SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE PRODUCT

OLMETHATE® **(Colistimethate Sodium) 150mg Injection (4.5MIU)**

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

OLMETHATE® 150mg Injection (4.5MIU)
Each vial contains:
Colistimethate sodium USP (4.5MIU) equivalent to.....150mg
Colistin base activity (approx.) corresponds to 360mg Colistimethate sodium (base)

3. PHARMACEUTICAL FORM

Powder for solution for injection.

Appearance: White to slightly yellow lyophilized cake.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS:

OLMETHATE® by intravenous administration is indicated in adults and children including neonates for the treatment of serious infections due to selected aerobic Gram-negative pathogens in patients with limited treatment options. **OLMETHATE®** by inhalation is also indicated for the management of adult and paediatric chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:

Posology:
The following dose recommendations are made based on limited population-pharmacokinetic data in critically ill patients:

Adults and adolescents:

- Maintenance dose 9 million IU/day in 2-3 divided doses.
- In patients who are critically ill, a loading dose of 9 million IU should be administered.
- The most appropriate time interval for the first maintenance dose has not been established.
- Modeling suggests that loading and maintenance doses of up to 12 million IU may be required in patients with good renal function in some cases. Clinical experience with such doses is however, extremely limited, and safety has not been established.
- The loading dose applies to patients with normal and impaired renal functions including those on renal replacement therapy.

Renal impairment: Dose adjustments in renal impairment are necessary, but pharmacokinetic data available for patients with impaired renal function is very limited. The following dose adjustments are suggested as guidance. Dose reductions are recommended for patients with creatinine clearance < 50ml/min. Twice daily dosing is recommended.

Creatinine clearance (ml/min)	Daily Dose
< 50- 30	5.5- 7.5 MIU
<30- 10	4.5- 5.5 MIU
<10	3.5 MIU

MIU = million IU

Haemodialysis and continuous haemo (dia) filtration. Colistin appears to be dialyzable through conventional haemodialysis and continuous venovenous haemo (dia) filtration (CVVHF, CVVHDF). There are extremely limited data from population PK studies from very small numbers of patients on renal replacement therapy. The following regimes could be considered.

Haemodialysis:

- No-HD days: 2.25 MIU/day (2.2-2.3 MIU/day).
- HD days: 3 MIU/day on haemodialysis days, to be given after the HD session.
- Twice daily dosing is recommended.

CVVHF/ CVVHDF: As in patients with normal renal function. Three times daily dosing is recommended.
Hepatic impairment: There are no data on patients with hepatic impairment. Caution is advised when administering colistimethate sodium in these patients.
Elderly: No dose adjustments in older patients with normal renal function are considered necessary.
Paediatric population: The data supporting the dose regimen in paediatric patients are very limited. Renal maturity should be taken into consideration when selecting the dose. The dose should be based on lean body weight.

Children ≤ 40kg:

- 75,000-150,000 IU/kg/day divided into 3 doses.
- For children with a body weight above 40kg, use of the dosing recommendation for adults should be considered.
- The use of doses >150,000 IU/kg/day has been reported in children with cystic fibrosis.
- There are no data regarding the use or magnitude of a loading dose in critically ill children.
- No dose recommendations have been established in children with impaired renal function.

Intrathecal and intraventricular administration; The following dose is recommended in adults:
Intraventricular route:

- 125,000 IU/day. Intrathecally administered doses should not exceed those recommended for intraventricular use.
- No specific dosing recommendation can be made in children for intrathecal and intraventricular routes of administration.

