ARCHIFAR ® 500mg and 1g
Powder for solution for injection or infusion
Meropenem

PACKAGE LEAFLET: INFORMATION FOR THE USER

1. NAME OF THE MEDICINAL PRODUCT

ARCHIFAR 500mg powder for solution for injection or infusion
ARCHIFAR 1g powder for solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ARCHIFAR 500mg powder for solution for injection or infusion – Each vial contains Meropenem trihydrate equivalent to 500mg anhydrous meropenem
ARCHIFAR 1g powder for solution for injection or infusion – Each vial contains Meropenem trihydrate equivalent to 1g anhydrous meropenem
Excipients:
Each 500mg vial contains 104mg sodium carbonate which equates to approximately 2.0mEq of sodium (approximately 45mg)
Each 1g vial contains 208mg sodium carbonate which equates to approximately 4.0mEq of sodium (approximately 90mg)
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion. White to light yellow powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ARCHIFAR is indicated for treatment, in adults and children, of the following infections caused by single or multiple bacteria sensitive to meropenem.

- Pneumonias and Nosocomial pneumonias
- Urinary Tract Infections
- Intra-abdominal Infections
- Gynaecological Infections, such as endometritis and pelvic inflammatory disease.
- Bacterial Meningitis
- Septicaemia
- Empiric treatment, for presumed infections in patients with febrile neutropenia, used as monotherapy or in combination with anti-viral or anti-fungal agents.

ARCHIFAR has proved efficacious alone or in combination with other antimicrobial agents in the treatment of polymicrobial infections.

4.2 Posology and method of administration

The tables below provide general recommendations for dosing.
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 2g 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 nosocomial infections due to *Pseudomonas aeruginosa* or *Acinetobacter* spp.
Additional considerations for dosing are needed when treating patients with renal insufficiency (see further below).

Adults and adolescents Infection	Dose to be administered every 8 hours
Pneumonia including community-acquired pneumonia and nosocomial pneumonia	500mg or 1g
Broncho-pulmonary infections in cystic fibrosis	2g
Complicated urinary tract infections	500mg or 1g
Complicated intra-abdominal infections	500mg or 1g
Intra- and post-partum infections	500mg or 1g
Complicated skin and soft tissue infections	500mg or 1g
Acute bacterial meningitis	2g
Management of febrile neutropenic patients	1g

Meropenem is usually given by intravenous infusion over approximately 15 to 30 minutes (see section 6.2, 6.3 and 6.6). Alternatively, doses up to 1 g can be given as an intravenous bolus injection over approximately 5 minutes. There are

limited safety data available to support the administration of a 2 g dose in adults as an intravenous bolus injection.

Renal impairment
The dose for adults and adolescents should be adjusted when creatinine clearance is less than 51 ml/min, as shown below. There are limited data to support the application of these dose adjustments for a unit dose of 2g.

Creatinine clearance (ml/min)	**Dose (based on "unit" dose range of 500mg or 1g or 2g, see table above)**	**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 12 hours

Meropenem is cleared by haemodialysis and haemofiltration. The required dose should be administered after completion of the haemodialysis cycle.
There are no established dose recommendations for patients receiving peritoneal dialysis.

Hepatic impairment
No dose adjustment is necessary in patients with hepatic impairment (see section 4.4).

Dose in elderly patients
No dose adjustment is required for the elderly with normal renal function or creatinine clearance values above 50 ml/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. However, limited pharmacokinetic data suggest that 20 mg/kg every 8 hours may be an appropriate regimen (see section 5.2).
Children from 3 months to 11 years of age and up to 50 kg body weight
The recommended dose regimens are shown in the table below

Infection	**Dose to be administered every 8 hours**
Pneumonia including community-acquired pneumonia and nosocomial 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 infections	10 or 20mg/kg
Acute bacterial meningitis	40mg/kg
Management of febrile neutropenic patients	20mg/kg

Children over 50 kg body weight,
The adult dose should be administered.
There is no experience in children with renal impairment.
Meropenem is usually given by intravenous infusion over approximately 15 to 30 minutes (see sections 6.2, 6.3, and 6.6). Alternatively, meropenem doses of up to 20 mg/kg may be given as an intravenous bolus over approximately 5 minutes. There are limited safety data available to support the administration of a 40 mg/kg dose in children as an intravenous bolus injection.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.
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 warning 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.

