MERANTIZ-EDTA

(Meropenem &Edta for Injection-1037.50mg)
For Intravenous use.

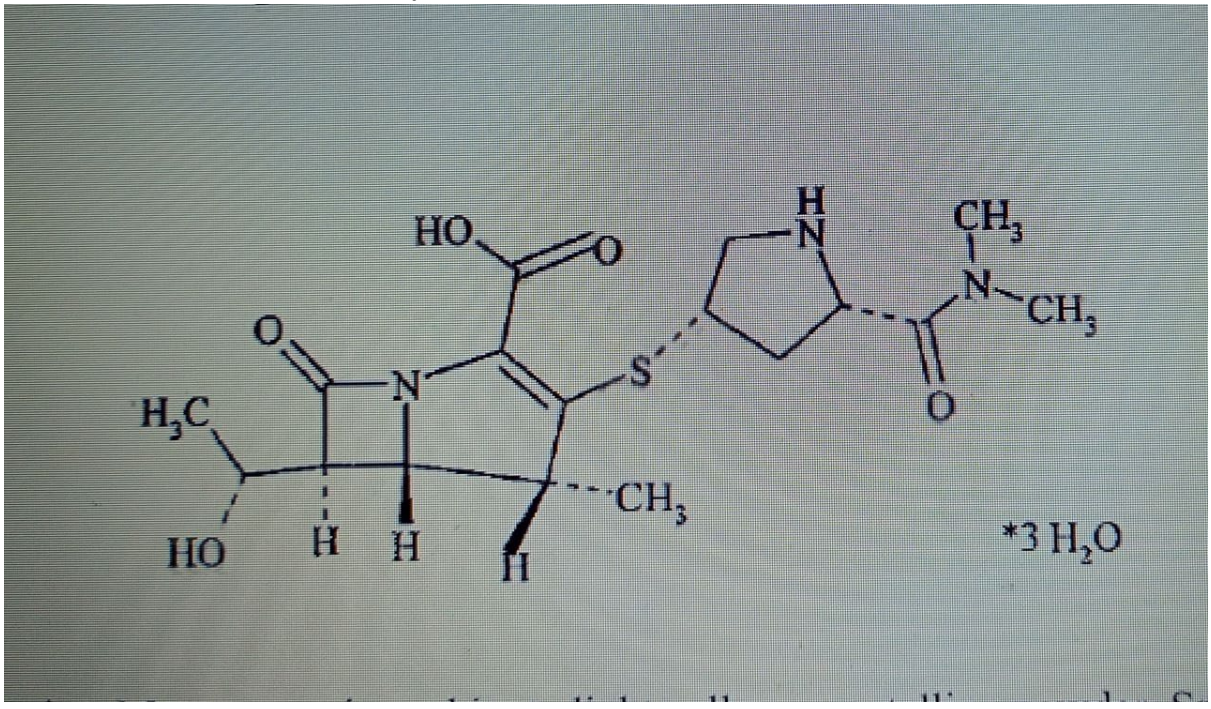
Each vial contains Meropenem 1000mg as Meropenem Trihydrate and EDTA 37.50 as EDTA Sodium

PHARMACEUTICAL INFORMATION

Meropenem.
Drug Substance

Proper name	Meropenem
Chemical Name	(-)-(4R,5S,6S)-3-[[(3S,5S)-5-(dimethylcarbamoyl)3-pyrrolidinyl]thio]-6-[(1R)-1-hydroxyethyl]-4-Methyl-7-oxo-1-azabicyclo(3,2,0)hept-2-ene-2-Carboxylic acid Trihydrate.
Molecular Formula and Molecular Mass	$C_{17}H_{31}N_3O_8S$ 437.51 g/mol (trihydrate) 383.47 g/mol (anhydrous)

Structural Formula-Meropenem.