Method of administration:
OLMETHATE® is administered intravenously as a slow infusion over 30 – 60 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. Colistimethate sodium undergoes hydrolysis to the active substance colistin in aqueous solution. For dose preparation, particularly where combination of multiple vials is needed, reconstitution of the required dose must be performed using strict aseptic technique.
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 sodium Parenteral 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
- 10% invert sugar solution

There are not sufficient data to recommend usage of Colistimethate sodium Parenteral with other drugs or other than the above listed infusion solutions. Administer the second half of the total daily dose by slow intravenous infusion, starting 1 to 2 hours after the initial dose, over the next 22 to 23 hours. 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.
Dose conversion table: In the EU, the dose of colistimethate sodium (CMS) must be prescribed and administered only as IU. The dose is expressed in the US, and other parts of the world, as milligrams of colistin base activity (mg CBA). The following conversion table is prepared for information and the values must be considered nominal and approximate only.
CMS conversion table:

Potency		≈ mass of CMS (mg)
IU	≈ mg CBA	
12,500	0.4	1
150,000	5	12
1,000,000	34	80
4,500,000	150	360
9,000,000	300	720

AEROSOL INHALATION: It is recommended that colistimethate sodium (CMS) should be administered under the supervision of physicians with appropriate experience in its use. **Posology:** The dosage can be adjusted depending on the severity of the condition and clinical response. Recommended dose range: Administration via inhalation Adults, adolescents and children ≥ 2 years 1-2 MIU two to three times per day (max 6 MIU/day), Children < 2 years 0.5-1 MIU twice daily (max 2 MIU/ day). Relevant clinical guidance on treatment regimens, including duration of treatment, periodicity and co-administration of other antibacterial agents should be adhered to.

Elderly: Dose adjustment is not considered necessary.
Renal impairment: Dose adjustment is not considered necessary; however, caution is advised in patients with renal impairment.
Hepatic impairment: Dose adjustment is not considered necessary.
Method of administration: For inhalation use: Suitable nebulizers are reusable jet nebulizers that are used with a suitable compressor, or the membrane nebulizer namely eFlow rapid. Colistimethate sodium is very soluble in the reconstitution medium. The recommended technique for dissolving the medicinal product is the addition of 3ml isotonic sodium chloride solution (0.9% w/w), to the vial containing colistimethate sodium 1 million IU by gentle shaking. Due to potential foaming, vigorous shaking should be avoided. The resulting solution for nebulization should be clear and carefully transferred into the medication reservoir of the nebulizer. The solution is for single use only and any remaining solution should be discarded. The nebulizer must be kept according to the instructions of the corresponding nebulizer during operation. The patient should sit in an upright position and breathe normally during inhalation. Inhalation should be performed without any interruption to normal breathing. The nebulizer must be cleaned and disinfected after use as described in the 'instruction of use' of the corresponding nebulizer. Colistimethate sodium undergoes hydrolysis to the active substance colistin in aqueous solution. For special precautions for disposal and handling of reconstituted solutions, if other treatments are being taken, they should be taken in the order recommended by the physician.
Drug conversion: See above for the CMS conversion table.
Direction for reconstitution: Dissolve vial contents with 2ml Sterile Water for Injection, provided in the pack and swirl gently to avoid foaming.

