SAME SIZE ARTWORK
LEAFLET SIZE : 264 mm x 186 mm

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

MEROPENEM

AMERO 500 / AMERO IV

500 mg / 1 g Powder For Injection
Antibacterial

Composition of the product:

AMERO IV
Each vial contains :

Meropenem Trihydrate USP equivalent to Anhydrous Meropenem	1000mg
Sodium Carbonate USP equivalent to Sodium (as buffer)	90.2 mg

AMERO 500
Each vial contains :

Meropenem Trihydrate USP equivalent to Anhydrous Meropenem	500 mg
Sodium Carbonate USP equivalent to Sodium (as buffer)	45.1 mg

Pharmaceutical form:
Powder for solution for injection or infusion.
A white to off white crystalline powder.

Clinical Particulars:

Therapeutic Indications: Meropenem is indicated for the treatment of the following infections in adults and children over 3 months of age:

- Pneumonia, including community acquired pneumonia and nosocomial pneumonia
- Broncho pulmonary infections in cystic fibrosis
- Complicated urinary tract infections
- Complicated intra-abdominal infections
- Intra- and post-partum infections
- Complicated skin and soft tissue infections
- Acute bacterial meningitis

Meropenem may be used in the management of neutropenic patients with fever that is suspected to be due to bacterial infection. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Posology and method of administration

Adults:
The tables below provide general recommendations for dosing.

The dose of Meropenem administered and the duration of treatment should take into account the type of infection to be treated, including its severity, and the clinical response.

A dose of 2 g three times daily in adults and adolescents and a dose of up to 40 mg/kg three times daily in children may be particularly appropriate when treating some types of infections, such as nosocomial infections due to *Pseudomonas aeruginosa or Acinetobacter spp.*

Additional considerations for dosing are needed when treating patients with renal insufficiency (see further below).

Adults and adolescents

Infection	Dose to be administered every 8 hours
Pneumonia including community-acquired pneumonia and nosocomial pneumonia	500 mg or 1 g
Broncho-pulmonary infections in cystic fibrosis	2 g
Complicated urinary tract infections	500 mg or 1 g
Complicated intra-abdominal infections	500 mg or 1 g
Intra- and post-partum infections	500 mg or 1 g
Complicated skin and soft tissue infections	500 mg or 1 g
Acute bacterial meningitis	2 g
Management of febrile neutropenic patients	1 g

Meropenem is usually given by intravenous infusion over approximately 15 to 30 minutes. Alternatively, doses up to 1 g can be given as an intravenous bolus injection over approximately 5 minutes. There are limited safety data available to support the administration of a 2 g dose in adults as an intravenous bolus injection.

Renal impairment: The dose for adults and adolescents should be adjusted when creatinine clearance is less than 51 ml/min, as shown below. There are limited data to support the application of these dose adjustments for a unit dose of 2 g.

Creatinine clearance (ml/min)	Dose (based on "unit" dose range of 500 mg or 1 g or 2 g, see table above)	Frequency
26 - 50	one unit dose	every 12 hours
10 - 25	half of one unit dose	every 12 hours
< 10	half of one unit dose	every 24 hours

Meropenem is cleared by haemodialysis and haemofiltration. The required dose should be administered after completion of the haemodialysis cycle.

There are no established dose recommendations for patients receiving peritoneal dialysis.

Hepatic impairment
No dose adjustment is necessary in patients with hepatic impairment.

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

Paediatric population
Children under 3 months of age

The safety and efficacy of Meropenem 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.

Children from 3 months to 11 years of age and up to 50 kg body weight

The recommended dose regimens are shown in the table below:

Infection	Dose to be administered every 8 hours
Pneumonia including community-acquired pneumonia and nosocomial pneumonia	10 or 20 mg/kg
Broncho-pulmonary infections in cystic fibrosis	40 mg/kg
Complicated urinary tract infections	10 or 20 mg/kg
Complicated intra-abdominal infections	10 or 20 mg/kg
Complicated skin and soft tissue infections	10 or 20 mg/kg
Acute bacterial meningitis	40 mg/kg
Management of febrile neutropenic patients	20 mg/kg

Children over 50 kg body weight

The adult dose should be administered.

There is no experience in children with renal impairment.

Meropenem is usually given by intravenous infusion over approximately 15 to 30 minutes. Alternatively, meropenem doses of up to 20 mg/kg may be given as an intravenous bolus over approximately 5 minutes. There are limited safety data available to support the administration of a 40 mg/kg dose in children as an intravenous bolus injection.

Contraindications
Hypersensitivity to the active substance or to any of the excipients.
Hypersensitivity to any other carbapenem antibacterial agent.
Severe hypersensitivity (e.g. anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial agent (e.g. penicillins or cephalosporins).

