**XELCOL**
**(1 MIU of Colistimethate Sodium Powder for Solution For injection or infusion or inhalation)**

## 1. NAME OF THE MEDICINAL PRODUCT

XELCOL 1 MIU Powder for Solution For injection or infusion or inhalation

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1 million international units (IU) which is approximately equivalent to 80 mg of colistimethate sodium.

## 3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion or inhalation.

The powder is white to almost white powder dispensed in colourless vials with red-flip-off-caps.

After reconstitution: Reconstitution vial to obtain the required dose by adding an appropriate volume of water for injection or 0.9% sodium chloride solution not exceeding 10 mL per vial. Clear solution of colistimethate sodium free from visible particles is obtained.

The product is clear solution after further dilution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

Treatment by inhalation of *Pseudomonas aeruginosa* lung infection in patients with cystic fibrosis (CF). Intravenous administration for the treatment 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.

### 4.2 Posology and method of administration

*Systemic Treatment*
Xelcol can be given as a 50 ml 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 10 ml 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 up to 12 days.

*Children and adults (including 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 dose 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 60 kg bodyweight or greater. It is emphasised 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 8 hours |
| Moderate | 10-20 | 1 million units every 12 – 18 hours |
| Severe | <10 | 1 million units every 18-24 hours |

*Aerosol Inhalation*

For local treatment of lower respiratory tract infections Xelcol is dissolved in 2 - 4ml of water for injections or 0.9% sodium chloride 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.

Route of Administrations
Parenteral administration : intravenous infusion
Inhalation : nebulizer

## 4.3 Contraindications

Hypersensitivity to colistimethate sodium (colistin) or to polymyxin B. Patients with myasthenia gravis.

## 4.4 Special warnings and precautions for use

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.

Few cases of pseudo-Bartter syndrome have been reported in children and adults with the intravenous use of colistimethate sodium. Monitoring of serum electrolytes should be started in suspected cases and appropriate management should be implemented; however, normalisation of electrolyte imbalance might not be achieved without discontinuation of colistimethate sodium.

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.

## 4.5 Interaction with other medicinal products and other forms of interaction

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.

## 4.6 Fertility, pregnancy and lactation

Pregnancy
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 fetal 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 risks to the fetus.

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

## 4.7 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 disturbances. Patients should be warned not to drive or operate machinery if these effects occur.

## 4.8 Undesirable effects

Systemic Treatment
The likelihood of adverse events may be related to the age, renal function, and condition of the patient. In cystic fibrosis patients, neurological events have been reported in up to 27% of patients. These are generally mild and resolve during or shortly after treatment.

Neurotoxicity may be associated with overdose, failure to reduce the dose in patients with renal insufficiency and concomitant use of either neuromuscular blocking drugs or other drugs with similar neurological effects. Reducing the dose may alleviate symptoms. Effects may include apnoea, transient sensory disturbances (such as facial paraesthesia and vertigo) and rarely, vasomotor instability, slurred speech, visual disturbances, confusion, or psychosis.

Adverse effects on renal function have been reported, usually following use of higher than recommended doses in patients with normal renal function, or failure to reduce the dosage in patients with renal impairment or during concomitant use of other nephrotoxic drugs. The effects are usually reversible on discontinuation of therapy.

Pseudo-Bartter syndrome has been reported after intravenous administration of colistimethate sodium with unknown frequency.

In cystic fibrosis patients treated within the recommended dosage limits, nephrotoxicity appears to be rare (less than 1%). In seriously ill hospitalised non-CF patients, signs of nephrotoxicity have been reported in approximately 20% of patients.

Hypersensitivity reactions including skin rash and drug fever have been reported. If these occur treatment should be withdrawn.

Local irritation at the site of injection may occur.

Inhalation treatment

Inhalation may induce coughing or bronchospasm.

Sore throat or mouth has been reported and may be due to Candida albicans infection or hypersensitivity.

Skin rash may also indicate hypersensitivity, if this occurs treatment should be withdrawn.

### 4.9 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 characterized 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.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, Other antibacterials

Mechanism of action
Colistin is a cyclic polypeptides antibacterial agent belonging to the polymyxin group. Polymyxins work by damaging the cell membrane and the resulting physiological effects are lethal to the bacterium. Polymyxins are selective for aerobic gram-negative bacterial that have a hydrophobic outer membrane.

Resistance
Resistant bacteria are characterised by modification of the phosphate groups of lipopolysaccharides, which become substituted with ethanolamine or amino arabinose. Naturally resistant Gram-negative bacteria, such as *Proteus mirabilis* and *Burkholderia cepacian*, show complete substitution of their lipid phosphate by ethanolamine or amino arabinose.

Cross resistance
Cross resistance between colistimethate sodium and polymyxin B would be expected. Since the mechanism of action of the polymyxin is different from that of other antibiotics, resistance to colistin and polymyxin by the above mechanism alone would not be expected to result in resistance to other drug classes.

Breakpoint
The suggested general MIC breakpoint to identify bacterial susceptible to colistimethate sodium is $\leq 4$ mg/L. Bacteria for which the MIC of colistimethate sodium is $\geq 8$ mg/L should be considered resistant.

Susceptibility
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent, in at least some types of infections, is questionable.