4.3. CONTRAINDICATIONS:
Hypersensitivity to the active substance, colistin or to polymyxin B.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
Consideration should be given to co-administering intravenous colistimethate sodium with another antibacterial agent whenever this is possible, taking into account the remaining susceptibilities of the pathogen(s) under treatment. There are limited clinical data on the efficacy and safety of intravenous colistimethate sodium. In particular, there are limited safety data for the use of high doses (>6MIU/day) and the use of a loading dose, and for special populations (patients with renal impairment and the Pediatric population). Colistimethate sodium should only be used when other, more commonly prescribed antibiotics are not effective or not appropriate. Renal function monitoring should be performed at the start of treatment and regularly during treatment in all patients. The dose of colistimethate sodium should be adjusted according to creatinine clearance. Patients who are hypovolaemic or those receiving other potentially nephrotoxic drugs are at increased risk of nephrotoxicity from colistin. The benefit of prolonged treatment duration should be balanced against the potentially increased risk of renal toxicity. 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, normalization of electrolyte imbalance might not be achieved without discontinuation of colistimethate sodium. Caution is advised when administering colistimethate sodium to infants <1 year of age as renal function is not fully mature in this age group. Further, the effect of immature renal and metabolic function on the conversion of colistimethate sodium to colistin is not known. In case of an allergic reaction, treatment with colistimethate sodium must be discontinued and appropriate measures implemented. High serum concentrations of colistimethate sodium, which may be associated with overdosage or failure to reduce the dosage in patients with renal impairment, have been reported to lead to neurotoxic effects such as facial paraesthesia, muscle weakness, vertigo, slurred speech, vasomotor instability, visual disturbances, confusion, psychosis and apnoea. Monitoring should be performed for perioral paraesthesia and paraesthesia in the extremities, which are signs of overdose. Colistimethate sodium is known to reduce the presynaptic release of acetylcholine at the neuro-muscular junction and should be used in patients with myasthenia gravis with the greatest caution and only if clearly needed. Respiratory arrest has been reported following intramuscular administration of colistimethate sodium. Impaired renal function increases the possibility of apnoea and neuromuscular blockade following administration of colistimethate sodium. Colistimethate sodium should be used with extreme caution in patients with porphyria. Antibiotic-associated colitis and pseudomembranous colitis have been reported with nearly all anti-bacterial agents and may occur with colistimethate sodium. They may range from mild to life-threatening in severity. Discontinuation of therapy and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given. Intravenous colistimethate sodium does not cross the blood brain barrier to a clinically relevant extent. The use of intrathecal or intraventricular administration of colistimethate sodium in the treatment of meningitis was not systematically investigated in clinical trials and is supported by case reports only. Data supporting the posology are very limited. 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.
Sodium: The sodium content is approximately 0.07mg (0.003mEq) of sodium per milligram of colistimethate sodium.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:
Concomitant use of intravenous colistimethate sodium with other medications that are potentially nephrotoxic or neurotoxic should be undertaken with great caution. Caution should be taken with concomitant use with other formulations of colistimethate sodium as there is little experience and there is a possibility of summative toxicity. Colistimethate sodium or colistin did not induce the activity of any CYP450 enzyme tested (CYP1A2, 2B6, 2C8, 2C9, 2C19, and 3A4/5) in in vitro studies in human hepatocytes. Due to the effects of colistin on the release of acetylcholine, non-depolarizing muscle relaxants should be used with caution in patients receiving colistimethate sodium as their effects could be prolonged. Co-treatment with colistimethate sodium and macrolides such as azithromycin and clarithromycin, or fluoroquinolones such as norfloxacin and ciprofloxacin should be undertaken with caution in patients with myasthenia gravis. 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.

4.6. FERTILITY, PREGNANCY AND LACTATION:
Fertility: No data is available.
Pregnancy: Colistimethate sodium crosses the placental barrier and there may be a risk of foetal toxicity if repeated doses are given to pregnant patients. Colistimethate sodium should be used in pregnancy only if the benefit to the mother outweighs the potential risk to the foetus.
Breast-feeding: Colistimethate sodium is secreted in breast milk. Colistimethate sodium should be administered to breast-feeding 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 disturbance. 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. 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 a 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: Antibacterial for systemic use, other antibacterial, polymyxins. **ATC Code:** J01XB01.
Mechanism of action: Colistin is a cyclic polypeptide 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 bacteria 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 aminoarabinose. Naturally resistant Gram-negative bacteria, such as *Proteus mirabilis* and *Burkholderia cepacia*, show complete substitution of their lipid phosphate by ethanolamine or aminoarabinose. Cross resistance between colistin (polymyxin E) and polymyxin B is expected. Since the mechanism of action of the polymyxins is different from that of other antibacterial agents, resistance to colistin and polymyxin by the above mechanism alone would not be expected to result in resistance to other drug classes.
PK/PD relationship: Polymyxins have been reported to have a concentration-dependent bactericidal effect on susceptible bacteria. fAUC/ MIC is considered to be correlated with clinical efficacy.