Warnings and Precautions:

The selection of meropenem to treat an individual patient should take into account the appropriateness of using a carbapenem antibacterial agent based on factors such as severity of the infection, the prevalence of resistance to other suitable antibacterial agents and the risk of selecting for carbapenem-resistant bacteria.

As with all beta-lactam antibiotics, serious and occasionally fatal hypersensitivity reactions have been reported.

Patients who have a history of hypersensitivity to carbapenems, penicillins or other beta-lactam antibiotics may also be hypersensitive to Meropenem. Before initiating therapy with Meropenem, careful enquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics.

If severe allergic reaction occurs, the medicinal product should be discontinued and appropriate measures taken.

Antibiotic-associated colitis and pseudomembranous colitis have been reported with nearly all anti-bacterial agents, including meropenem, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of meropenem. Discontinuation of therapy with meropenem and the administration of specific treatment for Clostridium difficile should be considered.

Medicinal products that inhibit peristalsis should not be given.

Seizures have infrequently been reported during treatment with carbapenems, including meropenem.

Hepatic function should be closely monitored during treatment with meropenem due to the risk of hepatic toxicity (hepatic dysfunction with cholestasis and cytolysis).

Use in patients with liver disease: patients with pre-existing liver disorders should have liver function monitored during treatment with meropenem. There is no dose adjustment necessary.

A positive direct or indirect Coombs test may develop during treatment with meropenem.

The concomitant use of meropenem and valproic acid/sodium valproate is not recommended.

Meropenem contains sodium.

Meropenem 500 mg Powder for Solution for Injection or Infusion contains approximately 2.0 mEq of sodium per vial which should be taken into consideration by patients on a controlled sodium diet.

Drug and Laboratory Interactions
No specific medicinal product interaction studies other than probenecid have been conducted. Probenecid competes with meropenem for active tubular secretion and thus inhibits the renal excretion of meropenem with the effect of increasing the elimination half-life and plasma concentration of meropenem. Caution is required if probenecid is co-administered with meropenem.

The potential effect of meropenem on the protein binding of other medicinal products or metabolism has not been studied. However, the protein binding is so low that no interactions with other compounds would be expected on the basis of this mechanism.

Decreases in blood levels of valproic acid have been reported when it is co-administered with carbapenem agents resulting in 60-100% decrease in valproic acid levels in about two days. Due to the rapid onset and the extent of the decrease, co-administration of valproic acid with carbapenem agents is not considered to be manageable and therefore should be avoided.

Oral anti-coagulants
Simultaneous administration of antibiotics with warfarin may augment its anti-coagulant effects. There have been many reports of increases in the anti-coagulant effects of orally administered anti-coagulant agents, including warfarin in patients who are concomitantly receiving antibacterial agents. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the antibiotic to the increase in INR (international normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of antibiotics with an oral anti-coagulant agent.

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.

Lactation
It is unknown whether meropenem is excreted in human milk. Meropenem is detectable at very low concentrations in animal breast milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from meropenem therapy taking into account the benefit of therapy for the woman.

Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.

Undesirable effects
Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000) and very rare (<1/10,000) including isolated reports.

System Organ Class	Frequency	Event
Infections and infestations	Uncommon	Oral and vaginal candidiasis
Blood and lymphatic system disorders	Common	Thrombocythaemia
	Uncommon	Eosinophilia, thrombocytopenia, leucopenia, neutropenia
	Not known	Agranulocytosis, haemolytic anaemia
Immune system disorders	Not known	Angioedema, anaphylaxis
Nervous system disorders	Common	Headache
	Uncommon	Paraesthesiae
	Rare	Convulsions
Gastrointestinal disorders	Common	Diarrhoea, vomiting, nausea, abdominal pain
	Not known	Antibiotic-associated colitis
Hepatobiliary disorders	Common	Transaminases increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased
	Uncommon	Blood bilirubin increased
Skin and subcutaneous tissue disorders	Common	Rash, pruritis
	Uncommon	Urticaria
	Not known	Toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme
Renal and urinary disorders	Uncommon	Blood creatinine increased, blood urea increased
General disorders and administration site conditions		Common Inflammation, pain
	Uncommon	Thrombophlebitis
	Not known	Pain at the injection site

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Overdose
Relative overdose may be possible in patients with renal impairment if the dose is not adjusted as described. Limited post-marketing experience indicates that if adverse reactions occur following overdose, they are consistent with the adverse reaction profile described ealier, 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.

Pharmacological Properties

Pharmacodynamic properties
Pharmacotherapeutic group: antibacterials for systemic use, carbapenems, ATC code: J01DH02

Mode of action
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 antibacterial agents when the mechanism involved includes impermeability and/or an efflux pump(s).