As with all beta-lactam antibiotics, serious and occasionally fatal hypersensitivity reactions have been reported (see

sections 4.3 and 4.8).
Patients who have a history of hypersensitivity to carbapenems, penicillins or other beta-lactam antibiotics may also be hypersensitive to meropenem. Before initiating therapy with meropenem, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics.
If a severe allergic reaction occurs, the medicinal product should be discontinued and appropriate measures taken.
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. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of meropenem (see section 4.8). 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 have infrequently been reported during treatment with carbapenems, including meropenem (see section 4.8).
Hepatic function should be closely monitored during treatment with meropenem due to the risk of hepatic toxicity (hepatic dysfunction with cholestasis and cytolysis) (see section 4.8).
Use in patients with liver disease: patients with pre-existing liver disorders should have liver function monitored during treatment with meropenem. There is no dose adjustment necessary (see section 4.2).
A positive direct or indirect Coombs test may develop during treatment with meropenem.
The concomitant use of meropenem and valproic acid/sodium valproate is not recommended (see section 4.5).

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients receiving therapy with beta-lactams. Before initiating therapy with [product name], careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, carbapenems or other beta-lactam agents. If an allergic reaction occurs, Archifar must be discontinued immediately and appropriate alternative therapy instituted.

ARCHIFAR contains sodium.
ARCHIFAR 500mg: This medicinal product contains approximately 2.0mEq of sodium per 500mg dose which should be taken into consideration by patients on a controlled sodium diet.
ARCHIFAR 1.0g: This medicinal product contains approximately 4.0mEq of sodium per 1.0g dose which should be taken into consideration by patients on a controlled sodium 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.
The potential effect of meropenem on the protein binding of other medicinal products or metabolism has not been studied. However, the protein binding is so low that no interactions with other compounds would be expected on the basis of this mechanism.
Decreases in blood levels of valproic acid have been reported when it is co-administered with carbapenem agents resulting in a 60-100% decrease in valproic acid levels in about two days. Due to the rapid onset and the extent of the decrease, co-administration of valproic acid with carbapenem agents is not considered to be manageable and therefore should be avoided (see section 4.4).
Oral anti-coagulants
Simultaneous administration of antibiotics with warfarin may augment its anti-coagulant effects. There have been many reports of increases in the anti-coagulant effects of orally administered anti-coagulant agents, including warfarin in patients who are concomitantly receiving antibacterial agents. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the antibiotic to the increase in INR (international normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of antibiotics with an oral anti-coagulant agent.

4.6 Pregnancy and lactation
Pregnancy
There are no or limited amount of data from the use of meropenem in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of meropenem during pregnancy.

Lactation
It is unknown whether meropenem is excreted in human milk. Meropenem is detectable at very low concentrations in animal breast milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from meropenem therapy taking into account the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The most frequently reported adverse reactions were diarrhoea, rash, nausea/vomiting and injection site inflammation. The most commonly reported meropenem- related laboratory adverse events were thrombocytosis and increased hepatic enzymes.

The following adverse reactions were reported for meropenem:

System Organ Class Event

Infections and infestations: oral and vaginal candidiasis

Blood and lymphatic system disorders: Thrombocytothaemia, eosinophilia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis, haemolytic anaemia.

Immune system disorders: angioedema, anaphylaxis

Nervous system disorders: Headache, paraesthesiae, convulsions

Gastrointestinal disorders: Diarrhoea, vomiting, nausea, abdominal pain, antibiotic-associated colitis

Hepatobiliary disorders: Transaminases increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, blood bilirubin increased

Skin and subcutaneous tissue disorders: Rash, pruritis, urticaria, toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme

Renal and urinary disorders: Blood creatinine increased, blood urea increased

General disorders and administration site conditions: Inflammation, pain, thrombophlebitis, pain at the injection site

4.9 Overdose

Relative overdose may be possible in patients with renal impairment if the dose is not adjusted as described in section 4.2. Limited post-marketing experience indicates that if adverse reactions occur following overdose, they are consistent with the adverse reaction profile described in section 4.8, are generally mild in severity and resolve on withdrawal or dose reduction. 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

Mode 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).

Pharmacokinetic/Pharmacodynamic (PK/PD) relationship

Similar to other beta-lactam antibacterial agents, the time that meropenem concentrations exceed the MIC (T>MIC) has been shown to best correlate with efficacy. In preclinical models meropenem demonstrated activity when plasma concentrations exceeded the MIC of the infecting organisms for approximately 40% of the dosing interval. This target has not been established clinically.

Mechanism of resistance

Bacterial resistance to meropenem may result from:

1. decreased permeability of the outermembrane 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.

Localised clusters of infections due to carbapenem-resistant bacteria have been reported in the European Union. 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 (2009-06-05, v 3.1)

Organism	Susceptible (S) (mg/l)	Resistant (R) (mg/l)
Entrerobacteriaceae	≤2	>8
Pseudomonas	≤2	>8
Acinetobacter	≤2	>8
Streptococcus groups A, B, C, G	≤2	>2
Streptococcus pneumoniae[1]	≤2	>2
Other streptococci	2	2

Enterococcus	--	--
Staphylococcus[2]	Note 3	Note 3
Haemophilus influenzae[1] and Moraxella catarrhalis	≤2	>2
Neisseria meningitis[2,4]	≤0.25	>0.25
Gram-positive anaerobes	≤2	>8
Gram-negative anaerobes	≤2	>8
Non-species related breakpoints[5]	≤2	>8

[1] Meropenem breakpoints for *Streptococcus pneumoniae* and *Haemophilus influenzae* in meningitis are 0.25/1 mg/L.

