Summary of Product Characteristics
Aropem (Meropenem) 0.5 g and 1 g Powder for Solution for I.V. Injection or Infusion

1. Name of the medicinal product

Aropem 0.5 g Sterile powder for solution for I.V. injection or infusion
Aropem 1 g Sterile powder for solution for I.V. injection or infusion

2. Qualitative and quantitative composition

Aropem 0.5 g
Each vial contains meropenem trihydrate equivalent to 0.5 g of anhydrous meropenem.
Aropem 1 g
Each vial contains meropenem trihydrate equivalent to 1 g of anhydrous meropenem.
Excipients:

Each 0.5 g vial contains 104 mg sodium carbonate which equates to approximately 2.0 mEq of sodium (approximately 45 mg).
Each 1 g vial contains 208 mg sodium carbonate which equates to approximately 4.0 mEq of sodium (approximately 90 mg).

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Sterile powder for solution for I.V. injection or infusion.
A white to almost white or pale yellow powder.

4. Clinical particulars

4.1 Therapeutic indications

Aropem 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
- Skin and skin structure infections
- Meningitis
- Septicaemia
- Empiric treatment, for presumed infections in adult patients with febrile neutropenia, used as monotherapy or in combination with anti-viral or anti-fungal agents.

Aropem has proved efficacious alone or in combination with other antimicrobial agents in the treatment of polymicrobial infections.
There is no experience in paediatric patients with neutropenia or primary or secondary immunodeficiency.

4.2 Posology and method of administration

Adults:

The dosage and duration of therapy shall be established depending on type and severity of infection and the condition of the patient.

The recommended daily dosage is as follows:

0.5 g I.V. every 8 hours in the treatment of pneumonia, urinary tract infections, gynaecological infections such as endometritis, skin and skin structure infections.

1 g I.V. every 8 hours in the treatment of nosocomial pneumonias, peritonitis, presumed infections in neutropenic patients, septicaemia.

In cystic fibrosis, doses up to 2 g every 8 hours have been used; most patients have been treated with 2 g every 8 hours.

In meningitis the recommended dosage is 2 g every 8 hours.

As with other antibiotics, particular caution is recommended in using meropenem as monotherapy in critically ill patients with known or suspected *Pseudomonas aeruginosa* lower respiratory tract infection.

Regular sensitivity testing is recommended when treating *Pseudomonas aeruginosa* infection.

Dosage schedule for adults with impaired renal function:

Dosage should be reduced in patients with creatinine clearance less than 51 ml/min, as scheduled below:

Creatinine Clearance (ml/min)	**Dose** (based on unit doses of 0.5 g, 1 g, 2 g**)**	**Frequency**
26-50	one unit dose	every 12 hours
10-25	one-half unit dose	every 12 hours
<10	one-half unit dose	every 24 hours

Meropenem is cleared by haemodialysis; if continued treatment with Aropem is necessary, it is recommended that the unit dose (based on the type and severity of infection) is administered at the completion of the haemodialysis procedure to restore therapeutically effective plasma concentrations.

There is no experience with the use of Aropem in patients under peritoneal dialysis.

Dosage in adults with hepatic insufficiency:

No dosage adjustment is necessary in patients with hepatic insufficiency (see "Warnings and precautions").

Elderly patients:

No dosage adjustment is required for the elderly with normal renal function or creatinine clearance values above 50 ml/min.

Children:

The safety and efficacy of Aropem 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.

For children over 3 months and up to 12 years of age the recommended dose is 10 - 20 mg/kg every 8 hours depending on type and severity of infection, susceptibility of the pathogen and the condition of the patient. In children over 50 kg weight, adult dosage should be used.

For children with cystic fibrosis, 40 mg/kg every 8 hours has been used to treat acute exacerbations of chronic lower respiratory tract infections.
In meningitis the recommended dose is 40 mg/kg every 8 hours.
There is no experience in children with renal impairment.

Aropem can be given as an intravenous bolus injection over approximately 5 minutes or by intravenous infusion over approximately 15 to 30 minutes using the specific available presentations.

