For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory
This package insert is continually updated: Please read carefully before using a new pack

Meropenem Injection IP 500mg/1000mg

M-Nem ™
For IV use and infusion

COMPOSITION
M-Nem ™ 500 mg

Each vial contains:
Sterile Meropenem Trihydrate IP
Equivalent to Anhydrous Meropenem ……. 500mg
Sterile Sodium Carbonate IP
Equivalent to Sodium (added as Buffer) ……. 45.1mg

M-Nem ™ 1000 mg

Each vial contains :
Sterile Meropenem Trihydrate IP
Equivalent to Anhydrous Meropenem ……. 1000mg
Sterile Sodium Carbonate IP
Equivalent to Sodium (added as Buffer) ……. 90.2mg

INDICATIONS
M-Nem™ 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

M-Nem™ has been found to be effective in eliminating concurrent bacteraemia in association with bacterial meningitis.

M-Nem™ may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.

DOSAGE AND METHOD OF ADMINISTRATION
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 up to 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 infections due to less susceptible bacterial species (e.g. *Enterobacteriaceae*, *Pseudomonas aeruginosa, Acinetobacter* spp.), or very severe infections. Additional considerations for dosing are needed when treating patients with renal insufficiency (see below).

For preparation of solution for IV bolus Injection and for IV infusion administration, please refer to section on shelf life.

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.

Pediatric 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.

Method of administration
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
M-Nem ™ is contraindicated in patients with known hypersensitivity to any component of this product or 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.

Enterobacteriaceae, *Pseudomonas aeruginosa* and *Acinetobacter* spp. resistance
Resistance to penems of *Enterobacteriaceae, Pseudomonas aeruginosa, Acinetobacter* spp.
Prescribers are advised to take into account the local prevalence of resistance in these bacteria to penems.

Hypersensitivity reactions
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 inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics.
If a severe allergic reaction occurs, the medicinal product should be discontinued and appropriate measures taken.

Antibiotic-associated colitis
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.

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCAR) such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme (EM) and acute generalized exanthematous pustulosis (AGEP) have been reported in patients receiving meropenem .If signs and symptoms suggestive of these reactions appear, meropenem should be withdrawn immediately and an alternative treatment should be considered.

Seizures

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

Hepatic function monitoring

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

Direct antiglobulin test (Coombs test) seroconversion

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

Concomitant use with valproic acid/sodium valproate/valpromide

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

M-Nem contains sodium.

M-Nem 500 mg: This medicinal product contains 45.1 mg of sodium per 500 mg dose which should be taken into consideration by patients on a controlled sodium diet.

M-Nem 1.0 g: This medicinal product contains 90.2 mg of sodium per 1.0 g dose which should be taken into consideration by patients on a controlled sodium diet.

Interaction with other medicinal products and other forms of interaction

No specific medicinal product interaction studies other than probenecid were 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 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 valproic acid/sodium valproate/valpromide 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

Small amounts of meropenem have been reported to be excreted in human milk. Meropenem should not be used in breast feeding women unless the potential benefit for the mother justifies the potential risk to the baby.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effect 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, paresthesia and convulsions have been reported for meropenem.

ADVERSE REACTIONS

In a review of 4,872 patients with 5,026 meropenem treatment exposures, meropenem-related adverse reactions most frequently reported were diarrhoea (2.3 %), rash (1.4 %), nausea/vomiting (1.4 %) and injection site inflammation (1.1 %). The most commonly reported meropenem-related laboratory adverse events were thrombocytosis (1.6 %) and increased hepatic enzymes (1.5-4.3 %).

Tabulated risk of adverse reactions

In the table below all adverse reactions are listed by system organ class and frequency: very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1

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, agranulocytosis, haemolytic anaemia
Immune system disorders	Uncommon	angioedema, anaphylaxis
Nervous system disorders	Common	headache
	Uncommon	paraesthesiae
	Rare	convulsions
Gastrointestinal disorders	Common	diarrhoea, vomiting, nausea, abdominal pain
	Uncommon	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, toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme.
	Not Known	Drug Reactions with Eosinophilia and Systemic Symptoms (DRESS Syndrome)

Renal and urinary disorders	Uncommon	blood creatinine increased, blood urea increased
General disorders and administration site conditions	Common	inflammation, pain
	Uncommon	thrombophlebitis, pain at the injection site

OVERDOSE

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

INCOMPATIBILITIES

M-Nem™ should not be mixed with other medicinal products except those mentioned under section: After reconstitution.

SHELF LIFE: Unopened Vial: See outer carton
After reconstitution:
Intravenous bolus injection administration
A solution for bolus injection is prepared by dissolving the drug product in water for injection to a final concentration of 50 mg/ml. Chemical and physical in-use stability for a prepared solution for bolus injection has been demonstrated for 3 hours at up to 25°C or 12 hours under refrigerated conditions (2-8°C).
From a microbiological point of view, unless the method of opening/reconstitution/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.

Intravenous infusion administration
A solution for infusion is prepared by dissolving the drug product in either 0.9% sodium chloride solution for infusion or 5% dextrose solution for infusion to a final concentration of 1 to 20 mg/ml. Chemical and physical in-use stability for a prepared solution for infusion using 0.9% sodium chloride solution has been demonstrated for 3 hours at up to 25°C or 24 hours under refrigerated conditions (2-8°C).
From a microbiological point of view, unless the method of opening/reconstitution/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.
Reconstituted solution of the product in 5% dextrose solution should be used immediately.
The constituted solutions should not be frozen.

STORAGE

Store in airtight containers , at a temperature not exceeding 25^0C
Protect from moisture. Keep out of the reach of children.

PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Injection
Meropenem to be used for bolus intravenous injection should be constituted with sterile water for injection.

Infusion
For intravenous infusion meropenem vials may be directly constituted with 0.9 % sodium chloride or 5% dextrose solutions for infusion.
Each vial is for single use only.
Standard aseptic techniques should be used for solution preparation and administration.

The solution should be shaken before use.
Any unused product or waste material should be disposed of in accordance with local requirements.

Manufactured by:
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Marketed by:
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Source:

- Prescribing Information for Merrem , Pfizer May 2019(accessed on 01st April 2021)

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