Systemic Adverse Reactions

Systemic adverse clinical reactions that were reported irrespective of the relationship to meropenem I.V. occurring in greater than 1.0% of the patients were diarrhoea (4.8%), nausea/vomiting (3.6%), headache (2.3%), rash (1.9%), sepsis (1 .6%), constipation (1 .4%), apnea (1.3%), shock (1.2%), and pruritus (1.2%).

Additional adverse systemic clinical reactions that are reported irrespective of relationship to therapy with meropenem I.V. and occurring in less than or equal to 1.0 % but greater than 0.1% of the patients are listed below within each body system in order of decreasing frequency: Bleeding events were seen as follows: gastrointestinal haemorrhage (0.5%), melena (0.3%), epistaxis (0.2%), haemoperitoneum (0.2%), summing to 1.2%.

Adverse Laboratory Changes

Laboratory abnormalities seen in the paediatric-aged patients in both the paediatric and the meningitis studies are similar to those reported in adult patients.

Adverse laboratory changes that were reported irrespective of relationship to meropenem IV. and occurring in greater than 0.2% of the patients were as follows:

Hepatic: Increased SGPT (ALT), SGOT (AST), alkaline phosphatase, LDH, and bilirubin

Hematologic: Increased platelets, increased eosinophils, decreased platelets, decreased haemoglobin, decreased hematocrit, decreased WBC, shortened prothrombin time and shortened partial thromboplastin time, leukocytosis, hypokalemia.

Renal: Increased creatinine and increased BUN

NOTE: For patients with varying degrees of renal impairment, the incidence of heart failure, kidney failure, seizure and shock reported irrespective of relationship to meropenem I.V., increased in patients with moderately severe renal impairment (creatinine clearance >10 to 26 ml/min).

Urinalysis: Presence of red blood cells

Paediatric Patients

Clinical Adverse Reactions

Meropenem I.V. was studied in 515 paediatric patients (≥ 3 months to < 13 years of age) with serious bacterial infections (excluding meningitis) at dosages of 10 to 20 mg/kg every 8 hours. The types of clinical adverse events seen in these patients are similar to the adults, with the most common adverse events reported as possibly, probably or definitely related to meropenem I.V. and their rates of occurrence as follows: Diarrhoea 3.5%, rash 1.6% nausea and vomiting 0.8%. Meropenem I.V. was studied in 321 paediatric patients (≥3 months to < 17 years of age) with meningitis at a dosage of 40 mg/kg every 8 hours. The types of clinical adverse events seen In these patients are similar to the adults, with the most common adverse events reported as possibly, probably, or definitely related to meropenem I.V. and their rates of occurrence as follows:

Diarrhoea 4.7%, Rash (mostly diaper area moniliasis) 3.1%, Oral Moniliasis 1.9%, Glossitis 1.0%

In the meningitis studies the rates of seizure activity during therapy were comparable between patients with no CNS abnormalities who received meropenem and those who received comparator agents (either cefotaxime or ceftriaxone). In the meropenem I.V. treated group, 12/15 patients with seizures had late onset seizures (defined as occurring on day 3 or later) versus 7/20 in the comparator arm.

Adverse Laboratory Changes

Laboratory abnormalities seen in the paediatric-aged patients in both the paediatric and the meningitis studies are similar to those reported in adult patients

There is no experience in paediatric patients with renal impairment.

OVERDOSAGE

The largest dose of meropenem administered in clinical trials has been 2 g given intravenously every 8 hours. At this dosage, no adverse pharmacological effects or increased safety risks have been observed.

Treatment of over dosage should be symptomatic. 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.

INCOMPATIBILITY

Meropenem I.V. should not be mixed with or physically added to solutions containing other drugs.

SHELF-LIFE : See on pack.

