For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory.

℞ Meropenem for Injection I.P.

AMERICAN **Morenam** Injection — 500 mg / 1000 mg

FOR I.V. USE ONLY
COMPOSITION

MORENAM 500 mg
Each vial contains

Meropenem (Sterile)	IP	
Eq. to anhydrous Meropenem		500 mg
Sodium Carbonate anhydrous(Sterile)	IP	
Eq. to Sodium		45.1 mg

MORENAM 1000 mg
Each vial contains

Meropenem (Sterile)	IP	
Eq. to anhydrous Meropenem		1000 mg
Sodium Carbonate anhydrous(Sterile)	IP	
Eq. to Sodium		90.2 mg

PRESENTATION
MORENAM is presented as a sterile white powder filled in clear glass vial containing meropenem IP; 500 mg or 1g as the trihydrate blended with anhydrous sodium carbonate for constitution. **MORENAM** injection contains 208 mg sodium carbonate for each gram of meropenem IP (anyhydrous potency).

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

Pharmaceutical Form:
MORENAM is presented as a powder for constitution for intravenous administration.

INDICATIONS
MORENAM is indicated for treatment, in adults and children, for 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.

'**MORENAM**' 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:-

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

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

In meningitis the recommended dosage is 2g 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, 1g, 2g)	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 '**MORENAM**' 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 '**MORENAM**' in patients under peritoneal dialysis.

Dosage in Adults with Hepatic Insufficiency
No dosage adjustment is necessary in patients with hepatic insufficiency **(See "Special Warning 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 40mg/kg every 8 hours.

There is no experience in children with renal impairment.

Method of Administration
'**MORENAM**' can be given as an intravenous bolus injection over approximately 5 minutes or by intravenous infusion over approximately 15-30 minutes using the specific available presentations.

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

'Meropenem' for intravenous infusion may be constituted with compatible infusion fluids (50 to 200 ml) (see **"Incompatibilities and Special Precautions Storage"**)

CONTRA-INDICATIONS
'**MORENAM**' 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 "Possible Adverse Drug Reactions"). Before initiating therapy with meropenem, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics. '**MORENAM**' should be used with caution in patients with such a history. If any allergic reaction to meropenem occurs, the drug should be discontinued and appropriate measures taken.

Use of '**MORENAM**' 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 '**MORENAM**' 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 '**MORENAM**'. 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 '**MORENAM**' with potentially nephrotoxic drugs should be considered with caution. (For dosage see **"Dosage and Administration"**)

Paediatric use
Efficacy and tolerability in infants under 3 months old have not been established; therefore, '**MORENAM**' 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.

INTERACTION WITH OTHER MEDICAMENTS 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 '**MORENAM**' dosed without probenecid are adequate, the co-administration of probenecid with '**MORENAM**' is not recommended.

The potential effect of '**MORENAM**' on the protein binding of other drugs or metabolism has not been studied. The protein binding of '**MORENAM**' is low (approximately 2%) and, therefore, no interactions with other compounds based on displacement from plasma proteins would be expected. 'Meropenem' may reduce serum valproic acid levels. Subtherapeutic levels may be reached in some patients.

'**MORENAM**' 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 '**MORENAM**' 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 monkey at 13 times the expected exposure in man. '**MORENAM**' 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 concentions in animal breast milk. '**MORENAM**' should not be used in breast-feeding women unless the potential benefit justifies the potential risk to the baby.

EFFECT ON ABILITY TO DRIVE OR OPERATE MACHINERY
No data is available, but it is not anticipated that '**MORENAM**' will affect the ability to drive and use machines.

