:

During parenteral treatment with colistimethate sodium neurotoxicity may occur with the possibility of dizziness, confusion or visual disturbance. Patients should be warned not to drive or operate machinery if these effects occur.

SIDE EFFECTS

Frequency convention: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000), Not known (cannot be estimated from the available data).

System organ class	Systemic Treatment	Inhalation Treatment
Infections and infestations		Not known (cannot be calculated from the available data): Sores in the mouth or throat have been reported and may be due to infection by Candida spp. or hypersensitive.
Psychiatric disorders	Rare (≥ 1/10.000, <1/1.000): confusion, psychotic.	
Nervous system disorders	Very common (≥ 1/10): neurological effects (cystic fibrosis). Rare (≥ 1/10.000, <1/1.000): slowing of speech. vasomotor instability. Not known (cannot be estimated from available data): disorders sensory transient paresthesia as facial vertigo.	
Eye disorders	Rare (≥ 1/10.000, <1/1.000): blurred vision.	
Respiratory, thoracic and mediastinal disorders	Not known (cannot be estimated from available data): apnea.	Not known (cannot be calculated from the available data): Nebulization may induce bronchospasm or cough.
Skin and subcutaneous tissue disorders	Not known (cannot be estimated from available data): reactions hypersensitivity reactions including rash.	Not known (cannot be estimated from available data): reactions hypersensitivity reactions including rash.
Renal and urinary disorders	Very common (≥ 1/10): nephrotoxicity (without CF). Uncommon (≥ 1/1.000, <1/100): nephrotoxicity (cystic fibrosis). Not known (cannot be estimated from available data): decreased urine output, increased concentrations of urea and creatinine, proteinuria, hematuria, detection of urinary casts, acute tubular necrosis	
General disorders and administration site conditions	Not known (cannot be estimated from available data): local irritation at the injection site.	

Pediatric population
The available information suggests that the safety profile of the treatment of pediatric patients with Colistin, is not different from that observed in adult patients.

OVERDOSE
Overdose can result in neuromuscular blockade that can lead to muscular weakness, apnoea and possible respiratory arrest. Overdose can also cause acute renal failure characterised by decreased urine output and increased serum concentrations of BUN and creatinine.
There is no specific antidote, manage by supportive treatment. Measures to increase the rate of elimination of colistin e.g. mannitol diuresis, prolonged haemodialysis or peritoneal dialysis may be tried, but effectiveness is unknown.
Incompatabilities:
Mixed infusions, injections and nebuliser solutions involving colistimethate sodium should be avoided.
Special Precautions for Handling:
Parenteral administration:
The normal adult dose of 2 million units should be dissolved in 10-50ml of 0.9% sodium chloride intravenous infusion or water for injections to form a clear solution. The solution is for single use only and any remaining solution should be discarded.
Inhalation:
The required amount of powder is dissolved preferably in 2-4ml 0.9% sodium chloride solution and poured into the nebuliser. Alternatively, water for injections may be used. The solution will be slightly hazy and may froth if shaken. Usually jet or ultrasonic nebulisers are preferred for antibiotic delivery. These should produce the majority of their output in the respirable particle diameter range of 0.5-5.0 microns when used with a suitable compressor. The instructions of the manufacturers should be followed for the operation and care of the nebuliser and compressor. The output from the nebuliser may be vented to the open air or a filter may be fitted. Nebulisation should take place in a well ventilated room.
The solution is for single use only and any remaining solution should be discarded.

STORAGE
Store below 30°C. Keep the vials in the outer carton in order to protect from light.
Special Precautions for Storage:
Reconstituted solutions
Solutions for injection or infusion:
Solutions should be used immediately.
Solutions for nebulisation
Solutions for nebulisation have similar in-use stability and should be treated as above. Patients self-treating with nebulised antibiotic should be advised to use solutions immediately after preparation.

PRESENTATIONS
Vials
Colistin Hikma: Colistimethate sodium 1 Million International Unit
Excipients: Water for Injection

Council of Arab Health Ministers, Union of Arab Pharmacists

THIS IS A MEDICAMENT

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous.
- Follow the doctor's prescription strictly, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Manufactured by:
Hikma Italy, SpA, Italy
For: Hikma Pharmaceuticals, Amman-Jordan

hikma.

Keep medicament out of the reach of children
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Dimenions:
140x300 mm

Pantone. 2766