For the use only of a Registered Medical Practitioner

PRESCRIBING INFORMATION

NURONEM INJECTION 500 mg/1 gm
(Meropenem for Injection)

COMPOSITION

NURONEM INJECTION 500 mg
Each vial contains:
Meropenem trihydrate (sterile)
equivalent to anhydrous Meropenem ……500 mg
Anhydrous Sodium Carbonate (sterile) 104 mg

NURONEM INJECTION 1g
Each vial contains:
Meropenem trihydrate (sterile)
equivalent to anhydrous Meropenem ……1g
Anhydrous Sodium Carbonate (sterile) 208 mg

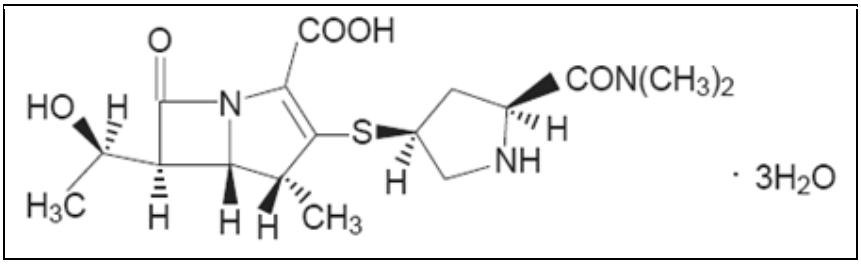
DESCRIPTION

For dry powder - White to pale yellow crystalline powder in clear glass vial sealed with grey rubber stopper and flip off seal.

For constituted solution - Clear colourless to pale yellow coloured solution.

DESCRIPTION

NURONEM INJECTION contains meropenem, a synthetic, broad-spectrum, carbapenem antibiotic for intravenous administration. Its empirical formula is $C_{17}H_{25}N_3O_5S \cdot 3H_2O$ with a molecular weight of 437.52. Its structural formula is:



STRUCTURAL FORMULA

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES

Pharmacodynamic properties

Meropenem is a potent bactericidal agent against most Gram-positive and Gram-negative bacteria. It acts by interfering with vital bacterial cell wall synthesis of the susceptible bacteria by binding to penicillin-binding-protein (PBP) targets, eventually causing cell wall lysis. Meropenem's high affinity for the PBP's and its resistance to serine β-lactamases makes it a potent bactericidal agent. Its strongest affinities are toward PBPs 2, 3 and 4 of *Escherichia coli* and *Pseudomonas aeruginosa*; and PBPs 1, 2 and 4 of *Staphylococcus aureus*.

Resistance

Bacteria may develop resistance to carbapenems due to one of the following four mechanisms: 1) diminished permeability of the outer membrane of Gram-negative bacteria (due to diminished production of porins) causing reduced bacterial uptake, 2) low affinity of the target penicillin binding proteins (PBP), 3) Increased efflux of drugs across the outer membrane in gram negative bacteria and 4) production of β lactamases which hydrolyse carbapenems & β lactams.

Cross-Resistance

Isolates resistant to other carbapenems are sometimes cross-resistant to meropenem.

Microbiology

Meropenem is a carbapenem antibiotic with a broad-spectrum antimicrobial activity against most gram-positive and gram-negative bacteria and clinically significant aerobic, and anaerobic bacterial species. Following is a list of microorganisms sensitive to meropenem both *in vitro* and in clinical infections:

Aerobic and facultative Gram-positive microorganisms:

- *Enterococcus faecalis* (excluding vancomycin-resistant isolates)
- *Staphylococcus aureus* (β-lactamase and non-β-lactamase producing, methicillin-susceptible isolates only)
- *Streptococcus agalactiae*
- *Streptococcus pneumoniae* (penicillin-susceptible isolates only)
- *Streptococcus pyogenes*
- *Viridans group streptococci*

Aerobic and facultative Gram-negative microorganisms:

- *Escherichia coli*
- *Haemophilus influenzae (β-lactamase and non-β-lactamase producing)*
- *Klebsiella pneumoniae*
- *Neisseria meningitidis*
- *Pseudomonas aeruginosa*
- *Proteus mirabilis*

Anaerobic microorganisms
- *Bacteroides fragilis*
- *Bacteroides thetaiotaomicron*
- *Peptostreptococcus species*

Meropenem is also active against the following organisms *in vitro*. At least 90% of organisms show *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoints for meropenem. However, the clinical significance of this *in vitro* data has not been established in adequate and well controlled clinical trials.

Aerobic and facultative Gram-positive microorganisms
Staphylococcus epidermidis (β-lactamase and non- β -lactamase-producing, methicillin-susceptible isolates only).

Aerobic and facultative Gram-negative microorganisms
- *Acinetobacter species*
- *Aeromonas hydrophila*
- *Campylobacter jejuni*
- *Citrobacter diversus*
- *Moraxella catarrhalis (β-lactamase and non- β -lactamase-producing isolates)*
- *Citrobacter freundii*
- *Morganella morganii*
- *Enterobacter cloacae*
- *Pasteurella multocida*
- *Haemophilus influenzae (ampicillin-resistant, non-β-lactamase-producing isolates[BLNAR isolates])*
- *Proteus vulgaris*
- *Salmonella species*
- *Serratia marcescens*
- *Hafnia alvei*
- *Shigella species*
- *Klebsiella oxytoca*
- *Yersinia enterocolitica*

Anaerobic microorganisms
- *Bacteroides distasonis*
- *Bacteroides ovatus*
- *Bacteroides uniformis*
- *Bacteroides vulgatus*
- *Clostridium difficile*
- *Clostridium perfringens*
- *Eubacterium lentum*
- *Fusobacterium species*
- *Prevotella bivia*
- *Bacteroides ureolyticus*

- *Prevotella intermedia*
- *Prevotella melaninogenica*
- *Porphyromonas asaccharolytica*
- *Propionibacterium acnes*

Pharmacokinetics

Absorption

In healthy subjects, following intravenous bolus injection of meropenem 0.5 and 1 g over 5 minutes, mean peak plasma concentrations of approximately 45 µg/mL and 112 µg/mL respectively are reached. The same dose infused over 30 minutes produces peak plasma concentrations of 23 and 49 µg/mL, respectively. Mean peak plasma concentrations of meropenem reduce to approximately 1 µg/mL at 6 hours after administration of 0.5g meropenem intravenous injection.

However, there is no absolute pharmacokinetic proportionality with the administered dose with respect to C_{max} and AUC. Also, decline in plasma clearance from 287 to 205 mL/min for the dose range of 0.250 g to 2 g has been observed.

Distribution

Meropenem is approximately 2% bound to plasma proteins. It is extensively distributed into body tissues and fluids including the CSF and bile, achieving concentrations matching or exceeding those required to inhibit most susceptible bacteria.

Meropenem penetrates well into most body fluids and tissues including cerebrospinal fluid of patients with bacterial meningitis, achieving concentrations in excess of those required to inhibit most bacteria.

Meropenem has a plasma elimination half-life of about 1 hour in subjects with normal renal function.

Metabolism and elimination:

Meropenem is mostly excreted in the urine by tubular secretion and glomerular filtration. About 70% of the dose is recovered unchanged in the urine over a 12 hour period, following which little further urinary excretion is detectable. Urinary concentrations in excess of 10 µg/mL are maintained for up to 5 hours after a 500 mg dose.

No accumulation of meropenem in plasma / urine was observed following regimens of meropenem 500 mg administered at 8 hourly interval or 1 g every 6 hours in subjects with normal renal function.
Meropenem is reported to have one major metabolite which is microbiologically inactive and excreted in urine.

