MEROPENEM

AROPEN

500 mg Powder for Injection (IV)
1 g Powder for Injection (IV)
Antibacterial
(Carbapenem)

Formulation:
Each vial contains:
Meropenem (as trihydrate) USP..... 500 mg.

Each vial contains:
Meropenem (as trihydrate) USP..... 1 g.

Product Description:
Aropen 500 mg IV Injection/Infusion: White to yellowish crystalline powder.
Aropen 1 g IV Injection/Infusion: White to yellowish crystalline powder.

Pharmacokinetics:
After intravenous injection of meropenem 0.5 and 1g over 5 minutes, peak plasma concentrations of about 50 and 112 micrograms/mL respectively are attained. The same doses infused over 30 minutes produce peak plasma concentrations of 23 and 49 micrograms/mL, respectively. Meropenem has a plasma elimination half-life of about 1 hour; this may be prolonged in patients with renal impairment and is also slightly prolonged in children. Meropenem is widely distributed into body tissues and fluids including the CSF and bile. It is about 2% bound to plasma proteins. It is more stable to renal dehydropeptidase-I than imipenem and is mainly excreted in the urine by tubular secretion and glomerular filtration. About 70% of a dose is recovered unchanged in the urine over a 12-hour period and urinary concentrations above 10 micrograms/mL are maintained for up to 5 hours after a 500 mg dose. Meropenem is reported to have one metabolite (ICI-213689), which is inactive and is excreted in the urine. Meropenem is removed by haemodialysis.

Pharmacodynamics:
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 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 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 0.25 mg/l (Susceptible) and 1 mg/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.

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 pneumonia
$ Species that show natural intermediate susceptibility
£ All methicillin-resistant staphylococci are resistant to meropenem
† Resistance rate≥ 50% in one or more EU countries.
Glanders and melioidosis: Use of meropenem in humans is based on in vitro B.mallei and
B. pseudomallei susceptibility data and on limited human data. Treating physicians should refer to national and/or international consensus documents regarding the treatment of glanders and melioidosis.

Indications:
For the treatment of susceptible infections including intra-abdominal infections, gynaecological infections, meningitis, respiratory tract infections (including in cystic fibrosis patients), septicaemia, skin and skin structure infection, urinary tract infection and infection in immunocompromised patients.

Drug Interactions:
Probenecid inhibits the renal excretion of meropenem thereby increasing its plasma concentrations and prolonging its elimination half- life.

Contraindications:
Meropenem is contraindicated in patients with known hypersensitivity to any component of this product or to other drugs in the same class of in patients who have demonstrated anaphylactic reactions to ß- lactams.

Reporting of Suspected Adverse Reactions: To allow continued monitoring of the benefit/risk balance of the medicinal product, reporting of suspected adverse reaction is necessary. Healthcare professional are encouraged to report any suspected adverse reactions directly to the importer/ distributor and/or report to FDA: www.fda.gov.ph.
Patients are advised to seek immediate medical attention at the first sign/s of adverse reaction.

Adverse Effects:
Meropenem is more stable to renal dehydropeptidase-I than imipenem and use with cilastatin, which inhibits this enzyme, is not required. Meropenem may have less potential to induce seizures than imipenem.
Meropenem is always given with the enzyme inhibitor cilastatin and thus clinical experience relates to the combination. Adverse effects with imipenem-cilastatin are similar in general to those with other beta lactams. Hypersensitivity reactions such as skin rashes, urticaria, eosinophilia, fever, and, rarely, anaphylaxis may occur. Gastrointestinal effects include nausea, vomiting, diarrhoea, tooth or tongue discoloration, and altered taste. Superinfection with non-susceptible organisms such as Enterococcus faecium, strains of *Pseudomonas aeruginosa* with acquired resistance, and Candida may also occur. Pseudomembranous colitis may develop. Erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported rarely. Increases in liver enzymes and abnormalities in haematological parameters, including a positive

Coombs' test, have been noted. Local reactions such as pain or thrombophlebitis may occur after injection. Seizures or convulsions have been reported with imipenem-cilastatin, particularly in patients with a history of CNS lesions and/or poor renal function, but sometimes in those without predisposing factors for seizures given recommended doses. Mental disturbances and confusion have also been reported. Cilastatin has protected against the nephrotoxicity seen with high doses of imipenem given experimentally to animals. A harmless reddish coloration of urine has been observed in children.

Precaution:
Should not be given to patients who are hypersensitive to meropenem.

Dosage and Administration:
Meropenem is given intravenously as the trihydrate, but doses are expressed in terms of the amount of anhydrous meropenem; 1.14 g of meropenem trihydrate is equivalent to about 1 g of anhydrous meropenem. It is given by slow injection over 3 to 5 minutes or by infusion over 15 to 30 minutes in a usual adult dose of 0.5 to 1 g every 8 hours, increased to 2 g every 8 hours for meningitis; doses of up to 2 g every 8 hours have also been used in cystic fibrosis. Children over 3 months of age and weighing less than 50 kg may be given 10 to 20 mg/kg every 8 hours, increased to 40 mg/kg every 8 hours for meningitis. Doses of 25 to 40 mg/kg every 8 hours have been used in children with cystic fibrosis.

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.

As a precautionary measure, it is preferable to avoid the use of meropenem during pregnancy.

Breastfeeding
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.

Antimicrobial Action:
Meropenem is slightly more active than imipenem against Enterobacteriaceae

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 1000 mg x 3 daily administered intravenously over 30 minutes as the lowest dose. 2 g x 3 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.

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

Isolates may be reported as R without prior testing.

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)£
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 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

and slightly less active against Gram-positive organisms.

Direction for Reconstitution:
Dissolve the Meropenem 500 mg in 10mL and 1g in 20 mL of sterile water for injection for bolus administration. Add reconstituted injection to an IV container and further diluted with an appropriate infusion set. Constituted solution of IV Injection may be stored up to 2 hours at temperature not exceeding (30^{O}C). Freshly prepared solution of Meropenem should be used whenever possible.

Each vial is for single use only.

Before you administer Meropenem, look at the solution closely. It should be inspected visually for particulate matter and discoloration prior to administration.

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.

Keep your supplies in a clean, dry place when you are not using them, and keep all medications and supplies out of reach of children.

Overdose and Treatment
Relative overdose may be possible in patients with renal impairment if the dose is not adjusted as described dosage & administration. If adverse reactions occur following overdose, they are consistent with the side effects profile, 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.

Caution:
Foods, Drugs, Devices & Cosmetic Act prohibits dispensing without prescription.

Storage:
Store at temperatures not exceeding 30°C.

Availability:
500 mg Powder for Injection: One (1) box contains: USP type II colorless glass vial (as active) + USP type II colorless glass ampoule in 10mL (as diluent) wrapped in Alu/Clear PVC.

1 g Powder for Injection: One (1) box contains: USP type II colorless glass vial (as active) + 2 USP type II colorless glass ampoules in 10mL (as diluent) x 2's wrapped in Alu/Clear PVC.

500 mg Powder for Injection	: FDA Registration No. : DRP-10150
1 g Powder for Injection	: FDA Registration No. : DRP-10152
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