4.3 Contraindications
Aropem is contraindicated in patients who have demonstrated hypersensitivity to this product.

4.4 Special warnings and precautions for use
There is some clinical and laboratory evidence of partial cross-allergenicity between other carbapenems and beta-lactam antibiotics, penicillins and cephalosporins. As with all beta-lactam antibiotics, rare hypersensitivity reactions have been reported (see "Undesirable effects"). Before initiating therapy with meropenem, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics. Aropem should be used with caution in patients with such a history. If an allergic reaction to meropenem occurs, the drug should be discontinued and appropriate measures taken.
Use of Aropem in patients with hepatic disease should be made with careful monitoring of transaminase and bilirubin levels.
As with other antibiotics, overgrowth of non-susceptible organisms may occur and, therefore, continuous monitoring of each patient is necessary.
Use in infections caused by methicillin resistant staphylococci is not recommended. Rarely, pseudomembranous colitis has been reported with meropenem as with practically all antibiotics and may vary in severity from slight to life-threatening. Therefore, antibiotics should be prescribed with care for individuals with a history of gastro-intestinal complaints, particularly colitis.
It is important to consider the diagnosis of pseudomembranous colitis in the case of patients who develop diarrhoea in association with the use of Aropem. Although studies indicate that a toxin produced by *Clostridium difficile* is one of the main causes of antibiotic-associated colitis, other causes should be considered.
The co-administration of Aropem with potentially nephrotoxic drugs should be considered with caution.
Aropem may reduce serum valproic acid levels. Subtherapeutic levels may be reached in some patients.
Aropem 0.5 g: This medicinal product contains approximately 2.0 mEq of sodium per 0.5 g dose which should be taken into consideration by patients on a controlled sodium diet.
Aropem 1 g: This medicinal product contains approximately 4.0 mEq of sodium per 1.0 g dose which should be taken into consideration by patients on a controlled sodium diet.
Paediatric use: Efficacy and tolerability in infants under 3 months old have not been established; therefore, Aropem is not recommended for use below this age. There is no experience in children with altered hepatic or renal function.

4.5 Interaction with other medicinal products and other forms of interaction

Probenecid competes with meropenem for active tubular secretion and thus inhibits the renal excretion, with the effect of increasing the elimination half-life and plasma concentration of meropenem. As the potency and duration of action of Aropem dosed without probenecid are adequate, the co-administration of probenecid with Aropem is not recommended.

The potential effect of Aropem on the protein binding of other drugs or metabolism has not been studied. The protein binding of Aropem is low (approximately 2%) and, therefore, no interactions with other compounds based on displacement from plasma proteins would be expected.

Aropem may reduce serum valproic acid levels. Subtherapeutic levels may be reached in some patients.

There have been many reports of increases in the anticoagulant effects including warfarin in patients who are concomitantly receiving antibacterial agents. It is recommended that the INR should be monitored frequently during and shortly after co-adminstration of antibiotics with an oral anti-coagulant agent.

4.6 Pregnancy and lactation

Pregnancy: The safety of Aropem in human pregnancy has not been evaluated. Aropem should not be used in pregnancy unless the potential benefit justifies the potential risk to the foetus. In every case, it should be used under the direct supervision of the physician.

Lactation: Meropenem is detectable at very low concentrations in animal breast milk. Aropem should not be used in breast-feeding women unless the potential benefit justifies the potential risk to the baby.

4.7 Effects on ability to drive and use machines

No data is available, but it is not anticipated that Aropem will affect the ability to drive and use machines.

4.8 Undesirable effects

Aropem is generally well tolerated. Undesirable effects rarely lead to cessation of treatment. Serious undesirable effects are rare.

The following undesirable effects, listed by body system/organ and frequency (common: ≥ 1% and <10%; uncommon: ≥0.1% and <1%; rare: ≥0.01% and <0.1%; very rare: < 0.01%), have been reported with the use of meropenem:

Blood and lymphatic system disorders: A positive direct or indirect Coombs test may develop in some subjects; there have been reports of reduction in partial thromboplastin time.

Common: thrombocythaemia. Uncommon: eosinophilia, thrombocytopenia. Rare: leucopenia, neutropenia, agranulocytosis. Very rare: haemolytic anemia.

Gastrointestinal disorders: Common: nausea, vomiting, diarrhea. Very rare: pseudomembranous colitis.

Hepato-biliary disorders: Common: increases in serum transaminases, bilirubin, alkaline phosphatase and lactic dehydrogenase.