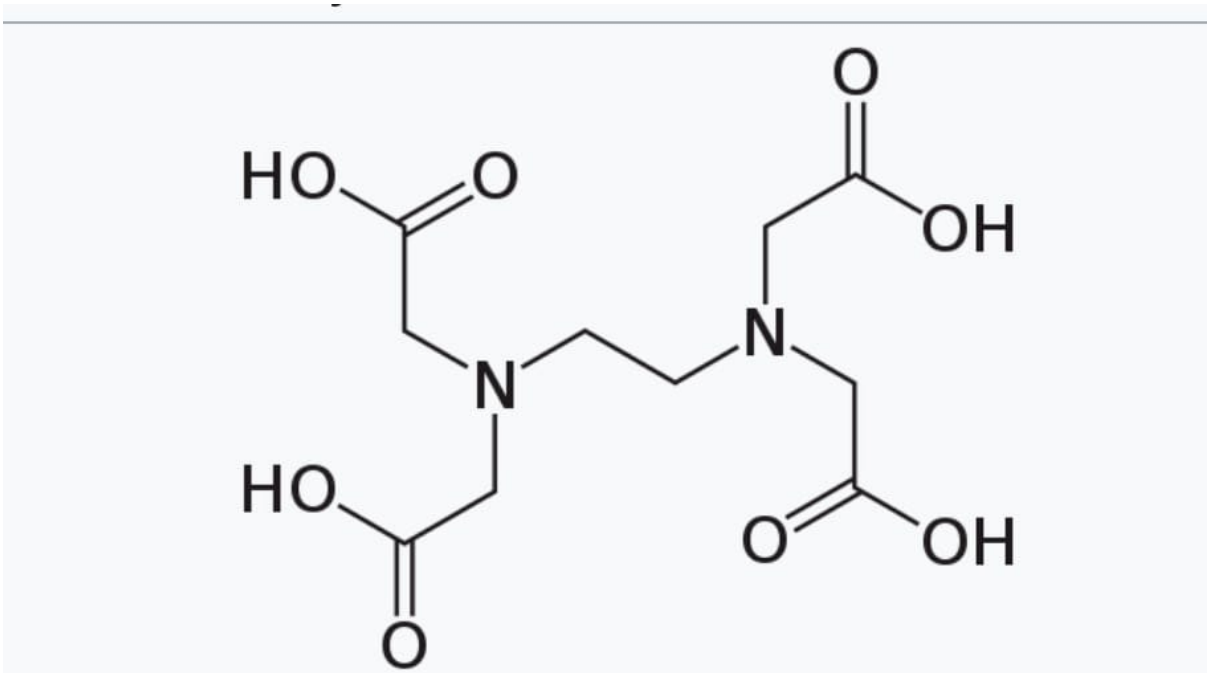


EDTA

Proper Name	EDTA
Chemical Name	2,2',2",2"'-(Ethane-1,2-diyldinitro)tetra acetic Acid.
Molecular formula	

And Molecular mass C10H16N2O8
336.21-AS Disodium EDTA.

Structural formula



PHARMACOLOGY

Meropenem failed to cause any changes of biological significance in the following series of general pharmacology tests.

Autonomic Pharmacology In Vitro

Sympathetic Function In Vivo

Gastrointestinal system

Cardiovascular Function

Renal Pharmacology

Central Nervous System Pharmacology

Metabolic Homeostasis

Haemostasis

Respiratory Function

Immune function.

MICROBIOLOGY

The in vitro susceptibility to meropenem of a given isolate should be determined by standard methods. Interpretations of in vitro test results should be made in accordance with local infectious diseases and clinical microbiology guidelines. Meropenem has been shown to be active against the following microorganisms (List1) in clinical infections as described in the INDICATIONS AND CLINICAL USE section. In vitro data from clinical isolates collected over the period 2005 to 2011 indicate that the following species remain susceptible to meropenem.

List 1

Aerobic and facultative Gram-positive microorganisms

Staphylococcus aureus (methicillin- susceptible strains only)
Staphylococcus epidermidis (methicillin- susceptible strains only)
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes
Viridans group streptococci
Aerobic and facultative Gram-negative microorganisms
Citrobacter freundii
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae (including β-lactamase-producing
Klebsiella pneumoniae
Morganella morganii
Neisseria meningitidis
Proteus mirabilis
Pseudomonas aeruginosa
Serratia marcescens
Gram-positive anaerobes
Clostridium perfringens
Peptostreptococcus species
Gram-negative anaerobes

Bacteroides fragilis
Bacteroides ova
Bacteroides thetaiotaomicron
Bacteroides vulgatus
Prevotella bivia

The published medical microbiology literature describes in vitro Meropenem-susceptibilities of many other bacterial species. However, the clinical significance of in vitro findings should be obtained from local infectious diseases and clinical microbiology experts and local professional
guidelines. The clinical safety and efficacy of meropenem have not been established for treatment of infections caused by the organisms presented in List 2.