Breakpoints
European Committee on Antimicroibial Susceptibility Testing (EUCAST) clinical breakpoints for MIC testing are presented below.

EUCAST clinical MIC breakpoints for meropenem (2009-06-05, v 3.1)

Organism	Susceptible (S) (mg/l)	Resistant (R) (mg/l)
Enterobacteriaceae	≤2	>8
Pseudomonas	≤2	>8
Actinobacter	≤2	>8
Streptococcus groups A, B, C, G	≤2	>2
Streptococcus pneumoniae[1]	≤2	>2
Other streptococci	2	2
Enterococcus	--	--
Staphylococcus[2]	note[3]	note[3]
Haemophilus influenzae1 and Moraxella catarrhalis	≤2	>2
Neisseria meningitides[2,4]	≤0.25	>0.25
Gram-positive anaerobes	≤2	>8
Gram-negative anaerobes	≤2	>8
Non-species related breakpoints[5]	≤2	>8

1 Meropenem breakpoints for Streptococcus pneumoniae and Haemophilusinfluenzae in meningitis are 0.25/1 mg/L.
2 Strains with MIC values above the S/I breakpoint are 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 above the current breakpoint (in italics) they should be reported as resistant.
3 Susceptibility of staphylococci to meropenem is inferred from the methicillin susceptibility.
4 Meropenem breakpoints in Neisseria meningitides relates to meningitis only.
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 for species not mentioned in the table and footnotes.
-- = Susceptibility testing not recommended as the species is a poor target for therapy with the medicinal product.

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)[£]
Stahylococcus species (methicillin-susceptible) including Staphylococcus epidermis
Streptococcus agalactiae (Group B)
Streptococcus milleri group (S. anginosus, S. constellatus, and S. intermedius)
Streptococcus pneumoniae
Streptococcus pyogenes (Group A)
Gram-negative aerobes
Citrobacterfreudii
Citrobacterkoseri
Enterobacteraerogenes
Enterobacter cloacae
Escherichia coli
Haemophilusinfluenzae
Klebsiellaoxytoca
Klebsiellapneumoniae
Morganellamorganii
Neisseria meningitides
Proteus mirablis
Proteus vulgaris
Serratiamarcescens
Gram-positive anaerobes
Clostridium perfringens
Peptoniphilusasaccharolyticus
Peptostreptococcus species (including P. micros, P. anaerobius, P. magnus)
Gram-negative anaerobes
Bacteroidescaccae
Bacteroidesfragilis group
Prevotellabivia
Prevotelladisiens
Species for which acquired resistance may be a problem
Gram-positive aerobes
Enterococcus faecium[¥]
Gram-negative aerobes
Actinobacter species
Burkholderiacepacia
Pseudomonas aeruginosa
Inherently resistant organisms
Gram-negative aerobes
Stenotrophomonasmaltophilia
Legionella species
Other micro-organisms
Chlamydophilapneumoniae
Chlamydophilapsittaci
Coxiellaburnetti
Mycoplasma pneumoniae
‡ Species that show natural intermediate susceptibility
£ All methicillin-resistant staphylococci are resistant to meropenem
¥ Resistance rate ≥ 50% in one or more EU countries

Pharmacokinetic properties
In healthy subjects the mean plasma half-life is approximately 1 hour; the mean volume of distribution is approximately 0.25 l/kg (11-27 l) and the mean clearance is 287 ml/min at 250 mg falling to 205 ml/min at 2 g. Doses of 500, 1000 and 2000 mg doses infused over 30 minutes give mean C_{max} values of approximately 23, 49 and 115 µg/ml respectively, corresponding AUC values were 39.3, 62.3 and 153 µg.h/ml. After infusion over 5 minutes C_{max} values are 52 and 112 µg/ml after 500 and 1000 mg doses respectively. When multiple doses are administered 8-hourly to subjects with normal renal function, accumulation of meropenem does not occur.

Distribution
The average plasma protein binding of meropenem was approximately 2% and was independent of concentration. After rapid administration (5 minutes or less) the pharmacokinetics are biexponential but this is much less evident after 30 minutes infusion. Meropenem has been shown to penetrate well into several body fluids and tissues: including lung, bronchial secretions, bile, cerebrospinal fluid, gynaecological tissues, skin, fascia, muscle, and peritoneal exudates.

Metabolism
Meropenem is metabolised by hydrolysis of the beta-lactam ring generating a microbiologically inactive metabolite. In vitro meropenem shows reduced susceptibility to hydrolysis by human dehydropeptidase-I (DHP-I) compared to imipenem and there is no requirement to co-administer a DHP-I inhibitor.

Elimination
Meropenem is primarily excreted by the kidneys; approximately 70% (50-75%) of the dose is excreted unchanged within 12 hours. A further 28% is recovered as the microbiologically inactive metabolite. Faecal elimination represents only approximately 2% of the dose. The measured renal clearance and the effect of probenecid show that meropenem undergoes both filtration and tubular secretion.