Nervous system disorders: Uncommon: headache, paraesthesiae. Rare: convulsions. Convulsions have been observed in a temporal association with the administration of meropenem; a causal relationship with meropenem has not been established.
Immune system disorders: Very rare: angioedema, manifestations of anaphylaxis.
General disorders and administration site disorders: Common: inflammation, thrombophlebitis, pain. Rare: oral and vaginal candidiasis.
Skin and subcutaneous tissue disorders: Uncommon: rash, urticaria, pruritis. Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.

4.9 Overdose
Accidental overdosage could occur during therapy, particularly in patients with renal impairment. Limited post-marketing experience indicates that adverse events following overdosage are consistent with the adverse event profile described in the undesirable effects section. Treatment of overdosage should be symptomatic. In normal individuals rapid renal elimination will occur; in subjects with renal impairment, 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 is a carbapenem antibiotic for parenteral use, that is relatively stable to human dehydropeptidase-1 (DHP-1) and therefore, does not require the addition of an inhibitor of DHP-1.
Meropenem exerts its bactericidal action by interfering with vital bacterial cell wall synthesis in Gram-positive and Gram-negative bacteria through binding to penicillin-binding proteins (PBPs). The ease with which it penetrates bacterial cell walls, its high level of stability to all serine β-lactamases and its marked affinity for the Penicillin Binding Proteins (PBPs) explain the potent bactericidal action of meropenem against a broad spectrum of aerobic and anaerobic bacteria.
Minimum bactericidal concentrations (MBC) are commonly the same as the minimum inhibitory concentrations (MIC). For 76% of the bacteria tested, the MBC: MIC ratios were 2 or less.
Meropenem is stable in susceptibility tests and these tests can be performed using normal routine methods. *In vitro* tests show that meropenem acts synergistically with various antibiotics. It has been demonstrated both *in vitro* and *in vivo* that meropenem has a post-antibiotic effect.
A single set of meropenem susceptibility criteria are recommended based on pharmacokinetics and correlation of clinical and microbiological outcomes with zone diameter and minimum inhibitory concentrations (MIC) of the infecting organisms.

Categorisation	Method of assessment	
	Zone diameter (mm)	MIC breakpoints (mg/L)
Susceptible	≥14	≤4
Intermediate	12 to 13	8
Resistant	≤11	≥16

The *in vitro* antibacterial spectrum of meropenem includes the majority of clinically significant Gram-positive and Gram-negative, aerobic and anaerobic strains of bacteria, as shown below:

Gram-positive aerobes: *Bacillus* spp.*, Corynebacterium diphtheriae, Enterococcus faecalis, Enterococcus liquifaciens, Enterococcus avium, Listeria monocytogenes, Lactobacillus* spp.*, Nocardia asteroides, Staphylococcus aureus* (penicillinase negative and positive)*, Staphylococci-coagulase-negative;* including, *Staphylococcus epidermidis, Staphylococcus saprophyticus, Staphylococcus capitis, Staphylococcus cohnii, Staphylococcus xylosus, Staphylococcus warneri, Staphylococcus hominis, Staphylococcus simulans, Staphylococcus intermedius, Staphylococcus sciuri, Staphylococcus lugdunensis, Streptococcus pneumoniae* (penicillin susceptible and resistant), *Streptococcus agalactiae, Streptococcus pyogenes, Streptococcus equi, Streptococcus bovis, Streptococcus mitis, Streptococcus mitior, Streptococcus milleri, Streptococcus sanguis, Streptococcus viridans, Streptococcus salivarius, Streptococcus morbillorum, Streptococcus* Group G, *Streptococcus* Group F*, Rhodococcus equi.*