List 2
Aerobic and facultative Gram-positive microorganisms
Streptococcus anginous
Aerobic and facultative Gram-negative microorganisms
Enterobacter aerogenes

MICs and MBCs are little affected by changes in inoculum concentration from 10^4 to 10^8 cfu/Ml or when conducted in broth adjusted in pH over the range of 5-7 or in test medium supplemented with 50% human serum. At pH 8, only P. aeruginosa showed increased MICs and MBCs. Meropenem post-antibiotic effects ≥ 0.5 h were obtained with 87% of all strains tested including Enterobacteriaceae strains, Gram-positive aerobes, B. fragilis and in vivo in neutropenic mice infected with *P. aeruginosa*. In vitro tests show Meropenem to act synergistically with aminoglycoside antibiotics against some isolates of Pseudomonas aeruginosa and some of the Enterobacteriaceae. Meropenem and vancomycin act synergistically against some enterococci and coagulase-positive and coagulase-negative staphylococcal strains, including those resistant to methicillin. These in vitro tests show meropenem does not act antagonistically with aminoglycosides or vancomycin against Gram-negative and Gram-positive aerobes, respectively.

INDICATIONS AND CLINICAL USE
Meropenem edta for Injection is indicated for treatment of the following infections

when caused by susceptible strains of the designated micro-organisms:

Lower Respiratory Tract

Community-acquired pneumonia caused by Staphylococcus aureus (methicillin-susceptible strains only), Streptococcus pneumoniae, Escherichia coli and Haemophilus influenzae (including β-lactamase-producing strains).

Nosocomial pneumonia caused by Staphylococcus aureus (methicillin-susceptible strains only), Escherichia coli, Haemophilus influenzae (non-β-lactamase-producing), Klebsiella pneumoniae and Pseudomonas aeruginosa.

Urinary Tract

Complicated urinary tract infections caused by Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa and Serratia marcescens.

Intra-abdominal

Complicated intra-abdominal infections caused by Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Morganella morganii, Pseudomonas aeruginosa, Bacteroides fragilis, Bacteroides ovatus, Bacteroidesthetaiotaomicron, Bacteroides vulgatus, Clostridium perfringens and Peptostreptococcus species.

Gynaecology

Gynaecologic infections caused by Staphylococcus aureus (methicillin-susceptible strains only),Staphylococcus epidermidis (methicillin-susceptible strains only), Escherichia coli, Prevotella bivia and Peptostreptococcus species.

Pelvic inflammatory disease caused by Staphylococcus epidermidis (methicillin-susceptible strains only), Streptococcus agalactiae, Escherichia coli and Prevotella bivia.

Uncomplicated Skin and Skin Structure

Uncomplicated skin and skin structure infections caused by Staphylococcus aureus (methicillin-susceptible strains only),

Streptococcus agalactiae, Streptococcus pyogenes and Escherichia coli.

Complicated Skin and Skin Structure

Complicated skin and skin structure infections, except infected burns, due to Staphylococcus aureus (methicillin-susceptible strains), Streptococcus pyogenes, Streptococcus agalactiae,Viridans group streptococci, Escherichia coli, Pseudomonas aeruginosa, Proteus mirabilis, Klebsiella pneumoniae, Peptostreptococcus species and Bacteroides fragilis.

Bacterial Meningitis

Bacterial meningitis caused by Streptococcus pneumoniae, Haemophilus influenzae (including β-lactamase-producing strains) and Neisseria meningitidis.

NOTE: There is limited adult efficacy data for meropenem in the treatment of bacterial meningitis. Support for the adult meningitis indication is largely provided by paediatric data.

Bacterial Septicaemia

Bacterial septicaemia caused by Escherichia coli.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Meropenem and other antibacterial drugs, Meropenem should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Therapy with Meropenem for Injection may be initiated on the basis of clinical judgement before results of sensitivity testing are available. Continuation of therapy should be re-evaluated on the basis of bacteriological findings on patients' clinical conditions. Regular sensitivity testing recommended when treating Pseudomonas aeruginosa infections.

Appropriate use of meropenem edta should be guided by local susceptibility data accumulated for key bacterial pathogens

Localised clusters of infections due to carbapenem-resistant bacteria have been reported in some regions.
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.
Paediatrics (≥ 3 months of age):

The safety and effectiveness of Meropenem for Injection in the paediatric population 3 months of age and older have been established. Meropenem for Injection is not recommended for use in infants under the age of 3 months (see WARNINGS AND PRECAUTIONS, Special Populations).

CONTRAINDICATIONS
Meropenem is contraindicated in patients with known hypersensitivity to any component of this product or in patients who have demonstrated anaphylactic reactions to β-lactam antibiotics

(See DOSAGE FORMS, COMPOSITION AND PACKAGING).

WARNINGS AND PRECAUTIONS)
Serious Warning and Precautions
SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC)REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING THERAPY WITH β-LACTAM ANTIBIOTICS, INCLUDING MEROPENEM. THESE REACTIONS ARE MORELIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF SENSITIVITY TOMULTIPLE ALLERGENS (see ADVERSE REACTIONS).

THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN
HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHENTREATED WITH ANOTHER β-LACTAM

ANTIBIOTIC. BEFORE INITIATING THERAPYWITH MEROPENEM FOR INJECTION, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, OTHER ALLERGENS. IFAN ALLERGIC REACTION TO MEROPENEM FOR INJECTION OCCURS, DISCONTINUE THE DRUG IMMEDIATELY. **ANAPHYLACTIC REACTIONSREQUIRE IMMEDIATE TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, ANTIHISTAMINES AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, MAY BE REQUIRED.**

Seizures

Meropenem for Injection, like all β-lactam antibiotics, has the potential to cause seizures. Diminished renal function and central nervous system lesions may increase the risk of seizures. When Meropenem for Injection is indicated in patients with these risk factors, caution is advised. Convulsions have been observed in a temporal association with use of meropenem.

Valproic Acid Interaction

Case reports in the literature have shown that co-administration of carbapenems, including meropenem, to patients receiving valproic acid or divalproex sodium results in a reduction in valproic acid concentrations. The valproic acid concentrations may drop below the therapeutic range as a result of this interaction, therefore increasing the risk of breakthrough seizures. Increasing the dose of valproic acid or divalproex sodium may not be sufficient to overcome this interaction. The concomitant use of meropenem and valproic acid or divalproex sodium is generally not recommended. Antibacterials other than carbapenems should be considered to treat infections in patients whose seizures are well controlled on valproic acid or divalproex sodium. If administration of Meropenem for Injection is necessary, supplemental anti-convulsant therapy should be considered. The concomitant use of valproic acid/sodium valproate and Meropenem for Injection is not recommended (see DRUG INTERACTIONS, Drug-Drug Interactions).

General

As with other broad-spectrum antibiotics, prolonged use of Meropenem

for Injection may result overgrowth of no susceptible organisms. Repeated evaluation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

No studies on the ability to drive and use machines have been performed. However, when driving or operating machines, it should be taken into account that headache, paraesthesia, and convulsions have been reported for meropenem.

Meropenem edta for Injection should not be used to treat infections caused by methicillin resistant staphylococci.

When treating infections known or suspected to be caused by *Pseudomonas aeruginosa*, higher doses are recommended based on pharmacokinetic/ pharmacodynamic modelling and probability of target attainment simulation for susceptible strains *of Pseudomonas aeruginosa* (MIC < 2 mcg/mL) (see DOSAGE AND ADMINISTRATION and MICROBIOLOGY). Caution may be required in critically ill patients with known or suspected *Pseudomonas aeruginosa* lower respiratory tract infections.

Gastrointestinal

Clostridium difficile-associated disease

Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents, including meropenem. CDAD may range in severity from mild diarrhoea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhoea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of colon
subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agent.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of Clostridium difficile. C. difficile produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against Clostridium difficile. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against Clostridium difficile. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases
(see ADVERSE REACTIONS).

Hepatic/Biliary/Pancreatic
Patients with pre-existing liver disorders should have their liver function monitored during treatment with Meropenem edta for Injection.

Susceptibility/Resistance
Development of Drug-Resistant Bacteria
Prescribing Meropenem edta for Injection in the absence of a proven or strongly suspected bacteria infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

Special Populations
Pregnant Women: There are no adequate and well-controlled studies in pregnant women. Meropenem for Injection should be used during pregnancy only if the potential benefit justifies the potential risk to mother and foetus. Reproduction studies have been performed in rats and Cynomolgus monkeys at doses up to 1000 mg/kg/day (approximately 16 times the usual human dose of 1 g every 8 hours). These studies revealed no evidence of impaired fertility or harm to the foetus due to meropenem edta although there were slight changes in fatal body weight at doses of 240 mg/kg/day and above in rats.

Nursing Women: Meropenem has been reported to be excreted in human milk. Meropenem edta for Injection should not be given to breast-feeding women unless the potential benefit justifies the potential risk to the baby.
Paediatrics (≥ 3 months of age): The safety and effectiveness of meropenem edta in the Paediatrics 3 months of age and older have been established. Meropenem for Injection is not recommended for use in infants under the age of 3 months.

The use of meropenem in paediatric patients with bacterial meningitis is supported by evidence from adequate and well controlled studies in the paediatric population. Use of meropenem edta in
paediatric patients for all other indications, as listed in the INDICATIONS section, is supported by evidence from adequate and well controlled studies in adults with additional data from
paediatric pharmacokinetic studies and controlled clinical trials in paediatric patients (see DOSAGE AND ADMINISTRATION, Children).

