SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE PRODUCT

ROMERO® **(Meropenem) 500mg Injection**

ROMERO® **(Meropenem) 1gm Injection**

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ROMERO® 500mg Injection
Each vial contains:
Meropenem (as Trihydrate) USP.....500mg
(Blended with Sodium Carbonate)
Sodium content: 43mg (approx.)

ROMERO® 1gm Injection
Each vial contains:
Meropenem (as Trihydrate) USP.....1gm
(Blended with Sodium Carbonate)
Sodium content: 86mg (approx.)

3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion.

Appearance:

ROMERO® 500mg Injection: White or almost white, hygroscopic, crystalline powder.

ROMERO® 1g Injection: White or almost white, hygroscopic, crystalline powder.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS:

ROMERO® is indicated for the treatment of the following infections in adults and children aged 3 months and older.

- Severe pneumonia, including hospital and ventilator-associated pneumonia.
- Broncho-pulmonary infections in cystic fibrosis.
- Complicated urinary tract infections.
- Complicated intra-abdominal infections.
- Intra- and post-partum infections.
- Complicated skin and soft tissue infections.
- Acute bacterial meningitis.
- Meropenem may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.
- Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:

Posology: The dose of meropenem administered and the duration of treatment should take into account the type of infection to be treated, including its severity, and the clinical response.
A dose of up to 2gm three times daily in adults and adolescents and a dose of up to 40mg/kg three times daily in children may be particularly appropriate when treating some types of infections, such as infections due to less susceptible bacterial species (e.g. *Enterobacteriaceae, Pseudomonas aeruginosa* or *Acinetobacter* spp.) or very severe infections.
Additional considerations for dosing are needed when treating patients with renal insufficiency are mentioned below:
Adults and adolescents:

Infection	Dose to be administered every 8 hours
Severe pneumonia including hospital and ventilator-associated pneumonia	500mg or 1gm
Broncho-pulmonary infections in cystic fibrosis	2gm
Complicated urinary tract infections	500mg or 1gm
Complicated intra-abdominal infections	500mg or 1gm
Intra- and post-partum infections	500mg or 1gm
Complicated skin and soft tissue infections	500mg or 1gm
Acute bacterial meningitis	2gm
Management of febrile neutropenic patients	1gm

Meropenem is usually given by intravenous infusion over approximately 15 to 30 minutes. Alternatively, doses up to 1gm can be given as an intravenous bolus injection over approximately 5 minutes.
Renal impairment: The dose for adults and adolescents should be adjusted when creatinine clearance is less than 51ml/min. Dose and frequency with respect to the creatinine level are mentioned below:

Creatinine clearance (ml/min)	Dose (based on "unit" dose range of 500mg or 1gm or 2gm)	Frequency
26-50	one unit dose	every 12 hours
10-25	half of one unit dose	every 12 hours
<10	half of one unit dose	every 24 hours

Meropenem is cleared by haemodialysis and haemofiltration. The required dose should be administered after completion of the haemodialysis cycle.
Hepatic impairment: No dose adjustment is necessary in patients with hepatic impairment.
Dose in elderly patients: No dose adjustment is required for the elderly with normal renal function or creatinine clearance values above 50ml/min.
Paediatric population: ***Children under 3 months of age:*** The safety and efficacy of meropenem in children under 3 months of age have not been established and the optimal dose regimen has not been identified.
Children from 3 months to 11 years of age and up to 50kg body weight. The recommended dose regimens are mentioned below:

Infection	Dose to be administered every 8 hours
Severe pneumonia including hospital and ventilator-associated pneumonia	10 or 20mg/kg
Broncho-pulmonary infections in cystic fibrosis	40mg/kg
Complicated urinary tract infections	10 or 20mg/kg
Complicated intra-abdominal infections	10 or 20mg/kg
Complicated skin and soft tissue infections	10 or 20mg/kg
Acute bacterial meningitis	40mg/kg
Management of febrile neutropenic patients	20mg/kg

Children over 50kg body weight: The adult dose should be administered. There is no experience in children with renal impairment.
Method of administration: Meropenem is usually given by intravenous infusion over approximately 15 to 30 minutes. Alternatively, meropenem doses of up to 20mg/kg may be given as an intravenous bolus over approximately 5 minutes.
Direction for Reconstitution: 500mg and 1gm vials should be reconstituted with 10ml and 20ml solvent respectively. Swirl until dissolved.