STORAGE AND HANDLING INSTRUCTIONS

Storage : Store below 30°C. Protect from light

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PIRONEM

Meropenem for injection USP 125 mg / 250 mg / 500 mg / 1000 mg

Composition

Each vial contains :

Sterile Meropenem USP equivalent to Anhydrous Meropenem	1000gm/500mg/250mg/125mg
Sterile Sodium Carbonate USP eq. to Sodium	90.2mg/45.1mg/22.55mg/11.275mg

DOSAGE FORM

Powder for Injection

PHARMACOLOGY

Pharmacodynamics

Meropenem is a broad-spectrum carbapenem antibiotic. The bactericidal activity of meropenem results from the inhibition of cell wall synthesis. Meropenem readily penetrates the cell wall of most Gram-positive and Gram-negative bacteria to reach penicillin-binding-protein (PBP) targets. 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. Meropenem has significant stability to hydrolysis by ß-lactamases of most categories, both penicillinases and cephalosporinases produced by Gram-positive and Gram-negative bacteria. Meropenem should not be used to treat methicillin-resistant staphylococci (MRSA). In vitro tests show meropenem to act synergistically with aminoglycoside antibiotics against some isolates of Pseudomonas aeruginosa. Meropenem has been shown to be active against most isolates of the following microorganisms, both in vitro and in clinical infections.

Aerobic and facultative Gram—positive microorganisms

Enterococcus faecalis (excluding vancomycin-resistant isolates) Staphylococcus aureus (beta-lactamase and non-beta -lactamase producing, methicillin-susceptible isolates only) Streptococcus agalactiae Streptococcus pneumoniae (penicillin-susceptible isolates only).

NOTE: Penicillin-resistant isolates had meropenem MIC90 values of 1 or 2 mcg/mL, which is above the 0.12 mcg/mL susceptible breakpoint for this species.

Streptococcus pyogenes
Viridans group streptococci

Aerobic and facultative Gram-negative microorganisms

Escherichia coli, Haemophilus influenzae (beta –lactamase and non- beta -lactamase-producing) Klebsiella pneumoniae, Neisseria meningitidis, Pseudomonas aeruginosa, Proteus mirabilis.

Anaerobic microorganisms

Bacteroides fragilis, Bacteroides thetaiotaomicron, Peptostreptococcus species.

The following in vitro data are available, but their clinical significance is unknown.

At least 90% of the following microorganisms exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoints for meropenem. However, the safety and effectiveness of meropenem in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Aerobic and facultative Gram-positive microorganisms. Staphylococcus epidermidis (beta -lactamase and non- beta-lactamase-producing, methicillin-susceptible isolates only).

Aerobic and facultative Gram-negative microorganisms

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

Anaerobic microorganisms

Bacteroides distasonis, Bacteroides ovatus, Bacteroides uniformis, Bacteroides ureolyticus, Bacteroides vulgatus, Clostridium difficile. Clostridium perfringens, Eubacterium lentum, Fusobacterium species, Prevotella bivia, Prevotella intermedia, Prevotella melaninogenica, Porphyromonas asaccharolytica, Propionibacterium acnes.

Pharmacokinetics

At the end of a 30-minute intravenous infusion of a single dose of meropenem I.V. in normal volunteers, mean peak plasma concentrations are approximately 23 µg/ml (range 14-26) for the 500 mg dose and 49 µg/ml (range 39-58) for the 1 g dose. A 5-minute intravenous bolus injection of meropenem I.V. in normal volunteers results in mean peak plasma concentrations of approximately 45 µg/ml (range 18-65) for the 500 mg dose and 112 µg/ml (range 83-140) for the 1 g dose. Following intravenous doses of 500 mg, mean plasma concentrations of meropenem usually decline to approximately 1 µg /ml at 6 hours after administration. Meropenem penetrates well into most body fluids and tissues including cerebrospinal fluid, achieving concentrations matching or exceeding those required to inhibit most susceptible bacteria. Plasma protein binding of meropenem is approximately 2%.

In subjects with normal renal function, the elimination half-life of meropenem I.V. is approximately 1 hour. Approximately 70% of the intravenously administered dose is recovered as unchanged meropenem in the urine over 12 hours, after which little further urinary excretion is detectable. Urinary concentrations of meropenem in excess of
10 mcg/ml are maintained for up to 5 hours after a 500 mg dose. No accumulation of meropenem in plasma or urine was observed with

Studies performed in pediatric patients using intravenous meropenem 10 to 40 mg/kg infused over 30 minutes have demonstrated that the volume of distribution at steady-state (0.45 L/kg in neonates) and the elimination half-life (3 hours in preterm neonates, 2 hours in full term neonates, 1.4 to 2.3 hours in infants aged 3 to 5 months, 1.1 to 1.5 hours in infants aged 6 to 23 months, and about 1 hour in children aged 2 to 12 years) are increased in infants compared with adults, Total body clearance (0.12 to 0.19 L/h/kg) and renal clearance (0.05 to 0.07 L/h/kg), and the percentage of drug recovered in the urine, appear to be decreased in neonates versus adults. It is suggested that the volume of distribution is linearly related to weight, and that clearance is nonlinearly related to age after normalization for creatinine clearance.