EUCAST Breakpoints	Susceptible (S)	Resistant (R)
Acinetobacter	S≤2	R>2mg/L
Enterobacteriaceae	S≤2	R>2mg/L
Pseudomonas spp.	S≤4	R>4mg/L

5.2. PHARMACOKINETIC PROPERTIES:
Absorption: The information on the pharmacokinetics of colistimethate sodium and colistin is limited. There are indications that pharmacokinetics in critically ill patients differ from those in patients with less severe physiological derangement and from those in healthy volunteers. After infusion of colistimethate sodium the inactive pro-drug is converted to the active colistin. Peak plasma concentrations of colistin have been shown to occur with a delay of up to 7 hours after administration of colistimethate sodium in

critically ill patients. Absorption from the gastrointestinal tract does not occur to any appreciable extent in the normal individual. When given by nebulization, variable absorption has been reported that may depend on the aerosol particle size, nebulizer system, and lung status.
Distribution: The volume of distribution of colistin in healthy subjects is low and corresponds approximately to extracellular fluid (ECF). The volume of distribution is relevantly enlarged in critically ill subjects. Protein binding is moderate and decreases at higher concentrations. In the absence of meningeal inflammation, penetration into the cerebrospinal fluid (CSF) is minimal but increases in the presence of meningeal inflammation. Both colistimethate sodium and colistin display linear PK in the clinically relevant dose range.
Elimination: Colistimethate sodium is eliminated predominantly by the kidneys via glomerular filtration. In healthy subjects, 60% to 70% of colistimethate sodium is excreted unchanged in the urine within 24 hours. The elimination of the active colistin is incompletely characterized. Colistin undergoes extensive renal tubular reabsorption and may either be cleared non-really or undergo renal metabolism with the potential for renal accumulation. Colistin clearance is decreased in renal impairment, possibly due to increased conversion of colistimethate sodium. The half-life of colistin in healthy subjects and those with cystic fibrosis is reported to be around 3h and 4h, respectively, with a total clearance of around 3L/h. In critically ill patients, half-life has been reported to be prolonged to around 9-18h.

5.3. PRECLINICAL SAFETY DATA:
Data on potential genotoxicity are limited and carcinogenicity data for colistimethate sodium are lacking. Colistimethate sodium has been shown to induce chromosomal aberrations in human lymphocytes, in vitro. This effect may be related to a reduction in mitotic index, which was also observed. Reproductive toxicity studies in rats and mice do not indicate teratogenic properties. However, colistimethate sodium given intramuscularly during organogenesis to rabbits at 4.15 and 9.3mg/kg resulted in talipes varus in 2.6 and 2.9% of foetuses respectively. These doses are 0.5 and 1.2 times the maximum daily human dose. In addition, increased resorption occurred at 9.3mg/kg. There are no other preclinical safety data of relevance to the prescriber which are additional to safety data derived from patient exposure and already included in other sections of the SPC.

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 vial: See expiry on the pack.
Reconstituted solution: The reconstituted solution should be used within 24 hours at 15 to 30°C.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:
Do not store over 30°C, and protect from heat and moisture. Improper storage may deteriorate the medicine.
Keep out of reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:
Powder For Injection: 10ml clear colourless glass vial USP Type-I, with bromobutyl rubber stopper with flip off seal. **Water For Injection:** Clear 2ml glass ampoule (USP Type-I). Pack size is 1 vial and 1x2ml ampoule.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:
Solutions are for single use only and remaining solution should be discarded. Any unused medicinal product must be disposed of in accordance with local regulations.

6.7. DRUG PRODUCT SPECIFICATIONS:
USP Specs.

7. MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, Off Hub River Road, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com
Mfg. Lic. No. 000072

8. MARKETING AUTHORISATION NUMBER(S)

116087

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10th July, 2023

10. DATE OF REVISION OF THE TEXT

اولمیتھیٹ® انجکشن

(کولسٹی میتھیٹ سوڈیم)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔
بچوں کی پہنچ سے دور رکھیں۔
دوا کو ۳۰ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں،
گرمی اور نمی سے محفوظ رکھیں ورنہ دوا خراب ہو جائیگی۔
تیار شدہ انجکشن ۱۵ سے ۳۰ ڈگری سینٹی گریڈ پر ۲۴ گھنٹے قابل استعمال رہتا ہے۔