4.3. CONTRAINDICATIONS:

- Hypersensitivity to the active substance.
- Hypersensitivity to any other carbapenem antibacterial agent.
- Severe hypersensitivity (e.g. anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial agent (e.g. penicillins or cephalosporins).

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

The selection of meropenem to treat an individual patient should take into account the appropriateness of using a carbapenem antibacterial agent based on factors such as severity of the infection, the prevalence of resistance to other suitable antibacterial agents and the risk of selecting for carbapenem-resistant bacteria.

***Enterobacteriaceae, Pseudomonas aeruginosa and Acinetobacter* spp resistance:**
Resistance to penems of *Enterobacteriaceae*, *Pseudomonas aeruginosa, Acinetobacter* spp. varies. Prescribers are advised to take into account the local prevalence of resistance in these bacteria. **Hypersensitivity reactions:** Patients who have a history of hypersensitivity to carbapenems, penicillins or other beta-lactam antibiotics may also be hypersensitive to meropenem. If a severe allergic reaction occurs, the medicinal product should be discontinued. Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme (EM) and acute generalised exanthematous pustulosis (AGEP) have been reported in patients receiving meropenem. If signs and symptoms suggestive of these reactions appear, meropenem should be withdrawn immediately and an alternative treatment should be considered. **Antibiotic-associated colitis:** Antibiotic-associated colitis and pseudomembranous colitis have been reported with nearly all anti-bacterial agents, including meropenem, and may range in severity from mild to life threatening. Discontinuation of therapy with meropenem and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given. **Seizures:** Seizures have infrequently been reported during treatment with carbapenems, including meropenem. **Hepatic function monitoring:** Hepatic function should be closely monitored during treatment with meropenem due to the risk of hepatic toxicity (hepatic dysfunction with cholestasis and cytolysis). Patients with pre-existing liver disorders should have liver function monitored during treatment with meropenem. There is no dose adjustment necessary. **Direct antiglobulin test (Coombs test) seroconversion:** A positive direct or indirect Coombs test may develop during treatment with meropenem. **Concomitant use with valproic acid/sodium valproate/valpromide:** The concomitant use of meropenem and valproic acid/sodium valproate/valpromide is not recommended. The maximum daily dose of this product is equivalent to ≥27% of the WHO recommended maximum daily intake for sodium. Meropenem is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:
No specific medicinal product interaction studies other than probenecid were conducted. Probenecid competes with meropenem for active tubular secretion and thus inhibits the renal excretion of meropenem with the effect of increasing the elimination half-life and plasma concentration of meropenem. Caution is required if probenecid is co-administered with meropenem. Due to the rapid onset and the extent of the decrease, co-administration of valproic acid/sodium valproate/valpromide with carbapenem agents is not considered to be manageable and therefore should be avoided.
Oral anti-coagulants: Simultaneous administration of antibiotics with warfarin may augment its anti-coagulant effects. It is recommended that the INR should be monitored frequently during and shortly after co-administration of antibiotics with an oral anti-coagulant agent.
Paediatric population: Interaction studies have only been performed in adults.

4.6. PREGNANCY AND LACTATION:
Pregnancy: There are no or limited amount of data from the use of meropenem in pregnant women. As a precautionary measure, it is preferable to avoid the use of meropenem during pregnancy.
Breast-feeding: Small amounts of meropenem have been reported to be excreted in human milk. Meropenem should not be used in breast-feeding women unless the potential benefit for the mother justifies the potential risk to the baby.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:
When driving or operating machines, it should be taken into account that headache, paresthesia and convulsions have been reported for meropenem.

