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

Meropenam injection IP

VARNEM® 1000 mg

Each Vial Contains:

Meropenem IP eq. to Anhydrous Meropenem	1000 mg
Sodium Carbonate eq. to Sodium	90.2 mg

VARNEM® 500 mg

Each Vial Contains:

Meropenem IP eq. to Anhydrous Meropenem	500 mg
Sodium Carbonate eq. to Sodium	45.1 mg

DESCRIPTION:
Meropenem is a sterile, Pyrogen-free, synthetic, broad-spectrum, carbapenem antibiotic for intravenous administration. The chemical name of Meropenem is (4R,5S,6S)-3-[(3S,5S)-5-(dimethylcarbamoyl)-3-pyrrolidinyl[thio]-6-[(1R)-1-hydroxy ethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carbo xylic acid trihydrate. Its empirical formula is $C_{17}H_{25}N_3O_5S.3H_2O$ with a molecular weight of 437.52. g/mol.

THERAPEUTIC INDICATIONS:
Meropenem is indicated for the treatment of the following infections in adults and children over 3 months of age.
- Severe pneumonia, including hospital and ventilator-associated 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

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.
Meropenem may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

POSOLOGY 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 or Acinetobacter spp.), or very severe infections.
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
Severe pneumonia including hospital and ventilator-associated 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.

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
Severe pneumonia including hospital and ventilator-associated 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, Meropenam doses up to 20 mg/kg may be given as an intravenous bolus injection 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.
Renal impairment
The dose for adults and adolescents should be adjusted when creatinine clearance is less than 51 ml/min, as shown below.

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.
When only serum creatinine is available, the following formula (Cockcroft and Gault equation) may be used to estimate creatinine clearance:

Males:	(weight in kg)× (140-age)
	(72)× serum creatinine (mg/100 ml)
Females:	(0.85)× (above value)

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.
Mode of administration
IV Bolus Injection administration
Constitute injection vial (500 mg & 1000 mg) with sterile water for injection. Shake to dissolve. Constituted solutions are clear or colorless or pale yellow.

Vial Size	Amout of diluent added (ml)	Approximate withdrawable volume (ml)	Approximate Average Concentration (mg/ml)
500 mg	10	10	50
1000 mg	20	20	50

Stability:

Reconstituted Solution	Stability duration Room Temperature (at 15 ˚C to 25 ˚C)	Stability duration in fridge (at 4˚C)
Sterile Water for Injection	36 hours	36 hours

Reconstituted solution should be used immediately after preparation. Do not use, if any particle, leakage or breakage is found.

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).

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
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. varies across the European Union. 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 (see contraindications, undesirable effects)
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.
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 generalised exanthematous pustulosis (AGEP) have been reported in patients receiving meropenem (see section undesirable effects). If signs and symptoms suggestive of these reactions appear, meropenem should be withdrawn immediately and an alternative treatment should be considered.
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 (see undesirable effects). 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
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). (See undesirable effects)
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 (see posology and method of administration)
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 (see drug interaction with other medicinal products).
This medicinal product contains 90 mg sodium per dose, equivalent to 4.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
The maximum daily dose of this product is equivalent to ≥27% of the WHO recommended maximum daily intake for sodium.
Meropenem is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

DRUG INTERACTION WITH OTHER MEDICINAL PRODUCTS:
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 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/sodium valproate/valpromide with carbapenem agents is not considered to be manageable and therefore should be avoided (see special warnings and precautions for use).
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.

FERTILITY, PREGNANCY AND LACTATION
Pregnancy
There are no or limited amount of data from the use of meropenem in pregnant women.
As a precautionary measure, it is preferable to avoid the use of meropenem during pregnancy.
Breast-feeding
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.

UNDESIRABLE EFFECTS:
meropenem treatment exposures, meropenem-related adverse reactions are diarrhoea, rash, nausea/vomiting and injection site inflammation. The most commonly reported meropenem-related laboratory adverse events were thrombocytosis and increased hepatic enzymes.
Infections and infestations: oral and vaginal candidiasis
Blood and lymphatic system disorders: thrombocythaemia, eosinophilia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis, haemolytic anaemia
Immune system disorders: angioedema, anaphylaxis
Psychiatric disorders: Delirium
Nervous system disorders: headache, paraesthesiae, convulsions
Gastrointestinal disorders: diarrhoea, vomiting, nausea, abdominal pain, antibiotic-associated colitis
Hepatobiliary disorders: transaminases increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, blood bilirubin increased
Skin and subcutaneous tissue disorders: rash, pruritis, toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme, urticaria, Drug Reaction with Eosinophilia and Systemic Symptoms, acute generalised exanthematous pustulosis
Renal and urinary disorders: blood creatinine increased, blood urea increased
General disorders and administration site conditions: inflammation, pain, thrombophlebitis, pain at the injection site
Paediatric population
Meropenem is licensed for children over 3 months of age. There is no evidence of an increased risk of any adverse drug reaction in children. All reports received were consistent with events observed in the adult population.
OVERDOSAGE:
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, 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. When plasma concentrations exceeded the MIC of the infecting organisms for approximately 40% of the dosing interval.
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 antibacterials agents when the mechanism involved include impermeability and/or an efflux pump(s).
PHARMACOKINETICS:
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.
Biotransformation
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 unchanged 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 in severe impairment (CrCL 4-23 ml/min) and 10-fold in haemodialysis patients (CrCL <2 ml/min) when compared to healthy subjects (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 (see posology and method of administration).
Meropenem is cleared by haemodialysis with clearance during haemodialysis being approximately 4 times higher than in anuric patients.
Hepatic insufficiency
A study in patients with alcoholic cirrhosis shows no effect of liver disease on the pharmacokinetics of meropenem after repeated doses.
Adult patients
Pharmacokinetic studies performed in patients have not shown significant pharmacokinetic differences versus healthy subjects with equivalent renal function. A population model developed from data in 79 patients with intra-abdominal infection or pneumonia, showed a dependence of the central volume on weight and the clearance on creatinine clearance and age.
Paediatric population
The pharmacokinetics in infants and children with infection at doses of 10, 20 and 40 mg/kg showed Cmax values approximating to those in adults following 500, 1000 and 2000 mg doses, respectively. Comparison showed consistent pharmacokinetics 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
A reduction in plasma clearance, which correlated with age-associated reduction in creatinine clearance, and a smaller reduction in non-renal clearance. No dose adjustment is required in elderly patients, except in cases of moderate to severe renal impairment.

STORAGE CONDITION:
Store in a cool place (below 30°C). Protect from moisture.

PRESENTATION:
VARNEM 1000 MG:
Primary Packing: 20 ml clear glass vial, USP Type-I.
Secondary Packing: 20 ml clear glass vial, USP Type-I & 20 ml Plastic ampoule of Sterilized Water for Injection IP packed in monocarton along with package Insert.
VARNEM 500 MG:
Primary Packing: 20 ml clear glass vial, USP Type-I.
Secondary Packing: 20 ml clear glass vial, USP Type-I & 10 ml Plastic ampoule of Sterilized Water for Injection IP packed in monocarton along with package Insert.

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