Maxnem

(Meropenem) Injection USP

500mg

1g

میکسنیم

(میروپینم) انجکشن یو ایس پی

500 ملی گرام

1 گرام

COMPOSITION

Maxnem Injection 500mg:

Each vial contains:

Meropenem USP.....500mg

(as Meropenem Trihydrate)

(USP Specifications)

Contains: 45.1mg of Sodium as Sodium Carbonate.

Maxnem Injection 1g:

Each vial contains:

Meropenem USP.....1000mg

(as Meropenem Trihydrate)

(USP Specifications)

Contains: 90.2mg of Sodium as Sodium Carbonate.

DESCRIPTION

Meropenem is a broad-spectrum carbapenem antibiotic. It is active against gram positive and gram negative bacteria. Meropenem exerts its action by penetrating bacterial cells readily and interfering with the synthesis of vital cell wall components, which leads to cell death.

CLINICAL PHARMACOLOGY

Pharmacodynamics

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).

Susceptibility

Commonly susceptible species

Gram positive aerobes: Enterococcus faecalis, Staphylococcus aureus (methicillin-susceptible), Staphylococcus species (methicillin-susceptible) including Staphylococcus epidermidis, Streptococcus agalactiae (Group B), Streptococcus milleri group (S. anginosus, S. constellatus, and S. intermedius), Streptococcus pneumoniae, Streptococcus pyogenes (Group A).

Gram negative aerobes: Citrobacter freundii, Citrobacter koseri Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Klebsiella oxytoca, Klebsiella pneumoniae, Morganella morganii, Neisseria meningitidis, Proteus mirabilis, Proteus vulgaris, Serratia marcescens.

Gram positive anaerobes: Clostridium perfringens, Peptoniphilus asaccharo lyticus, Peptostreptococcus species (including P.micros, P. anaerobius, P. magnus).

Gram negative anaerobes: Bacteroides caccae, Bacteroides fragilis group, Prevotella bivia, Prevotella disiens.

Species for which acquired resistance may be a problem

Gram positive aerobes: Enterococcus faecium.

Gram negative aerobes: Acinetobacter species, Burkholderia cepacia, Pseudomonas aeruginosa.

Inherently resistant organisms

Gram negative aerobes: Stenotrophomonas maltophilia, Legionella species.

Other micro organisms

Chlamydophila pneumoniae, Chlamydophila psittaci, Coxiella burnetiid, Mycoplasma pneumoniae.

Pharmacokinetics

In healthy subjects the mean plasma half life is approximately 1 hour; the mean volume of distribution is approximately 0.25L/kg (11-27L) and the mean clearance is 287ml/min at 250mg falling to 205ml/min at 2g. Dose of 500mg infused over 30 minutes gives mean C_{max} value of approximately 23 µ g/ml, corresponding to AUC value of 39.3µg.h/ml. After infusion over 5 minutes C_{max} value is 52µg/ml after 500mg dose.

Distribution: The average plasma protein binding of meropenem is approximately 2% and is 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 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.

Special Population

Renal insufficiency: Renal impairment results in higher plasma AUC and longer half life for meropenem. There was AUC increase of 2.4 fold in patients with moderate impairment (CrCL 33-74ml/min), 5 fold in severe impairment (CrCL 4-23ml/min) and 10 fold in haemodialysis patients (CrCL < 2ml/min) when compared to healthy subjects (CrCL > 80ml/min). 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.

Paediatric population: The pharmacokinetics in infants and children with infection showed C_{max} values approximating to those in adults. Comparison showed consistent pharmacokinetics between the doses and half lives similar to those observed in adults in all but the youngest subjects (< 6 months $t_{1/2}$ 1.6 hours).

Elderly: Pharmacokinetic studies in healthy elderly subjects (65-80 years) have shown 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.

THERAPEUTIC INDICATIONS

Meropenem is indicated for the treatment of the following infections in adults and children aged 3 months and older:

- Severe pneumonia, including hospital & 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

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

DOSAGE AND ADMINISTRATION

Dosage:

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 2g three times daily in adults and adolescents and a dose of up to 40mg/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, P. aeruginosa, Acinetobacter spp.), or very severe infections. The tables below provide general recommendations for dosing.

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

Meropenem is usually given by intravenous infusion over approximately 15 to 30 minutes.

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

Special Population:

Renal impairment

The dose for adults and adolescents should be adjusted when creatinine clearance is less than 51ml/min, as shown in the table. There are limited data to support the administration of these dose adjustments for a unit dose of 2g. Additional considerations for dosing are needed when treating patients with renal insufficiency.

Creatinine clearance (ml/min)	Dose (based on "unit" dose range of 500mg, 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 50ml/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 20mg/kg every 8 hours may be an appropriate regimen.

Children from 3 months to 11 years of age and up to 50kg 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 20mg/kg
Broncho-pulmonary infections in cystic fibrosis	40mg/kg
Complicated urinary tract infections	10 or 20mg/kg
Complicated intra-abdominal infections	10 or 20mg/kg
Complicated skin and soft tissue infections	10 or 20mg/kg
Acute bacterial meningitis	40mg/kg
Management of febrile neutropenic patients	20mg/kg

Children over 50kg body weight

The adult dose should be administered.

There is no experience in children with renal impairment.

Reconstitution:

Injection

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

Infusion

For intravenous infusion meropenem may be directly constituted with 0.9% sodium chloride or 5% dextrose solutions for infusion.

ADVERSE REACTIONS

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
	Common	Rash, pruritus
Skin and subcutaneous tissue disorders	Uncommon	Urticaria, toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme
	Not Known	Drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis
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

Paediatric population:

Meropenem can be used in children aged 3 months and older. There is no evidence of an increased risk of any adverse drug reaction in children based on the limited available data. All reports received were consistent with events observed in the adult population.

CONTRAINDICATIONS

It is contraindicated in patients with:

- Hypersensitivity to the active substances or to any of its 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.

Enterobacteriaceae, Pseudomonas aeruginosa and Acinetobacter spp. Resistance:

Resistance to carbapenems of Enterobacteriaceae, Pseudomonas aeruginosa and Acinetobacter spp. varies across the European Union. Prescribers are advised to take into account the local prevalence of resistance in these bacteria to carbapenems.

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.

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.

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.

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 excretedin 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.

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. Caution is required if probenecid is co-administered with meropenem.

Valproic acid:

Decrease 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 increase in the anti-coagulant effects of orally administered anti-coagulant agents, including warfarin in patients who are concomitantly receiving antibacterial agents.

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.

INSTRUCTIONS

- Store below 30°C in dry form.
- Protect from heat, light and moisture.
- Use new syringe only.
- Use immediately after reconstitution.

PRESENTATION

Maxnem (Meropenem) Injection 500mg is available as pack of 1 vial with sterile water for injection.

Maxnem (Meropenem) Injection 1g is available as pack of 1 vial & sterile water for injection.

Shelf Life: Maxnem has a shelf life of 2 years from date of manufacturing.

To be sold on the prescription of a registered medical practitioner only.

Keep all medicines out of the reach of children

ہدایات:

دوا کو 30°C سے کم درجہ حرارت پر خشک حالت میں رکھیں۔
گرمی، روشنی اور نمی سے محفوظ رکھیں۔
صرف نئی سرنج استعمال کریں۔
تیار شدہ انجکشن فوری استعمال کرلیں۔
تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔

انتباہ:

صرف رجسٹرڈ ڈاکٹر کے نسخے پر فروخت کی جائے۔
صرف وریدی استعمال کے لئے۔

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