Gram-negative aerobes: *Achromobacter xylosoxidans, Acinetobacter anitratus, Acinetobacter lwoffii, Acinetobacter baumannii, Aeromonas hydrophila, Aeromonas sorbria, Aeromonas caviae, Alcaligenes faecalis, Bordetella bronchiseptica, Brucella melitensis, Campylobacter coli, Campylobacter jejuni, Citrobacter freundii, Citrobacter diversus, Citrobacter koseri, Citrobacter amalonaticus, Enterobacter aerogenes, Enterobacter (Pantoea) agglomerans, Enterobacter cloacae, Enterobacter sakazakii, Escherichia coli, Escherichia hermannii, Gardnerella vaginalis, Haemophilus influenzae* (including β-lactamase positive and ampicillin resistant strains), *Haemophilus parainfluenzae, Haemophilus ducreyi, Helicobacter pylori, Neisseria meningitidis, Neisseria gonorrhoeae* (including β-lactamase positive, penicillin resistant and spectinomycin resistant strains) *Hafnia alvei, Klebsiella pneumoniae, Klebsiella aerogenes, Klebsiella ozaenae, Klebsiella oxytoca, Moraxella (Branhamella) catarrhalis, Morganella morganii, Proteus mirabilis, Proteus vulgaris, Proteus penneri, Providencia rettgeri, Providencia stuartii, Providencia alcalifaciens, Pasteurella multocida, Plesiomonas shigelloides, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas alcaligenes, Burkholderia (Pseudomonas) cepacia, Pseudomonas fluorescens, Pseudomonas stutzeri, Pseudomonas pseudomallei, Pseudomonas acidovorans, Salmonella* spp., including *Salmonella enteritidis/typhi, Serratia marcescens, Serratia liquefaciens, Serratia rubidaea, Shigella sonnei, Shigella flexneri, Shigella boydii, Shigella dysenteriae, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificus, Yersinia enterocolitica.*

Anaerobic bacteria: *Actinomyces odontolyticus, Actinomyces meyeri, Bacteroides-Prevotella-Porphyromonas* spp.*, Bacteroides fragilis, Bacteroides vulgatus, Bacteroides variabilis, Bacteroides pneumosintes, Bacteroides coagulans, Bacteroides uniformis, Bacteroides distasonis, Bacteroides ovatus, Bacteroides thetaiotaomicron, Bacteroides eggerthii, Bacteroides capsillosis, Prevotella buccalis, Prevotella corporis, Bacteroides gracilis, Prevotella melaninogenica, Prevotella intermedia, Prevotella bivia, Prevotella splanchnicus, Prevotella oralis, Prevotella disiens, Prevotella rumenicola, Bacteroides ureolyticus, Prevotella oris, Prevotella buccae, Prevotella denticola, Bacteroides levii, Porphyromonas asaccharolytica, Bifidobacterium* spp.*, Bilophila wadsworthia, Clostridium perfringens, Clostridium bifermentans, Clostridium ramosum, Clostridium sporogenes, Clostridium cadaveris, Clostridium sordellii, Clostridium butyricum, Clostridium clostridiiformis, Clostridium innocuum, Clostridium subterminale, Clostridium tertium, Eubacterium lentum, Eubacterium aerofaciens, Fusobacterium mortiferum, Fusobacterium necrophorum, Fusobacterium nucleatum, Fusobacterium varium, Mobiluncus curtisii, Mobiluncus mulieris, Peptostreptococcus anaerobius, Peptostreptococcus micros, Peptostreptococcus saccharolyticus, Peptococcus saccharolyticus, Peptostreptococcus asaccharolyticus, Peptostreptococcus magnus, Peptostreptococcus prevotii, Propionibacterium acnes, Propionibacterium avidum, Propionibacterium granulosum.*

Stenotrophomonas maltophilia, Enterococcus faecium and methicillin-resistant *staphylococci* have been found to be resistant to meropenem.

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.

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 includes impermeability and/or an efflux pump(s).

5.2 Pharmacokinetic properties

A 30 minute intravenous infusion of a single dose of meropenem in healthy volunteers results in peak plasma levels of approximately 11 µg/ml for the 0.25 g dose, 23 µg/ml for the 0.5 g dose and 49 µg/ml for the 1 g dose.

However, there is no absolute pharmacokinetic proportionality with the administered dose both as regards Cmax and AUC. Furthermore, a reduction in plasma clearance from 287 to 205 ml/min for the range of dosage 0.25 g to 2 g has been observed.