NOTE: Inadequate data are available to support the paediatric indications for nosocomial pneumonia, septicaemia and complicated skin and skin structure infections.
Renal Impairment: Dosage adjustment is recommended for patients with renal insufficiency
(see DOSAGE AND ADMINISTRATION).

Geriatrics (≥ 65 years of age): This drug is known to be substantially excreted by the kidney. No dose adjustment is required in elderly patients, except in cases of moderate to severe renal
impairment (see DOSAGE AND ADMINISTRATION).

Monitoring and Laboratory Tests
Use of Meropenem for Injection may lead to the development of a positive direct or indirect Coombs test.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Meropenem edta is generally well tolerated. Many patients receiving meropenem edta are severely ill, have multiple background diseases, physiological impairments and receive multiple other drug
therapies. In such seriously ill patients, it is difficult to establish the relationship between adverse events and meropenem edta.

Serious adverse reactions include occasionally fatal hypersensitivity (anaphylactic) reactions and severe skin reactions (erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis) which require immediate discontinuation of the drug and standard of care treatment.
The most commonly reported drug-related adverse events in the clinical trial programme were inflammation at the site of injection, diarrhoea, nausea and vomiting, and rash. The most commonly reported laboratory adverse events included increased levels of ALT and AST and

increased platelets.

Clinical Trial Adverse Drug Reactions
Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates. The safety of meropenem has been evaluated in a clinical trial program of 3187 adults and children, in a range of bacterial infections including pneumonia, complicated urinary tract, intra-abdominal and skin/skin structure infections, gynaecological infections and meningitis

A subsequent safety review on an expanded clinical trial database of 4872 patients treated intravenously or intramuscularly with meropenem (5026 treatment exposures) was generally consistent with earlier findings. Table 1 presents a summary of clinical trial adverse drug reactions, judged by the investigator to be related to therapy with meropenem (possibly, probably or definitely), that occurred at frequencies greater than 0.2% in the 3187 patients treated intravenously with meropenem, plus those reactions only observed in the expanded clinical trial database at frequencies greater than or equal to 0.1%.

Table 1 Meropenem Clinical Trial Adverse Drug Reactions with Frequency ≥ 0.2% (N = 3187 patients) and Frequency ≥ 0.1% only observed in the expanded clinical database (N=4872 patients)

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System/organ	Frequency	Reaction
Blood and lymphatic system	Common Un common	Thrombocytopenia Eosinophelia,thrombocytopenia Neutropenia,leucopenia
GIT Disorders	Common	Diarrhoea,nausea,vomiting

General disorders and administration state condition	Common Un common	Fever, injection site inflammation Injection site phlebitis,thrombo Phlebitis, injection site reaction.
Infection and infestation	Un common	Oral and vaginal candidiasis, vaginitis
Nervous system disorders	Common Un common	Headache Paratheses
Skin and subcutaneous tissue disorders	Common Un common	Rash,Pruruitis Urticaria

Less Common Clinical Trial Adverse Drug Reactions (< 0.2%, N=3187)

Blood and lymphatic system disorders: Agranulocytosis

Gastrointestinal disorders: Constipation

General disorders and administration site conditions: Abdominal pain, chills, infection, injection site pain and injection site oedema

Metabolism and nutrition disorders: Peripheral oedema

Nervous system disorders: Agitation, convulsions, dizziness, hallucinations, neuropathy, taste perversity

Renal and urinary disorders: Renal impairment

Skin and subcutaneous tissue disorders: Sweating

DRUG INTERACTIONS

Overview

Other than probenecid and valproic acid, no specific drug interaction studies were conducted.

Drug-Drug Interactions

• Probenecid

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. The coadministration of probenecid with meropenem is neither required nor recommended.

• Valproic Acid

Decreases in blood levels of valproic acid have been reported when it is co-administered with carbapenem agents resulting in a 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 meropenem in patients stabilized on valproic acid is not considered to be manageable and therefore should be avoided (see WARNINGS AND PRECAUTIONS, General).

Drug-Laboratory Interactions
Use of Meropenem for Injection may lead to the development of a positive direct or indirect Coombs test.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Adults
The usual dose is 500 mg to 1 g by intravenous infusion every 8 hours, depending on the type and severity of infection, the known or suspected susceptibility of the pathogens and the condition of the patient (see Table 3). Doses up to 2 g every 8 hours have been used.

Meropenem for Injection should be given by intravenous infusion over approximately 15 to30 minutes or as an intravenous bolus injection (5 to 20 mL) over approximately 5 minutes (see DOSAGE AND ADMINISTRATION, Administration and Reconstitution, Intravenous Bolus Administration and Infusion).