[2] Strains with MIC values above the S/I breakpoint are 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 above the current resistant breakpoint (in italics) they should be reported as resistant.

[3] Susceptibility of staphylococci to meropenem is inferred from the methicillin susceptibility.

[4] Meropenem breakpoints in *Neisseria meningitidis* relates 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 for species not mentioned in the table and footnotes.

--=Susceptibility testing not recommended as the species is a poor target for therapy with the medicinal product

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.

The following table of pathogens listed is derived from clinical experience and therapeutic guidelines.

Commonly susceptible species

Gram-positive aerobes

Enterococcus faecalis

Staphylococcus aureus (methicillin-susceptible)[x]

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 freudii

Citrobacter koseri

Enterobacter aerogenes

Enterobacter cloacae

Escherichia coli

Haemophilus influenzae

Klebsiella oxytoca

Klebsiella pneumoniae

Morganella morganii

Neisseria meningitides

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[y,z]

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 pneumonia

[x] Species that show natural intermediate susceptibility

[y] All methicillin-resistant staphylococci are resistant to meropenem

[z] Resistance rate ≥ 50% in one or more EU countries.

5.2 Pharmacokinetic properties

In healthy subjects the mean plasma half-life is approximately 1 hour; the mean volume of distribution is approximately 0.25l/kg (11-27L) and the mean clearance is 287 ml/min at 250 mg falling to 205 ml/min at 2g. Doses of 500, 1000 and 2000 mg doses infused over 30 minutes give mean Cmax values of approximately 23, 49 and 115µg/ml respectively, corresponding AUC values were 39.3, 62.3 and 153µg.h/ml. After infusion over 5 minutes Cmax values are 52 and 112 µg/ml after 500 and 1000 mg doses respectively. When multiple doses are administered 8-hourly to subjects with normal renal function, accumulation of meropenem does not occur.

Distribution

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.

Metabolism

Meropenem is metabolised 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.

5.3 Preclinical 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 increased evidence of abortions at 500mg/kg in a preliminary study in monkeys.

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

Sodium carbonate

6.2 Incompatibilities

The medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

24 months

6.4 Special precautions for storage
Store below 30°C in the original package.

After reconstitution
Intravenous bolus injection administration
A solution for bolus injection is prepared by dissolving the medicinal product in water for injection to a final concentration of 50 mg/ml. Chemical and physical in-use stability for a prepared solution for bolus injection has been demonstrated for 3 hours at up to 25°C or 12 hours under refrigerated conditions (2-8°C).
From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbiological contamination, the product should be used immediately.
If not used immediately in-use storage times and conditions are the responsibility of the user.

Intravenous infusion administration
A solution for infusion is prepared by dissolving the medicinal product in either 0.9% sodium chloride solution for infusion or 5% dextrose solution for infusion to a final concentration of 1 to 20mg/ml. Chemical and physical in-use stability for a prepared solution for infusion using 0.9% sodium chloride solution has been demonstrated for 3 hours at up to 25°C or 24 hours under refrigerated conditions (2-8°C).
From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbiological contamination, the product should be used immediately.
If not used immediately in-use storage times and conditions are the responsibility of the user.

Reconstituted solution of the product in 5% dextrose solution should be used immediately.

The constituted solutions should not be frozen.

6.5 Dosage forms and packaging available
Type I clear glass vials of 20ml and 30ml.
Packs of 10 vials/pack are available.

6.6 Special precautions for disposal and other handling
It is recommended to use freshly prepared solutions.
Injection: Meropenem to be used for bolus intravenous injection should be constituted with sterile water for injection.
Infusion: For intravenous infusion meropenem may be directly constituted with 0.9% sodium chloride or 5% glucose solution for infusion.
Each vial is for single use only.
Standard aseptic techniques should be used for solution preparation and administration.
The solution should be shaken before use.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER
Medochemie Ltd.,
1-10 Constantinoupoleos Street, 3011 Limassol, Cyprus

Manufacturing Site: Medochemie Ltd., Factory C, 2 Michael Erakleous Street, Agios Athanassios Industrial Area, 4101 Agios Athanassios, Limassol, Cyprus

8. PRODUCT REGISTRATION HOLDER
Komedic Sdn Bhd, 4 Jalan PJS 11/14, Bandar Sunway, 46150 Petaling Jaya

9. DATE OF REVISION
October 2022