MERONEM IV
Trademark

FOR INTRAVENOUS ADMINISTRATION

Qualitative and quantitative composition
Meronem IV is presented as a sterile white powder containing meropenem; 500 mg or 1g as the trihydrate blended with anhydrous sodium carbonate for constitution. Meronem IV injection contains 208 mg sodium carbonate for each gram of meropenem (anhydrous potency).

Vial for I.V. injection or infusion	**Meronem 500 mg**	**Meronem 1000 mg**
Active ingredient:		
Meropenem trihydrate	570 mg	1140 mg
equivalent to anhydrous meropenem	500 mg	1000 mg
Excipient:		
Anhydrous sodium carbonate	104 mg	208 mg

For each gram of meropenem (anhydrous potency) the vial contains 90 mg (3.9 mmol) of sodium.

Pharmaceutical form
Powder for solution for intravenous injection or infusion.

Therapeutic indications
Meronem IV 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.

Meronem 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.

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: -

500 mg IV every 8 hours in the treatment of pneumonia, UTI, gynaecological infections such as endometritis, skin and skin structure infections.

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

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 500 mg, 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 Meronem 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 Meronem in patients under peritoneal dialysis.

Dosage in Adults with Hepatic Insufficiency

No dosage adjustment is necessary in patients with hepatic insufficiency (see " Special warnings and precautions for use").

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.

In meningitis the recommended dose is 40 mg/kg every 8 hours.

There is no experience in children with renal impairment.

Method of Administration

Meronem IV 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.

Meronem IV to be used for bolus intravenous injection should be constituted with sterile Water for Injections (5 ml per 250 mg Meropenem). This provides an approximate concentration of 50 mg/ml. Constituted solutions are clear, and colourless or pale yellow.

Meronem IV for intravenous infusion may be constituted with compatible infusion fluids (50 to 200 ml) (see "Incompatibilities and Special precautions for storage").

Contraindications

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

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. Meronem 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 Meronem 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 on Meronem 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 Meronem. 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 Meronem with potentially nephrotoxic drugs should be considered with caution. (For dosage see "Posology and method of administration").

Meronem 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, Meronem is not recommended for use below this age. There is no experience in children with altered hepatic or renal function.

Keep all medicines away from children.

Interactions 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 Meronem dosed without probenecid are adequate, the co-administration of probenecid with Meronem is not recommended.

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

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

Meronem has been administered concomitantly with other medications without adverse pharmacological interactions. However, no specific data regarding potential drug interactions is available (apart from probenecid as mentioned above).

Pregnancy and lactation

Pregnancy

The safety of Meronem in human pregnancy has not been evaluated. Animal studies have not shown any adverse effect on the developing foetus. The only adverse effect observed in animal reproductive studies was an increased incidence of abortions in monkeys at 13 times the expected exposure in man. Meronem 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. Meronem should not be used in breast-feeding women unless the potential benefit justifies the potential risk to the baby.

Effect on ability to drive and use machines

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

Undesirable effects

Meronem is generally well tolerated. Adverse events rarely lead to cessation of treatment. Serious adverse events are rare.

Frequency	System Organ Class	Event
Common(≥ 1% and < 10%)	Blood and lymphatic system disorders[1]	Thrombocythaemia
	Gastrointestinal disorders	Nausea, Vomiting, Diarrhoea
	Hepato-biliary disorders	Increases in serum, Transaminases, Bilirubin, Alkaline Phosphatase, Lactic Dehydrogenase.
	General disorders and administration site conditions	Inflammation, Thrombophlebitis, Pain
Uncommon (≥0.1% and <1%)	Blood and lymphatic system disorders	Eosinophilia, Thrombocytopenia
	Nervous system disorders	Headache, Paraesthesiae
	Skin and subcutaneous tissue disorders	Rash, Urticaria, Pruritis
Rare (≥ 0.01% and <0.1%)	Blood and lymphatic system disorders	Leucopenia, Neutropenia, Agranulocytosis
	Nervous system disorders	Convulsions[2]
	General and administration site disorders	Oral and Vaginal Candidiasis
Very Rare (<0.01%)	Blood and lymphatic system disorders	Haemolytic Anaemia
	Immune system disorders	Angioedema, Manifestations of Anaphylaxis
	Gastrointestinal disorders	Pseudomembranous Colitis
	Skin and subcutaneous tissue disorders	Erythema Multiforme, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis

[1] A positive direct or indirect Coombs test may develop in some subjects; there have been reports of reduction in partial thromboplastin time.