Pharmacokinetics in special population

Renal impairment

In patients with renal impairment the plasma clearance of meropenem correlates with creatinine clearance and dosage adjustments are necessary in subjects with compromised renal function.

Pediatrics
The pharmacokinetics of meropenem in children is comparable to those in adults. The elimination half-life for meropenem was approximately 1.5 to 2.3 hours in children below 2 years of age and the pharmacokinetics parameters are linear over the dose range of 10 to 40 mg/kg.

Geriatrics
In the elderly a reduction in plasma clearance of meropenem correlates with age-associated reduction in creatinine clearance.

Hepatic impairment
Hepatic impairment doesn't alter the pharmacokinetic parameters of meropenem.

INDICATIONS

NURONEM INJECTION 500 mg & 1 gm are indicated for treatment, in adults and children, of the following infections caused by single or multiple bacteria sensitive to meropenem:

Pneumonias including hospital acquired pneumonias,

Urinary Tract Infection, Intra-abdominal Infections,

Gynaecological Infections, such as endometritis and pelvic inflammatory disease,

Bacterial Meningitis,

Septicaemia, and

Empiric treatment for presumed infections in patients with febrile neutropenia used as monotherapy or in combination with anti-viral or anti-fungal agents.

Meropenem has proved efficacious alone or in combination with other antimicrobial agents in the treatment of polymicrobial infections.

DOSE AND METHOD OF ADMINISTRATION

The recommended daily dosage schedule of NURONEM INJECTION is as follows:

Adults

- Pneumonia, UTI, gynaecological infections such as endometritis, skin and skin structure infections - 500 mg IV every 8 hours.

- Meningitis - the recommended dosage is 2 g every 8 hours.

Caution is warranted when using meropenem as monotherapy in critically ill patients with proven or suspected *Pseudomonas aeruginosa* lower respiratory tract infection. Regular culture and sensitivity tests should guide the use of antibiotic.

Adults with Impaired Renal Function

Dosage should be reduced in patients with creatinine clearance (CC) less than 51 mL/min, as scheduled below:

Creatinine clearance (mL/min)	Dose (Based on indication)
26-50	usual dose given every 12 hours
10-25	50% of usual dose given every 12 hours
≤10	50% of usual dose given every 24 hours

Meropenem is dialyzable. In patients on dialysis, meropenem can be administered at the end of the procedure to achieve therapeutic concentrations.

There is no experience with the use of meropenem in patients undergoing peritoneal dialysis.

Adults with Hepatic Insufficiency

No dosage adjustment is necessary in patients with hepatic insufficiency.

Elderly Patients

No dosage adjustment is required for the elderly with normal renal function with creatinine clearance values above 50 mL/min.

Children

The recommended daily dosage schedule of NURONEM INJECTION in children with normal renal functions is as follows

- 3 months - 12 years: 10 to 20 mg/kg every 8 hours (depending on type, severity of infection, susceptibility of the pathogen and the condition of the patient)
- In children over 50 kg weight: Adult dosage to be used.

In bacterial meningitis the recommended dose is 40 mg/kg every 8 hours.
Febrile episodes in neutropenic patients - the dose should be 20 mg/kg every 8 hours.

There is no experience in pediatric patients with renal impairment.

Method of Administration

NURONEM INJECTION can be given as an intravenous bolus injection over approximately 5 minutes or by intravenous infusion over approximately 15 to 30 minutes using the specific available preparations.

NURONEM INJECTION to be used for bolus intravenous injection should be constituted with sterile water for Injections (5 mL per 250 mg meropenem). This provides an approximate concentration of 50 mg/mL. Constituted solutions are clear, and colourless or pale yellow.

NURONEM INJECTION for intravenous infusion may be constituted with compatible infusion fluids (50 to 200 mL).

Incompatibilities
Meropenem should not be mixed with or added to other drugs.