4.8. UNDESIRABLE EFFECTS:
The most commonly reported meropenem-related laboratory adverse events were thrombocytosis and increased hepatic enzymes.
Local adverse reactions: Inflammation at the injection site 2.4%, injection site reaction 0.9% phlebitis/thrombophlebitis 0.8%, pain at the injection site 0.4%, edema at the injection site 0.2%. ***Common:*** Thrombocythaemia, headache, diarrhoea, vomiting, nausea, abdominal pain, transaminases increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, rash, pruritis, inflammation, pain. ***Uncommon:*** Oral and vaginal candidiasis, oeosinophilia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis, haemolytic anaemia, angioedema, anaphylaxis, paranesthesia antibiotic-associated colitis, blood bilirubin increased, toxic epidermal necrolysis, Stevens- Johnson syndrome, erythema multiforme, urticaria, blood creatinine increased, blood urea increased, thrombophlebitis, pain at the injection site. ***Rare/Notknown:*** Delirium, convulsions, drug reaction with oeosinophilia and systemic symptoms, acute generalised exanthematous pustulosis.
Paediatric population: Meropenem is licensed for children over 3 months of age. There is no evidence of an increased risk of any adverse drug reaction in children based on the limited available data. All reports received were consistent with events observed in the adult population.

4.9. OVERDOSE:
Symptomatic treatments should be considered. In individuals with normal renal function, rapid renal elimination will occur. Haemodialysis will remove meropenem and its metabolite.

5. PHARMACOLOGICAL PROPERTIES
5.1. PHARMACODYNAMIC PROPERTIES:
Pharmacotherapeutic group: Antibacterials for systemic use, carbapenems, **ATC code:** J01DH02
Mechanism of action: Meropenem exerts its bactericidal activity by inhibiting bacterial cell wall synthesis in Gram-positive and Gram-negative bacteria through binding to penicillin-binding proteins (PBPs).
Mechanism of resistance: Bacterial resistance to meropenem may result from: (1) Decreased permeability of the outer membrane of Gram-negative bacteria (due to diminished production of porins) (2) Reduced affinity of the target PBPs (3) Increased expression of efflux pump components, and (4) Production of beta-lactamases that can hydrolyse carbapenems. There is no target-based cross-resistance between meropenem and agents of the quinolone, aminoglycoside, macrolide and tetracycline classes. However, bacteria may exhibit resistance to more than one class of antibacterials agents when the mechanism involved include impermeability and/or an efflux pump(s).
Breakpoints: European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints for MIC testing are presented below:

EUCAST clinical MIC breakpoints for meropenem (2015-01-01, v5)

Organism	Susceptible (S) (mg/l)	Resistant (R) (mg/l)
Enterobacteriaceae	≤ 2	> 8
Pseudomonas spp.	≤ 2	> 8
Acinetobacter spp.	≤ 2	> 8
Streptococcus groups A, B, C, G	note 6	note 6
Streptococcus pneumoniae[1]	≤ 2	> 2
Viridans group *streptococci*[2]	≤ 2	> 2
Enterococcus spp.	--	--
Staphylococcus spp.	note 3	note 3
Haemophilus influenzae[1,2] and *Moraxella catarrhalis*[2]	≤ 2	> 2
Neisseria meningitidis[2,4]	≤ 0.25	> 0.25
Gram-positive anaerobes except *Clostridium difficile*	≤ 2	> 8
Gram-negative anaerobes	≤ 2	> 8
Listeria monocytogenes	≤ 0.25	> 0.25
Non-species related breakpoints[5]	≤ 2	> 8

[1] Meropenem breakpoints for *Streptococcus pneumoniae* and *Haemophilus influenzae* in meningitis are 0.25mg/l (Susceptible) and 1mg/l (Resistant).
[2] Isolates with MIC values above the susceptible breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC values above the current resistant breakpoint they should be reported resistant.
[3] Susceptibility of staphylococci to carbapenems is inferred from the cefoxitin susceptibility.
[4] Breakpoints relate to meningitis only.
[5] Non-species related breakpoints have been determined mainly from PK/PD data and are independent of the MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints. Non-species related breakpoints are based on the following dosages: EUCAST breakpoints apply to meropenem 1000mg x3 daily administered intravenously over 30 minutes as the lowest dose. 2gmx3 daily was taken into consideration for severe infections and in setting the I/R breakpoint.
[6] The beta-lactam susceptibility of streptococcus groups A, B, C and G is inferred from the penicillin susceptibility.