POSSIBLE ADVERSE DRUG REACTIONS
Serious adverse events are rare. During the clinical trials the following adverse events have been reported:

- Local intravenous injection site reactions: inflammation, thrombophlebitis, pain at the site of injection.
- Systemic allergic reactions: rarely, systemic allergic reactions (hypersensitivity) may occur following administration of meropenem. These reactions may include angioedema and manifestations of anaphylaxis.
- Skin reactions: rash, pruritus, urticaria ; Rarely severe skin reactions, such as erythema mutiforme, Stevens-Johnson Syndrome and toxic epidermal necrolysis, have been observed.
- Gastro-intestinal: abodominal pain, nausea, vomiting, diarrhoea. Pseudomembranous colitis has been reported.
- Blood: Reversible thrombocythaemia, eosinophilia, thrombocytopenia, leucopenia and neutropenia (including very rare cases of agranulocytosis). A positive direct or indirect Coombs test may develop in some subjects; there have been reports of reduction in partial thromboplastin time;
- Liver function: Increases in serum concentrations of bilirubin, transaminases, alkaline phosphatase and lactic dehydrogenase alone or in combination have been reported;
- Central nervous system: headache, paraesthesiae. Convulsions have been reported although a causal relationship with '**MORENAM**' has not been established.
- Other: Oral and vaginal candidosis.

* This drug may cause Hypokalemia as an adverse drug reaction.

OVERDOSAGE
Accidental overdosage could occur during therapy, particularly in patients with renal impairment. 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.

PHARMACOLOGICAL PROPERTIES
Pharmacological 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 B-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 concentration(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 show below:

Gram-positive aerobes:
Bacillus spp., Corynebacterium diphtheriae, Enterococcus faecalis, Enterococcus liquifaciens, Enterococcus avium, Listeria monocytogenes, Lactobacillus spp., Nocardia asteroides, Staphylococcus aureus (penicilinase 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* (pencillin susceptible and resistant), *Streptococcus agalactiae, Streptococcus pyogenes, Streptococcus equi, Streptococcus bovis, Streptococcus mitis, Streptococcus mitior, Streptococcus milleri, Streptococcus sanguis, Streptococcus viridans, Streptococcus salivarious, Streptococcus morbillorum Streptococcus Group G, Streptococcus Group F, Rhodococcus equi.*

Gram-negative aerobes:
Achromobacter xylosoxidans, Acinetobacter anitratus, Acinetobacter lwoffii Acinetobacter baumannii, Aeromons hydrophila, Aeromonas sorbria, Aeromonas caviae, Alcaligenes faecalis, Bordetella bronchiseptica, Brucella militensis, 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 b-lactamase positive and ampicillin resistant strains), *Haemophilus parainfluenzae, Haemophilus ducreyi, Helicobacter pylori, Neisseria meningitidis, Neisseria gonorrhoeae* (including b-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 rettegeri, Providencia stuartii, Providencia alcalifaciens, Pasteurella multocida, Plesiomonas shigelloides, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas alcaligenes, Burkholderia (Pseudomonas) cepacia, Pseudomonas fluorescens, Pseudomonas stutzeri, Pseudomonas pseudomallei, Pseudomonas acidovoran, 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, Eubactrium aerofaciens, Fusobacterium mortiferum, Fusobacterium necrophorum, Fusobacterium nucleatum, Fusobacterium varium, Mobiluncus curtisii, Mobiluncus mulieris, 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 '**MORENAM**' 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 '**MORENAM**' 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 microgram/ml, respectively.

After an IV dose of 500 mg, plasma levels of meropenem decline to values of 1µg/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 functions.

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 '**MORENAM**' 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 if F, 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.

PHARMACEUTICAL PARTICULARS
Incompatibilities
'**MORENAM**' should not be mixed with or added to other drugs.

'**MORENAM**' 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
0.9% Sodium Chloride and 5% Glucose solution
5% Glucose with 0.225% Sodium Chloride solution
5% Glucose with 0.15% Potassium Chloride solution
Mannitol 2.5% or 10% solution.

Special Precautions for Storage
Store protect from light at a temperature not exceeding 30°C.
Solutions of '**MORENAM**' should not be frozen.
It is recommended to use freshly prepared solutions of '**MORENAM**' for I.V. injection and infusion. Reconstituted product, constituted as described above, maintains satisfactory potency at room temperature (up to 25°C)or under refrigeration (4°C) as shown in the following table:-

Diluent	Hours stable	
	at 15-25°C	4°C
Vials constitute 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

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

All vials are for single use only.

Shelf Life
Please refer to the outer carton

Storage : Store below 25°C. Protected from light and moisture.
Improper storage may deteriorate the product.

Manufactured by:
AMERICAN REMEDIES
American Remedies Healthcare Pvt. Ltd.
(An ISO 9001:2015 Certified Company)