INDICATIONS

Meropenem is indicated for all age group including infants above 3 months of age as single agent therapy for the treatment of the following infections when caused by susceptible isolates of the designated microorganisms:

1. Pneumonias and Nosocomial Pneumonias
2. Urinary Tract Infections
3. Intra-abdominal Infections
4. Gynecological Infections, such as endometritis and pelvic inflammatory disease
5. Skin and Skin Structure Infections
6. Meningitis
7. Septicemia
8. Empiric treatment, for presumed infection in adult patients with febrile neutropenia, used as monotherapy or in combination with antiviral or antifungal agents

Appropriate cultures should usually be performed before initiating antimicrobial treatment in order to isolate and identify the organisms causing infection and determine their susceptibility to Meropenem .

Antimicrobial therapy should be adjusted, if appropriate, once the results of culture(s) and antimicrobial susceptibility testing are known.

DOSAGE AND ADMINISTRATION

Adults:

The dosage and duration of therapy shall be established depending on type and severity of the infection and the condition of the patient.

The recommended daily dosage is as follows:

500 mg every 8 hours in treatment of pneumonia, UTI, gynecological infections such as endometritis, skin and skin structure infections.

I g every 8 hours in treatment of nosocomial pneumonia, peritonitis, presumed infections in neutropenic patients and septicaemia.

In meningitis the recommended dosage is 2g every 8 hours.

Use in Adults with Renal Impairment:

Dosage should be reduced in patients with creatinine clearance less than 51 ml/min.

Recommended Meropenem IV. Dosage Schedule for adults with Impaired Renal Function		
Creatinine Clearance (ml/min)	**Dose (based on unit doses of500 mg, 1g)**	**Dosing Interval**
26-50O	One unit dose	Every 12 hours
10-25	One-half unit dose	Every 12 hours
<10	One-half unit dose	Every 24 hours

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

Males: Creatinine Clearance (ml/min) = Weight (kg) x (140 - age) /72 x serum creatinine (mg/dl)

Females: 0.85 x above value

Meropenem is cleared by haemodialysis; if continued treatment with meropenem is necessary, it is recommended that the unit dose (based on the type and severity of infection) is administered at the completion of the haemodialysis procedure to restore therapeutically effective plasma concentration.

There is no experience with peritoneal dialysis.

Pediatric use: For pediatric patients from 3 months of age and older, the Meropenem I.V. dose is 10, 20 every 8 hours (maximum dose is 2 g every 8 hours), depending on the type of infection. Pediatric patients weighing over 50 kg should be administered adult Meropenem I.V. dose. In meningitis the recommended dose is 40 mg/kg every 8 hours. There is no experience in children with renal impairment.

Method of Administration

Meropenem I.V. 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 diluents.

Preparation of solution:

Intravenous Bolus Administration

Constitute injection vials (500 mg and 1 g) with sterile water for injection. Shake to dissolve and solutions are clear, and colorless or pale yellow.

Vial Size	Approximate Withdrawable Volume (ml)	Approximate Average Concentration (mg/ml)	Amount of Diluent Added (ml)
250 mg	10	10	50
500 mg	10	10	50
1g	20	20	50

Intravenous Infusion Administration

Meropenem I.V. for intravenous infusion may be constituted with compatible infusion fluids (5O to 200 mL). Alternatively, an injection vial may be constituted, then the resulting solution added to an I.V. container and further diluted with an appropriate infusion fluid.

After reconstitution **Meropenem I.V.** with sterile water for injection it is stable at room temperature for 8 hrs and under refrigerator for 18 hrs at 4 °C.

Compatible Fluids

5% or 10% Glucose Solution
5% Glucose Solution with 0.02% Sodium Bicarbonate
0.9% Sodium Chloride and 5% Glucose Solution
5% Glucose with 0.225% Sodium Chloride Solution
5% Glucose with 0.15% Potassium Chloride Solution
Mannitol 2.5% or 10% Solution

Compatibility of meropenem I.V. with other drugs has not been established. Freshly prepared solutions of meropenem I.V. should be used whenever possible. However, constituted solutions of meropenem I V. maintain satisfactory potency at controlled room temperature 15—25°C (59—77°F) or under refrigeration 4°C (39°F) as described above. Solutions of intravenous meropenem I.V. should not be frozen.