Commonly susceptible species: Gram-positive aerobes: *Enterococcus faecalis, Staphylococcus aureus* (methicillin-susceptible), *Staphylococcus species* (methicillin-susceptible) including *Staphylococcus epidermidis*, *Streptococcus agalactiae* (Group B), *Streptococcus milleri* group (*S. anginosus, S. constellatus,* and *S. intermedius*), *Streptococcus pneumoniae, Streptococcus pyogenes* (Group A). **Gram-negative aerobes:** *Citrobacter freundii, Citrobacter koseri, Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Klebsiella oxytoca, Klebsiella pneumoniae, Morganella morganii, Neisseria meningitidis, Proteus mirabilis, Proteus vulgaris, Serratia marcescens.* **Gram-positive anaerobes:** *Clostridium perfringens, Peptoniphilus asaccharolyticus, Peptostreptococcus species* (including *P. micros, P. anaerobius, P. magnus*). **Gram-negative anaerobes:** *Bacteroides caccae, Bacteroides fragilis* group, *Prevotella bivia, Prevotella disiens.*
Species for which acquired resistance may be a problem: ***Gram-positive aerobes:*** *Enterococcus faecium.* **Gram-negative aerobes:** *Acinetobacter species, Burkholderia cepacia, Pseudomonas aeruginosa.* **Inherently resistant organisms:** ***Gram-negative aerobes:*** *Stenotrophomonas maltophilia, Legionella* species. ***Other micro-organisms:*** *Chlamydophila pneumoniae, Chlamydophila psittaci, Coxiella burnetii, Mycoplasma pneumoniae,* species that show natural intermediate susceptibility, All methicillin-resistant staphylococci are resistant to meropenem.

5.2. PHARMACOKINETIC PROPERTIES:
Absorption: Following intravenous doses of 500mg, mean plasma concentrations of meropenem usually decline to approximately 1mcg/mL at 6 hours after administration. No accumulation of meropenem in plasma was observed with regimens using 500mg administered every 8 hours or 1 gram administered every 6 hours in healthy volunteers with

SUMMARY OF PRODUCT CHARACTERISTICS

normal renal function. **Distribution:** The average plasma protein binding of meropenem was approximately 2% and was independent of concentration. Meropenem has been shown to penetrate well into several body fluids and tissues: including lung, bronchial secretions, bile, cerebrospinal fluid, gynaecological tissues, skin, fascia, muscle, and peritoneal exudates. **Biotransformation:** Meropenem is metabolized by hydrolysis of the beta-lactam ring generating a microbiologically inactive metabolite. **Elimination:** Meropenem is primarily excreted unchanged by the kidneys; approximately 70% (50-75%) of the dose is excreted unchanged within 12 hours. A further 28% is recovered as the microbiologically inactive metabolite. Faecal elimination represents only approximately 2% of the dose. The measured renal clearance and the effect of probenecid show that meropenem undergoes both filtration and tubular secretion. **Renal insufficiency:** Dose adjustment is recommended for patients with moderate and severe renal impairment. Meropenem is cleared by hemodialysis with clearance during haemodialysis being approximately 4 times higher than in anuric patients. **Hepatic insufficiency:** A study in patients with alcoholic cirrhosis shows no effect of liver disease on the pharmacokinetics of meropenem after repeated doses. **Paediatric Patients:** The pharmacokinetics of meropenem for injection IV, in paediatric patients 2 years of age or older, are similar to those in adults. **Elderly:** Pharmacokinetic studies in healthy elderly subjects (65-80 years) have shown a reduction in plasma clearance, which correlated with age-associated reduction in creatinine clearance, and a smaller reduction in non-renal clearance. No dose adjustment is required in elderly patients, except in cases of moderate to severe renal impairment.