[2] Convulsions have been observed in a temporal association with the administration of Meronem; a causal relationship with Meronem has not been established.

Overdose

Accidental overdosage could occur during therapy, particularly in patients with renal impairment. Limited post-marketing experience indicates that adverse events following over dosage 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.

Pharmacodynamic properties

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), *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.

Pharmacokinetic properties
A 30 minute intravenous infusion of a single dose of Meronem in healthy volunteers results in peak plasma levels of approximately 11 µg/ml for the 250 mg dose, 23 µg/ml for the 500 mg 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 250 mg to 2 g has been observed.

A 5 minute intravenous bolus injection of Meronem in healthy volunteers results in peak plasma levels of approximately 52 µg/ml for the 500 mg 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 IV dose of 500 mg, 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 500 mg dose. No accumulation of meropenem in plasma or urine was observed with regimens using 500 mg 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 Meronem 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 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.

Pre-clinical Safety Data
Animal studies indicate that meropenem is well tolerated by the kidney. In animal studies meropenem has shown nephrotoxic effects, only at high dose levels (500 mg/kg).

Effects on the CNS; convulsions in rats and vomiting in dogs, were seen only at high doses (>2000 mg/kg).

For an IV dose the LD_{50} in rodents is greater than 2000 mg/kg. In repeat dose studies (up to 6 months) only minor effects were seen including a small decrease in red cell parameters and an increase in liver weight in dogs treated with doses of 500 mg/kg.

There was no evidence of mutagenic potential in the 5 tests conducted and no evidence of reproductive and teratogenic toxicity in studies at the highest possible doses in rats and monkeys; the no effect dose level of a (small) reduction in F_1 body weight in rat was 120 mg/kg. There was an increased incidence 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.

List of excipients
Meronem for IV injection and infusion includes the excipient anhydrous sodium carbonate.

Incompatibilities
Meronem should not be mixed with or added to other drugs.

Meronem 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.

Shelf-life
Please refer to the expiry date on the outer carton

Special precautions for storage
Do not store above 30°C.
Do not freeze

It is recommended to use freshly prepared solutions of Meronem for IV injection and infusion. Reconstituted product, constituted as described above, should be used immediately and must be stored for no longer than 24 hours under refrigeration, only if necessary.

Diluent	**Hours stable at 15-25°C**	**4°C**
Vials constituted with Water for Injections for bolus injection	8	48
Solutions (1 - 20 mg/ml) prepared with:		
* 0.9% sodium chloride	8	48
* 5% glucose	3	14
* 5% glucose and 0.225% sodium chloride	3	14
* 5% glucose and 0.9% sodium chloride	3	14
* 5% glucose and 0.15% potassium chloride	3	14
* 2.5% or 10% mannitol intravenous infusion	3	14
* 10% glucose	2	8
* 5% glucose and 0.02% sodium bicarbonate Intravenous Infusion	2	8

Pack size
Please refer to the outer carton for pack size

Instructions for Use/Handling
Refer to " Posology and method of administration" above. Standard aseptic technique should be employed during constitution. Shake constituted solution before use.

All vials are for single use only.

Date of revision of text
January 2010

INF.000-064-520.2.0

Manufactured by ACS Dobfar SpA, Italy for AstraZeneca UK Limited, Macclesfield, Cheshire, SK10 2NA. United Kingdom.

AstraZeneca