CONTRAINDICATIONS

Meropenem I.V. is contraindicated in patients with known hypersensitivity to any component of this product or to other drugs in the some class or in patients who have demonstrated anaphylactic reactions to beta-lactams.

WARNINGS AND PRECAUTIONS

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with beta- lactams. These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe hypersensitivity reactions when treated with another beta -lactam. Before initiating therapy with Meropenem I.V., careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, other beta-lactams, and other allergens. If an allergic reaction to Meropenem I.V. occurs, discontinue the drug immediately. Serious anaphylactic reactions require immediate emergency treatment with epinephrine, oxygen, intravenous steroids, and airway management, including intubation. Other therapy may also be administered as indicated.

Seizures and other adverse CNS experiences have been reported during treatment with meropenem. These experiences have occurred most commonly is patients with CNS disorders (e.g., brain lesions or history of seizures) or with bacterial meningitis and/or compromised renal function. Close adherence to the recommended dosage regimens is urged, especially in patients with known factors that predispose to convulsive activity. Anticonvulsant therapy should be continued in patients with known seizure disorders. If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically, placed on anticonvulsant therapy if not already instituted, and the dosage of meropenem I.V. re-examined to determine whether It should be decreased or the antibiotic discontinued.

In patients with renal dysfunction, thrombocytopenia has been observed but no clinical bleeding reported. (See DOSAGE AND ADMINISTRATION - Use in Adults with Renal Impairment.)

There is inadequate information regarding the use of meropenem I.V. in patients on haemodialysis

Pseudomembranous colitis has been reported with nearly all antibacterial 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 subsequent to the administration of antibacterial agents. After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate-to-severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against Clostridium difficile colitis.

Drug Interactions

Probenecid competes with meropenem for active tubular secretion and thus inhibits the renal excretion of meropenem. This led to statistically significant increases in the elimination hall-life (38%) and in the extent of systemic exposure (56%). Therefore, the coadministration of probenecid with meropenem is not recommended.

There is evidence that meropenem may reduce serum levels of valproic acid to sub-therapeutic levels (therapeutic range considered to be 50 to 100 µg /ml total valproate).

Renal impairment

Please refer under D**OSAGE AND ADMINISTRATION.**

Hepatic impairment

No dosage adjustment is necessary in patients with impaired hepatic function

Pregnancy Category B

Reproductive studies have been performed with meropenem in rats at doses of up to 1000 mg/kg/day, and cynomolgus monkeys at doses of up to 360 mg/kg/day (on the basis of AUC comparisons, approximately 1.8 times and 3.7 times, respectively, to the human exposure at the usual dose of 1 g every 8 hours). These studies revealed no evidence of impaired fertility or harm to the fetus due to meropenem, although there were slight changes in fetal body weight at doses of 250 mg/kg/day (on the basis of AUC comparisons, 0.4 times the human exposure at a dose of 1 g every 8 hours) and above inrats. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Lactation

Because many drugs are excreted in human milk, caution should be exercised when Meropenem is administered to a nursing woman.

Paediatric use

The safety and effectiveness of meropenem have been established for paediatric patients ≥ 3 months of age. Use of **Meropenem I.V.** in paediatric patients with bacterial meningitis is supported by evidence from adequate and well-controlled studies in the paediatric population. Use of Meropenem I.V. in paediatric patients with intra-abdominal infections is supported by evidence from adequate and well-controlled studies with adults with additional data from paediatric pharmacokinetics studies and controlled clinical trials in paediatric patients. Use of Meropenem I.V. in paediatric patients with complicated skin and skin structure infections is supported by evidence from an adequate and well-controlled study with adults and additional data from paediatric pharmacokinetics studies.

Geriatric use

Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

UNDESIRABLE EFFECTS

Adult patients

Local adverse reactions

Local adverse reactions that were reported irrespective of the relationship to therapy with meropenem I.V. were as follows:

Inflammation at the injection site 2.4%

Injection site reaction 0.9%