5.3. PRE-CLINICAL SAFETY DATA:
Animal studies indicate that meropenem is well tolerated by the kidney. Histological evidence of renal tubular damage was seen in mice and dogs only at doses of 2000mg/kg and above after a single administration and above and in monkeys at 500mg/kg in a 7-day study. Meropenem is generally well tolerated by the central nervous system. Effects were seen in acute toxicity studies in rodent at doses exceeding 1000mg/kg. The IV LD50 of meropenem in rodents is greater than 2000mg/kg. In repeat dose studies of up to 6 months duration only minor effects were seen including a decrease in red cell parameters in dogs. There was no evidence of mutagenic potential in a conventional test battery and no evidence of reproductive toxicity including teratogenic potential in studies in rats up to 750mg/kg and in monkeys up to 360mg/kg. There was no evidence of increased sensitivity to meropenem in juveniles compared to adult animals. The intravenous formulation was well tolerated in animal studies. The sole metabolite of meropenem had a similar profile of toxicity in animal studies.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:
ROMERO® 500mg Injection: Not applicable.
ROMERO® 1g Injection: Not applicable.

6.2. INCOMPATIBILITIES:
This medicinal product should not be mixed with or physically added to solutions containing other drugs.

6.3. SHELF LIFE:
Unopened vial: See expiry on the pack.
Reconstituted solution:
- Vials constituted with sterile Water for Injection for bolus administration may be stored for upto 3 hours at up to 25°C or for 13 hours at up to 2-8°C.
- Solution prepared for infusion, constituted with Sodium Chloride Injection 0.9% may be stored for 1 hour at up to 25°C or 15 hours at up to 2-8°C.
- Solution prepared for infusion, constituted with Dextrose Injection 5% should be used immediately.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:
Avoid exposure to heat, light and humidity. Do not store over 30°C. Do not freeze the reconstituted solution. Keep out of reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:
ROMERO® 500mg Injection:
Powder for Infusion: Clear glass vial (USP Type-II) with bromobutyl rubber stopper, sealed with flip off seal. **Water for Injection:** Clear 10ml glass ampoule (USP Type-I), pack size is 1 vial and 1 ampoule.
ROMERO® 1g Injection:
Powder for Infusion: Clear glass vial (USP Type-II) with bromobutyl rubber stopper, sealed with flip off seal. **Water for Injection:** Clear 10ml glass ampoule (USP Type-I), pack size is 1 vial and 2 ampoules.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING:
Dilution for Injection/Infusion:
- Meropenem to be used for bolus intravenous injection should be constituted with sterile water for injection.
- For intravenous infusion meropenem vial may be directly constituted with 0.9% sodium chloride or 5% glucose (dextrose) solutions for infusion.
- Vial is a single dose and discard any portion of the contents remaining after use.
- Standard aseptic techniques should be used for solution preparation and administration.
- The solution should be shaken before use.
- Reconstituted solution should be used immediately.
- The solution should be inspected visually for particles and discolouration prior to administration. Only clear colourless to yellow solution, free from particles should be used.

6.7. DRUG PRODUCT SPECIFICATION:
ROMERO® 500mg Injection: USP Specs.
ROMERO® 1g Injection: USP Specs.

7. MARKETING AUTHORISATION HOLDER

Manufactured by:
STALLION Pharmaceuticals (Pvt.) Ltd.
581-Sundar Industrial Estate, Lahore, Pakistan

Manufactured for:
Healthtek (Pvt.) Limited
Plot No. 14, Sector 19, Korangi
Industrial Area, Karachi - Pakistan

An associate company of:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com

8. MARKETING AUTHORISATION NUMBER(S)

ROMERO® 500mg Injection: 112480
ROMERO® 1g Injection: 112481

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

ROMERO® 500mg Injection: 31st March, 2022
ROMERO® 1g Injection: 31st March, 2022

10. DATE OF REVISION OF THE TEXT

رومیرو® انجکشن
(میروپینم)

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 گرمی، روشنی اور نمی سے محفوظ رکھیں۔
درجہ حرارت ۳۰ ڈگری سینٹی گریڈ سے زیادہ نہ ہو۔
تیار شدہ انجکشن کو منجمد ہونے سے محفوظ رکھیں۔