A 5 minute intravenous bolus injection of meropenem in healthy volunteers results in peak plasma levels of approximately 52 µg/ml for the 0.5 g dose and 112 µg/ml for the 1 g dose.
Intravenous infusions of 1 g over 2 minutes, 3 minutes and 5 minutes were compared in a three way crossover trial. These durations of infusion resulted in peak plasma levels of 110, 91 and 94 µg/ml, respectively.
After an I.V. dose of 0.5 g, plasma levels of meropenem decline to values of 1 µg/ml or less, 6 hours after administration.
When multiple doses are administered at 8 hourly intervals to subjects with normal renal function, accumulation of meropenem does not occur.
In subjects with normal renal function, meropenem's elimination half-life is approximately 1 hour.
Plasma protein binding of meropenem is approximately 2%.
Approximately 70% of the administered dose is recovered as unchanged meropenem in the urine over 12 hours, after which little further urinary excretion is detectable. Urinary concentrations of meropenem in excess of 10 µg/ml are maintained for up to 5 hours after the administration of a 0.5 g dose. No accumulation of meropenem in plasma or urine was observed with regimens using 0.5 g administered every 8 hours or 1 g administered every 6 hours in volunteers with normal renal function.
The only metabolite of meropenem is microbiologically inactive.
Meropenem penetrates well into most body fluids and tissues including cerebrospinal fluid of patients with bacterial meningitis, achieving concentrations in excess of those required to inhibit most bacteria.

Pediatrics

Studies in children have shown that the pharmacokinetics of meropenem in children are similar to those in adults. The elimination half-life for meropenem was approximately 1.5 to 2.3 hours in children under the age of 2 years and the pharmacokinetics are linear over the dose range of 10 to 40 mg/kg.

Elderly

Pharmacokinetic studies in the elderly have shown a reduction in plasma clearance of meropenem, which correlated with age-associated reduction in creatinine clearance.

Renal insufficiency

Pharmacokinetic studies in patients with renal insufficiency have shown that the plasma clearance of meropenem correlates with creatinine clearance. Dosage adjustments are necessary in subjects with renal impairment.

Hepatic insufficiency

Pharmacokinetic studies in patients with liver disease have shown no effects of liver disease on the pharmacokinetics of meropenem.

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 2000 mg/kg and above after a single administration and above and in monkeys at 500 mg/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 1000 mg/kg.

The IV LD50 of meropenem in rodents is greater than 2000 mg/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 750 mg/kg and in monkeys up to 360 mg/kg.
There was increased evidence of abortions at 500 mg/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

Aropem should not be mixed with or added to other drugs.
Aropem is compatible with the following infusion fluids:
0.9% Sodium Chloride solution
5% or 10% Glucose solution

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 30°C. Do not freeze.

Injection

After reconstitution: The reconstituted solutions for intravenous injection should be used immediately. The time interval between the beginning of reconstitution and the end of intravenous injection should not exceed:

- 3 hours when stored at up to 25°C;
- 12 hours when stored under refrigerated conditions (2-8°C).

Infusion

After reconstitution: The reconstituted solutions for intravenous infusion should be used immediately. The time interval between the beginning of reconstitution and the end of intravenous infusion should not exceed:

- 3 hours when stored at up to 25°C when Aropem is dissolved in sodium chloride;
- 24 hours when stored under refrigerated conditions (2-8°C) when Aropem is dissolved in sodium chloride;
- when Aropem is dissolved in dextrose the solution should be used immediately.

6.5 Nature and contents of container

Aropem 0.5 g vial: 27 ml Type I flint glass vial with bromobutylic rubber stopper and aluminium seal, containing a white to almost white or pale yellow powder.
Aropem 1 g vial: 43.5 ml Type I flint glass vial with bromobutylic rubber stopper and aluminium seal, containing a white to almost white or pale yellow powder.

6.6 Special precautions for disposal and other handling

Directions for use

Standard aseptic technique should be employed during constitution. Shake constituted solution before use. All vials are for single use only.
Aropem can be given as an intravenous bolus injection over approximately 5 minutes or by intravenous infusion over approximately 15 to 30 minutes using the specific available presentations.
Aropem to be used for bolus intravenous injection should be constituted with sterile water for injection (5 ml per 250 mg meropenem). This provides an approximate concentration of 50 mg/ml. Constituted solutions are clear, and colourless or pale yellow.
Aropem for intravenous infusion may be constituted with compatible infusion fluids (50 to 200 ml).

7. Marketing Authorization holder

Arwan Pharmaceutical Industries Jadra, Lebanon

8. Marketing Authorization number

Aropem 0.5 g: 96606/12
Aropem 1g: 96607/12

9. Date of first Authorization/renewal of the authorization

29/11/12

10. Date of revision of the text

28/07/2016