When treating infections known or suspected to be caused by Pseudomonas aeruginosa, a dose of at least 1g every 8 hours in adults

(maximum approved dose is 6 g daily given in 3 divided doses) is recommended. This dose is based on pharmacokinetic/ pharmacodynamic modelling and probability of target attainment simulation for susceptible strains of Pseudomonas aeruginosa (MIC ≤ 2 mcg/mL).

There is limited safety data available to support the administration of a 2 g bolus dose.

Recommended Dose and Dosage Adjustment

Complicated urinary tract 500 mg every 8 hours

Uncomplicated skin and skin structure 500 mg every 8 hours

Complicated skin and skin structure 500 mg every 8 hours

Gynaecologic and Pelvic Inflammatory Disease 500 mg every 8 hours

Community-acquired pneumonia 500 mg every 8 hours

Nosocomial pneumonia 1 g every 8 hours

Complicated intra-abdominal 1 g every 8 hours

Meningitis 2 g every 8 hours

Septicaemia 1 g every 8 hours

Impaired Renal Function

Dosage should be reduced in patients with creatinine clearance less than 51 mL/min (Table 4).

Dosage in Patients with Creatinine Clearance Less than 51 mL/min

Creatinine clearance	Dose (dependent on type of infection(mL/min)	Frequency
26-50	recommended dose (500 mg to 2000 mg)	every 12 hours

10-25	one-half recommended dose	every 12 hours
<10	one-half recommended dose	every 48 hours

Meropenem is removed by haemodialysis and hemofiltration; if continued treatment diterpene is necessary, the dose, based on the infection type and severity, should be administered at the completion of the haemodialysis procedure to reinstitute effective treatment.

There are no data on appropriate doses in patients requiring peritoneal dialysis.

Hepatic Impairment (Adults)

No dosage adjustment is necessary in patients with hepatic dysfunction as long as renal functions normal.

Geriatrics (≥ 65 years of age)
Dosage adjustment is recommended for the elderly with an estimated or measured creatinine clearance value below 51 mL/min. (See DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment, Impaired Renal Function.)

Paediatrics (≥ 3 months of age)

For infants and children over 3 months of age and weighing up to 50 kg, the recommended dose
of Meropenem for Injection is 10 to 40 mg/kg every 8 hours, depending on the type and severity of infection, the known or suspected susceptibility of the pathogens and the condition of the patient. Children weighing over 50 kg require the adult dosage. Meropenem for Injection should be given as an intravenous infusion over approximately 15 to 30 minutes or as an intravenous bolus injection (5 to 20 mL) over approximately 5 minutes (see DOSAGE AND ADMINISTRATION, Administration and Reconstitution, Intravenous Bolus Administration and Infusion).

When treating infections known or suspected to be caused by *Pseudomonas aeruginosa*, a dose of at least 20 mg/kg every 8 hours in children (maximum approved dose is 120 mg/kg daily given in 3 divided doses) is recommended. This dose is based on pharmacokinetic/pharmacodynamic modelling and probability of target attainment simulation for susceptible strains of Pseudomonas aeruginosa (MIC ≤ 2 mcg/mL).

There is limited safety data available to support the administration of a 40 mg/kg bolus dose.

Dosage in Paediatric Patients

Type of Infection	**Dose (mg/kg)**	**Dosing Interval**
Complicated urinary tract	10	every 8 hours
Uncomplicated skin and skin structure	10-20	every 8 hours
Community acquired pneumonia	10 - 20	every 8 hours
Complicated intra-abdominal	20	every 8 hours
Meningitis	40	every 8 hours

There are no data on appropriate doses for children with renal impairment.

Missed Dose

If a dose is missed then it should be given as soon as practically possible after the scheduled time and subsequent doses should be given at 8-hour intervals from the revised dose time.

Administration and Reconstitution
Parenteral Products
Compatibility of meropenem with other drugs has not been established. Meropenem for Injection should not be mixed with or physically added to solutions containing other drugs.

Freshly prepared solutions of Meropenem for Injection should be used

whenever possible.

Constituted solutions of Meropenem for Injection should not be frozen. All vials are for single use only. Standard aseptic technique should be employed during
constitution and administration. Shake constituted solution before use.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.

Intravenous Bolus Administration

A solution for bolus injection is prepared by dissolving the drug product Meropenem for Injection (injection vials 500 mg/20 mL and 1 g/20 mL) in sterile Water for Injection to a final concentration of 50 mg/mL. Shake to dissolve and let stand until clear.

Stability in Glass Vials

Meropenem injection vials reconstituted with sterile Water for Injection for bolus administration (up to 50 mg/mL of meropenem) may be stored for up to 3 hours at controlled room temperature (15 - 25°C) or for up to 16 hours under refrigerated conditions (2 - 8°C).