Meropenem is compatible with the following infusion fluids:
0.9% Sodium Chloride solution
5% or 10% Glucose solution
5% Glucose solution with 0.02% Sodium Bicarbonate
5% Glucose solution with 0.9% Sodium Chloride
5% Glucose with 0.225% Sodium Chloride solution
5% Glucose with 0.15% Potassium Chloride solution
Mannitol 2.5% or 10% solution

Special precautions for storage
Before reconstitution the dry powder should be stored at a temperature below 30°C. After reconstitution - do not freeze.

Reconstituted solutions should be used immediately

It is recommended to use freshly prepared solutions of meropenem for IV injection and infusion.

Diluent
Solutions (1 to 20 mg/ml) prepared with:
* 0.9% sodium chloride
* 5% glucose
* 5% glucose and 0.225% sodium chloride
* 5% glucose and 0.9% sodium chloride
* 5% glucose and 0.15% potassium chloride
* 2.5% or 10% mannitol intravenous infusion
* 10% glucose
* 5% glucose and 0.02% sodium bicarbonate intravenous infusion

Solutions of meropenem should not be frozen.

All Vials are for single use only.

ROUTE OF ADMINISTRATION
Intravenous (IV)

CONTRAINDICATIONS

NURONEM INJECTION is contraindicated in patients with known hypersensitivity to meropenem or to any of its excipients, other carbapenems or in patients with a documented history of anaphylactic reactions to beta-lactams.

WARNINGS AND PRECAUTIONS

General warnings

There have been reports of severe and occasionally fatal hypersensitivity (anaphylactic) reactions associated with β-lactams. These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens.

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients receiving therapy with beta-lactams. Before initiating therapy with NURONEM INJECTION, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, carbapenems or other beta-lactam agents. If an allergic reaction occurs, NURONEM INJECTION must be discontinued immediately and appropriate alternative therapy instituted.

Partial cross-allergenicity may occur between carbapenems and β--lactam antibiotics, penicillins and cephalosporins. Before initiating therapy with meropenem, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics. Meropenem should be used with caution in patients with such a history. If an allergic reaction to meropenem occurs, the drug should be discontinued immediately and appropriate measures taken. In case of serious anaphylactic reactions immediate emergency treatment with epinephrine, oxygen, intravenous steroids, and airway management, including intubation should be instituted and any other therapy administered as clinically indicated.

Rarely *Clostridium difficile* associated diarrhea (CDAD) has been reported with meropenem. This may vary in severity from slight to life-threatening. Toxins A & B produced by C. *difficile*. *contribute* to the development of CDAD. It is important to consider the diagnosis of CDAD in patients who develop diarrhea following the use of meropenem. Careful medication history should be recorded as CDAD is reported to occur over two months following an antibiotic use. If CDAD is suspected or confirmed, any antibiotic not directed against C. *difficil*e should be discontinued and appropriate measures like appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. *difficile,*and surgical evaluation should be taken as indicated.

Meropenem should be prescribed prudently for individuals with a history of gastro-intestinal disease, especially colitis.

General precautions:

Prescribing meropenem in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to benefit and may increase the risk of the development of drug-resistant bacteria. Also,

prolonged meropenem therapy may result in overgrowth of drug resistant organisms. Repeated evaluation of the patient is essential. In case of superinfection during therapy, appropriate measures should be taken.

Careful monitoring of transaminase and bilirubin levels is essential when using meropenem in patients with underlying liver diseases.

There is inadequate information regarding the use of meropenem in patients on hemodialysis.

Use of meropenem in infections caused by methicillin-resistant staphylococci is not recommended.

Prolonged use of meropenem may result in overgrowth of nonsusceptible organisms. Therefore, repeated evaluation of the patient is essential. Appropriate measures should be taken If superinfection occurs during therapy,

Laboratory tests

Though meropenem has low toxicity assessment of organ system functions, including renal, hepatic, and hematopoietic, is recommended during prolonged therapy.