Renal insufficiency
Renal impairment results in higher plasma AUC and longer half-life for meropenem. There were AUC increases of 2.4 fold in patients with moderate impairment (CrCL 33-74 ml/min), 5 fold severe impairment (CrCL 4-23 ml/min) and 10 fold haemodialysis patients (CrCL<2 ml/min) when compared to healthy patients (CrCL>80 ml/min). The AUC of the microbiologically inactive ring opened metabolite was also considerably increased in patients with renal impairment. Dose adjustment is recommended for patients with moderate and severe renal impairment.

Meropenem is cleared by haemodialysis with clearance during haemodialysis being approximately 4 times higher that in anuric patients.

Paediatrics
The pharmacokinetics in infants and children with infection at doses of 10, 20 and 40 mg/kg showed C_{max} values approximating to those in adults following 500, 1000 and 2000 mg doses respectively. Comparison showed consistent pharomacokinetics between the doses and half-lives similar to those observed in adults in all but the youngest subjects (<6 months t1/2 1.6 hours). The mean meropenem clearance values were 5.8 ml/min/kg (6-12 years), 6.2 ml/min/kg (2-5 years), 5.3 ml/min/kg (6-23 months) and 4.3 ml/min/kg (2-5 months). Approximately 60% of the dose is excreted in urine over 12 hours as meropenem with a further 12% as metabolite. Meropenem concentrations in the CSF of children with meningitis are approximately 20% of concurrent plasma levels although there is significant inter-individual variability.

The pharmacokinetics of meropenem in neonates requiring anti-infective treatment showed greater clearance in neonates with higher chronological or gestational age with an overall average half-life of 2.9 hours. Monte Carlo simulation based on a population PK model showed that a dose regimen of 20 mg/kg 8 hourly achieved 60% T>MIC for P. aeruginosa in 95% of pre-term and 91% of full term neonates.

Elderly
No dose adjustment is required in elderly patients, except in cases of moderate to severe renal impairment.

Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned.

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

For suspected adverse drug reactions, report to FDA: www.fda.gov.ph

Shelf life: 24 months

Storage: Store at temperatures not exceeding 30°C. Protect from light.

Availability:
1 vial x 500 mg Powder for Injection (DRP-7690-02)
1 vial x 1g Powder for Injection (DRP-7691-01)

Instructions for Use/Handling

Administer by IV injection or infusion.

IV Injection

Reconstitution and Dilution
Reconstitute single-use vials containing 0.5g/1 g with 10 or 20 mL, respectively, of sterile water for injection to provide a solution containing approximately 50 mg/mL. The vial should be shaken until dissolution occurs and then allowed to stand until the solution is clear.

Rate of Administration
The appropriate dose of reconstituted solution should be injected over a period of 3–5 minutes.

IV Infusion

Reconstitution and Dilution
Reconstitute infusion vials containing 0.5 g /1 g with a compatible IV solution 10 or 20 mL (e.g., 0.9% sodium chloride, 5% dextrose) to provide solutions containing approximately 50 mg/mL. Alternatively, reconstitute vials containing 0.5 g/ 1 g with 10 or 20 mL, respectively, of sterile water for injection and then further dilute in a compatible IV.

Rate of Administration
Infuse IV over 15-30 minutes.

Shake constituted solution before use.
It is recommended to use freshly prepared solutions of 'Meropenem' 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
Sterile water for injection	3 hours at 15-25°C 16 hours at 2-8°C
0.9% Sodium Chloride	6 hours at 15-25°C 30 hours at 2-8°C
5 % Dextrose Injection	2 hours at 15-25°C 6 hours at 2-8°C
10% Dextrose Injection	2 hours at 15-25°C 3 hours at 2-8°C
5% Dextrose and 0.9% Sodium Chloride Injection	2 hours at 15-25°C 3 hours at 2-8°C
Ringer Lactate Injection	6 hours at 15-25°C 16 hours at 2-8°C

Date of First Authorization: 06 February 2018

Date of Revision of Package Insert: June 2018

Manufactured by :
Zeiss Pharmaceuticals Pvt. Ltd.
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Manufactured for :
Glenmark Pharmaceuticals Ltd.
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Imported by :
GLENMARK PHILIPPINES, INC.
Units 901-902, 9th Floor, 11th Corporate Center Building, 11th Avenue cor. Triangle Drive, North Bonifacio, Bonifacio Global City, Taguig City 1634. PHILIPPINES

Distributed by :
BIOCARE LIFESCIENCES INC.
4th Floor, 393 Goodwill Bldg., Sen. Gil Puyat Ave., Brgy. Bel - air, Makati City

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