Infusion

A solution for infusion is prepared by dissolving the drug product Meropenem for Injection(500 mg/20 mL and 1 g/20 mL) in either 0.9% sodium chloride solution for infusion or 5%glucose (dextrose) solution for infusion, then the resulting solution is added to an IV container
and further diluted to a final concentration of 1 to 20 mg/mL (see Table 7).
Stability in Plastic IV Bags Solutions prepared for infusion (meropenem concentrations ranging from 1 to 20 mg/mL) may be stored in plastic IV bags with diluents as shown in Table 7 below. Meropenem for Injection vials reconstituted with 0.9% sodium chloride for infusion may be stored for up to 3 hours at controlled room temperature (15 - 25°C) or for up to 24 hours under refrigerated conditions (2-8°C). Constituted solutions of Meropenem for Injection in 5% glucose (dextrose) solution should
be used immediately.
From a microbiological point of view, unless the method of opening/constitution/dilution
precludes the risk of microbiological contamination, the product should be

used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Diluted Intravenous Infusion solutions should be inspected visually for discolouration, haziness, particulate matter and leakage prior to administration, whenever solution and container permit.
Discard unused portion.

Table - Number of Hours Stable after Reconstitution

Diluent	Number of Hours Stable at Controlled Room Temperature 15 - 25°	Number of hrs stable at 2-8 deg .cent
Sodium Chloride 0.9%	3	24
Glucose (Dextrose) 5.0%	Use immediately	Use immediately

OVERDOSAGE

Intentional overdosing of meropenem is unlikely, although accidental overdosing might occur
particularly in patients with reduced renal function. The largest dose meropenem administered in clinical trials has been 2 g given intravenously every 8 hours to adult patients with normal renal function and 40 mg/kg every 8 hours to children with normal renal function. At these dosages, no adverse pharmacological effects were observed.
Limited post-marketing experience indicates that if adverse events occur following overdosage, they are generally consistent with the adverse event profile described under ADVERSEREACTIONS.
In the event of an overdose, Meropenem for Injection should be discontinued and general supportive treatment given until renal elimination takes place. Meropenem and its metabolite are readily dialyzable and effectively removed by haemodialysis; however, no information is available on the use of haemodialysis to treat overdosage.

The intravenous LD_{50} of meropenem in mice and rats is more than 2500 mg/kg and is approximately 2000 mg/kg in dogs.
For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Meropenem for Injection (meropenem) is a broad spectrum, β-lactamase-resistant, carbapenem antibiotic for parenteral administration.

The bactericidal activity of meropenem results from the inhibition of bacterial cell wall synthesis. Meropenem readily penetrates through the cell wall of most Gram-positive and Gram-negative bacteria to reach penicillin binding protein (PBP) targets. Its greatest affinity is for PBP 2 of Escherichia coli, PBP 2 and 3 of Pseudomonas aeruginosa and 1, 2 and 4 of Staphylococcus aureus.
Meropenem is stable in the presence of most serine β-lactamases (both penicillinases and cephalosporinases) produced by Gram-positive and Gram-negative bacteria.

EDTA has been shown to remove Mg2+ and Ca 2+ ions from the outer cell wall of Gram negative bacteria, there by liberating up to 50% of LPS molecules and exposing phospholipids of the inner membrane, enhancing the efficacy of Meropenem.

The pharmacokinetics of meropenem are typical of those parenteral lactam antibiotics that have low protein binding and predominantly renal excretion.
Meropenem shows biexponential pharmacokinetics after intravenous administration in healthy adult volunteers with normal renal function. There is a rapid distribution phase followed by a terminal elimination phase with a half-life ($t_{½}$) of approximately 1 hour.

The area under AUC of Meropenem increases approximately 5.5-fold over the dose range of 500 mg to 2 g. There are no marked changes in the pharmacokinetic parameters. However, there is a reduction in renal clearance with higher doses probably due to the saturation of tubular clearance. These changes in kinetic parameters are not important in otherwise healthy adults.

There were no important changes in the pharmacokinetics of Meropenem when administered as a 5 minute infusion, compared with a 30 minute infusion. Peak plasma concentrations of meropenem were doubled after the bolus infusion, but from 1 hour after dosing, plasma concentrations for

both rates of administration were similar.
After multiple dose administration in healthy subjects, there was no accumulation of meropenem and no change in the pharmacokinetics of Meropenem as a consequence of repeated administration.