Pediatrics

The safety and effectiveness of meropenem has not been established in infants less than 3 months of age and children with compromised renal or hepatic functions. So its use is not recommended in this population.

Geriatrics

The overall efficacy and tolerability profile of meropenem in the elderly with normal renal function is similar to younger subjects. Nevertheless, dosage adjustment may be required in elderly patients with creatinine clearance ≤ 50 mL/min.

In a pharmacokinetic study performed in elderly patients with impaired renal function, a decline in plasma clearance of meropenem was observed, which was associated with age-related reduction in creatinine clearance.

Clinical experience and spontaneous reporting have not revealed any differences in meropenem responses between elderly and young subjects, however, it is important to note that greater sensitivity of some elderly individuals cannot be ruled out. As the drug is substantially excreted from the kidney, the risk of toxicity increases in patients with compromised renal function. As the elderly patients are more likely to have impaired renal function, close monitoring of renal function may be useful.

DRUG INTERACTIONS

Probenecid competitively inhibits active tubular secretion of meropenem, thereby reducing its renal excretion; increases its plasma concentration and significantly prolongs the elimination half-life (38%) and in the extent of systemic exposure (56%). Therefore, co-administration of probenecid with meropenem is not recommended.

Meropenem may reduce serum levels of valproic acid to subtherapeutic levels (therapeutic range 50-100 µg/mL total valproate).

UNDESIRABLE EFFECTS

Local intravenous injection site reactions: inflammation, thrombophlebitis, pain at the site of injection

Systemic allergic reactions: rarely, systemic allergic reactions (hypersensitivity) may occur following administration of meropenem. These reactions may include angioedema and manifestations of anaphylaxis.

Skin reactions: rash, pruritus, urticaria: Rarely severe skin reactions, such as erythema multiforme, Stevens-Johnson Syndrome and toxic epidermal necrolysis, have been observed.

Gastro intestinal: abdominal pain, nausea, vomiting, diarrhoea. Pseudomembranous colitis has been reported.

Blood: Reversible thrombocythaemia, eosinophilia, thrombocytopenia, leucopenia and neutropenia (including very rare cases of agranulocytosis), haemolytic anaemia.
A positive direct or indirect Coombs test may develop in some subjects; there have been reports of reduction in partial thromboplastin time;

Liver function: Increases in serum concentrations of bilirubin, transaminases, alkaline phosphatase and lactic dehydrogenase alone or in combination have been reported;
Central nervous system: headache, paraesthesiae. Convulsions have been reported although a causal relationship with meropenem injection has not been established.

Other: Oral and vaginal candidosis.

USE IN SPECIAL POPULATIONS

Pregnancy

NURONEM INJECTION should not be used in pregnancy unless the potential benefit justifies the potential risk to the foetus. In every case, it should be used under the direct supervision of the physician.

Lactation

Meropenem is detectable at very low concentrations in animal breast milk. NURONEM INJECTION should not be used in breast-feeding women unless the potential benefit justifies the potential risk to the baby.

OVERDOSE

Accidental overdosage could occur during therapy, particularly in patients with renal impairment. Treatment of overdosage should be symptomatic. In normal individuals, rapid renal elimination will occur; in subjects with renal impairment, haemodialysis will remove meropenem and its metabolite.

STORAGE

Before reconstitution the dry powder should be stored at a temperature below 30^{o}C.
After reconstitution - Reconstituted solutions should be used immediately. Please refer Method of administration.
Do not freeze.

KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN

SUPPLY
Pack of 30 mL vial

Manufactured in India by:
SUN PHARMACEUTICAL INDUSTRIES LIMITED
INDUSTRIAL AREA - 3
DEWAS- 455 001

Product Registration Holder:
RANBAXY (MALAYSIA) SDN. BHD.
(A Sun Pharma Company),
Lot 23, Bakar Arang Industrial Estate,
08000 Sungai Petani, Kedah
Malaysia

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