Meropenem®

Sterile powder for solution for I.V. injection or infusion

Composition

Each vial contains: Meropenem trihydrate equivalent to 0.5 g/1 g of anhydrous meropenem with sodium carbonate.
Each gram of meropenem contains 208 mg sodium carbonate which equates to 90 mg (3.9 mmol) of sodium.

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.

Dosage and 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:
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 aged 4 to 18 years with cystic fibrosis, doses ranging from 25 to 40 mg/kg every 8 hours have 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.
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).

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
5% Glucose solution with 0.02% Sodium Bicarbonate
5% Glucose solution and 0.9% Sodium Chloride
5% Glucose with 0.225% Sodium Chloride solution
5% Glucose with 0.15% Potassium Chloride solution
Mannitol 2.5% or 10% solution.

Contraindications

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

Warnings and precautions

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.
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.

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.

Driving and using machines

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

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.

Overdosage

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.

Interactions

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 interaction 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.

Pharmacodynamics

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. 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), *Staphylococcus epidermidis, Staphylococcus haemolyticus, 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 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 ruminicola, 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 saccharolytics, 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.

Pharmacokinetics

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.
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.
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.
Pharmacokinetic studies in the elderly have shown a reduction in plasma clearance of meropenem, which correlated with age-associated reduction in creatinine clearance.
Pharmacokinetic studies in patients with liver disease have shown no effects of liver disease on the pharmacokinetics of meropenem.

Expiry date and storage conditions

See the expiry date printed on the outer carton.
This date refers to the product correctly stored in unopened package.
Beware not to use **Aropem** after this date.
Store below 30°C. Do not freeze.
Keep all medicines out of reach of children.
It is recommended to use freshly prepared solutions of **Aropem** for I.V. injection or infusion. Reconstituted product may be stored for up to 2 hours at controlled room temperature (15-25°C) or for up to 12 hours if kept in a refrigerator (4°C).

Diluents	Stability (hours)	
	At temperatures between 15-25°C	At 4°C
Solutions (1 to 20 mg/ml) prepared with:		
0.9% sodium chloride	4	24
5% glucose	1	4
5% glucose and 0.225% sodium chloride	1	4
5% glucose and 0.9% sodium chloride	1	2
5% glucose and 0.15% potassium chloride	1	6
2.5% or 10% mannitol intravenous infusion	2	16
10% glucose	1	2
5% glucose and 0.02% sodium bicarbonate intravenous infusion	1	6

Presentation

Aropem sterile powder for solution for I.V. injection or infusion is available in packs of 1 vial containing 0.5 g/1 g of meropenem with sodium carbonate.

Manufactured by: Zambon Switzerland Ltd
Cadempino, Switzerland
For: ARWAN Pharmaceutical Industries Lebanon s.a.l.
Jadra, Lebanon

THIS IS A MEDICAMENT

- Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of the reach of children.

Council of Arab Health Ministers, Union of Arab Pharmacists