Table Pharmacokinetic Parameters of Meropenem in Healthy Volunteers Following Multiple Dose (1000 mg) Intravenous Infusions*
No dosage adjustment is necessary in patients with hepatic dysfunction as long as renal function

Table - Pharmacokinetic Parameters of Meropenem in Healthy Volunteers
Following Multiple Dose (1000 mg) Intravenous Infusions*

Day	**Cmax (mcg/ml)**	**AUC (mcgh/ml)**	**T1/2 h**	**Plasma clearance(Clp) (ml/mt)**	**Urinary recovery % dose**
1	42.40(13)	71.60(15)	0.96(9)	227(14)	59.40(6)
4	34.10(57)	60.40(25)	0.48(23)	293(23)	62.60(21)
7	40.50(14)	61.30(17)	1.11(32)	279(17)	53.20(19)

mean (coefficient of variation)
*25 infusions over 60 min at intervals of 6 h for 7 days

Distribution

At the end of a 30-minute intravenous infusion of a single dose of meropenem in healthy, male volunteers, mean peak plasma concentrations

are approximately 23 mcg/mL for the 500 mg dose,49 mcg/mL for the 1 g dose and 115 mcg/mL for the 2 g dose.
A 5 minute intravenous bolus injection of meropenem in healthy, male volunteers results in mean peak plasma levels of approximately 52 mcg/mL for the 500 mg dose and 112 mcg/mL for the 1 g dose.

Tissue Concentrations

Meropenem penetrates into body tissues in sufficient concentrations to treat most commonly occurring pathogens at the principal sites of infection. However, it does not penetrate readily into cerebrospinal fluid or aqueous humor in the absence of inflammation at the sites. In children and adults with bacterial meningitis, Meropenem concentrations in the cerebrospinal fluid, after intravenous administration of recommended doses, are in excess of those required to inhibit susceptible bacteria.

Metabolism and Excretion

Meropenem is cleared predominantly by renal excretion, with a combination of glomerular filtration and active tubular secretion.
At doses of 500 mg, mean plasma levels of meropenem decline to 1mcg/mL or less, 6 hours after administration. In vitro studies demonstrate that meropenem is stable to human renal administration. In. This finding is supported by the urinary excretion of meropenem which is typically 60% to 70% of the administered dose. Thus, there is no requirement to Coad minister an inhibitor of dehydropeptidase-1 with meropenem. Meropenem plasma protein binding is low, approximately 2%. Therefore the renal filtration rate should approximate the glomerular filtration rate (GFR). However, renal clearance values are generally in excess of the measured or calculated value for GFR: the difference is due to active tubular secretion of meropenem. The hydrolysis of the β-lactam bond can occur either chemically in solution or biologically under the influence of enzymes. The reduction in the non-renal clearance of meropenem that occurs as renal function declines suggests that the kidney may be a site of metabolism. The trend to reduction in the non-renal clearance of meropenem seen when meropenem was Coad ministered with probenecid implies that the proximal renal tubule may be involved in the metabolism of Meropenem. The only

identified metabolite of meropenem is ICI 213,689 which is produced by hydrolysis of the β-lactam bond and is bacteriologically inactive. In healthy subjects, the apparent elimination half-life of ICI 213,689 was longer than that of meropenem at approximately 2.3 hours (range 1.8 to 2.8 hours). The AUC for ICI 213,689 was approximately 10% of the AUC for meropenem,
showing that exposure to the circulating metabolite is small in subjects with normal renal function. The administration of probenecid with meropenem did not alter the urinary half-life of ICI213,689. Exposure to ICI 213,689 does not appear to change on repeated meropenem administration and there are no major changes in the excretion of ICI 213,689 after repeated Meropenem administration in persons with normal renal function.

In subjects with normal renal function, the elimination half-life of meropenem is approximately one hour. Urinary concentrations of meropenem in excess of 10 mcg/mL are maintained for at
least 5 hours at the 500 mg dose. The metabolism and excretion of meropenem were studied by means of administration of [^{14}C]-labelled meropenem. Radioactivity was very rapidly excreted with 95.4% of the dose recovered in the urine at 8 hours after dosing. This rapid excretion is consistent with the observed lack of accumulation on multiple dosing. Overall, 99.0% of the dose was recovered in the urine, with an additional 2.1% recovered in the faces.

Multiple dosing with meropenem in normal volunteers caused increases, decreases or no change in the faecal flora, depending on the organism. Changes were small and were reversed after cessation of meropenem administration. Meropenem is present in bile at concentrations of up to 25 mcg/mL.

This biliary excretion of a small proportion of the dose as active antibiotic could account for both the minor disturbance of focal flora and the faecal recovery of radioactivity.

STABILITY AND STORAGE RECOMMENDATIONS

Store between 15 - 30°C. Do not freeze.