*Commonly susceptible species*
*Acinetobacter baumannii**
*Citrobacter* species
*Escherichia coli*
*Haemophilus influenzae*
*Pseudomonas aeruginosa.*

*Species for which acquired resistance may be a problem*
*Enterobacter* species
*Klebsiella* species

*Inherently resistant organisms*
*Brucella* species
*Burkholderia capacia* and related species
*Neisseria* species
*Proteus* species
*Providencia* species
*Serratia* species
Anaerobes
All gram positive organisms
*In-vitro results may not correlate with clinical responses in the case of *Acinetobacter* spp.

## 5.2 Pharmacokinetic properties

Absorption
Absorption from the gastrointestinal tract does not occur to any appreciable extent in the normal individual. When given by nebulisation, variable absorption has been reported that may depend on the aerosol particle size, nebuliser system and lung status. Studies in healthy volunteers and patients with various infections have reported serum levels from nil to potentially therapeutic concentrations of 4 mg/l or more. Therefore, the possibility of systemic absorption should always be borne in mind when treating patients by inhalation.

Distribution
After the administration to patients with cystic fibrosis of 75 mg/kg/day in divided doses given as 30 min intravenous infusions to steady state the Cmax was determined to be 23±6 mg/l and Cmin at 8 h was 4.5±4 mg/l. In another study in similar patients given 2 million units every 8 hours for 12 days the Cmax was 12.9 mg/l (5.7-29.6 mg/l) and the Cmin was 2.76 mg/l (1.0-6.2 mg/l). In healthy volunteers given a bolus injection of 150 mg (2 million units approx.) peak serum levels of 18 mg/l were observed 10 minutes after injection. Protein binding is low. Polymyxins persist in the liver, kidney, brain, heart and muscle. One study in cystic fibrosis patients gives the steady state volume of distribution as 0.09 L /kg.

Biotransformation
Colistimethate sodium is converted to the base *in vivo*. As 80% of the dose can be recovered unchanged in the urine, and there is no biliary excretion, it can be assumed that the remaining drug is inactivated in the tissues. The mechanism is unknown.

Elimination
The main route of elimination after parenteral administration is by renal excretion with 40% of a parenteral dose recovered in the urine within 8 hours and around 80% in 24 hours. Because

colistimethate sodium is largely excreted in the urine, dose reduction is required in renal impairment to prevent accumulation. After intravenous administration to healthy adults the elimination half-life is around 1.5 hrs. In a study in cystic fibrosis patients given a single 30-minute intravenous infusion the elimination half-life was 3.4±1.4 hrs. The elimination of colistimethate sodium following inhalation has not been studied. A study in cystic fibrosis patients failed to detect any colistimethate sodium in the urine after 1 million units were inhaled twice daily for 3 months.

Colistimethate sodium kinetics appear to be similar in children and adults, including the elderly, provided renal function is normal. Limited data are available on use in neonates which suggest kinetics are similar to children and adults but the possibility of higher peak serum levels and prolonged half-life in these patients should be considered and serum levels monitored.

### 5.3 Preclinical safety data

None.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

None.

### 6.2 Incompatibilities

Mixed infusions, injections and nebuliser solutions involving colistimethate sodium should be avoided.

### 6.3 Shelf life

Unopened:
3 years

After Reconstitution:
Solutions should be used immediately.

Reconstituted vials stored at 2°C to 8°C and used within 24 hours of storage.

The solution is for single use only and any remaining solution should be discarded.

From a microbiological view, solutions should be used immediately. If not used immediately in-use storage times and conditions prior to use are the responsibility of the user. They would normally be no longer than 24 hours at 2 to 8°C, unless reconstituted under controlled and validated aseptic conditions.

### 6.4 Special precautions for storage

Unopened container: Store below 30°C and protect from sunlight.

After reconstitution
Solution for Infusion or IV injection
Solutions should be used immediately.

Reconstituted vials stored at 2°C to 8°C and used within 24 hours of storage.

From a microbiological view, solutions should be used immediately. If not used immediately in-use storage times and conditions prior to use are the responsibility of the user. They would normally be no longer than 24 hours at 2 to 8°C, unless reconstituted under controlled and validated aseptic conditions.

## 6.5 Nature and contents of container

CMS 1 MIU is filled into 10 ml neutral colourless borosilicate glass type I vial stoppered with a grey, siliconized chlorobutyl rubber stopper. The stoppered vials are sealed with an aluminum seal with red polypropylene flip-off cap. Such 10 vials of CMS 1 MIU primary packed vial is labelled and placed in one carton along with a Package insert.

Pack size: 10 vials of CMS 1 MIU packed in one carton.

## 6.6 Special precautions for disposal and other handling

Parenteral administration
The normal adult dose of 2 million units should be dissolved in 10-50 ml 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 - 4 ml 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.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

# 7. PRODUCT REGISTRATION HOLDER

Zulat Pharmacy Sdn Bhd,
No23 & 23A, Jalan Bandar 3,
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53100 Kuala Lumpur,
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# 8. MANUFACTURER

Xellia Pharmaceuticals ApS
Dalslandsgade 11,
2300 Copenhagen S, Denmark.

# 9. DATE OF REVISION OF THE TEXT

05 June 2025