120x300mm

Merzel™
(Meropenem)

Highnoon

COMPOSITION
Merzel Injection 500mg IV: Each pack contains:
Vial: Meropenem 500mg (Blended with Sterile Sodium Carbonate).
Ampoule: Sterile water for injection 10mL.

Merzel Injection 1g IV: Each pack contains:
Vial: Meropenem 1g (Blended with Sterile Sodium Carbonate).
Ampoule: Sterile water for injection 10mL (2 Ampoules).

DESCRIPTION
Merzel IV (meropenem for injection) is a sterile, pyrogen-free, synthetic, carbapenem antibacterial for intravenous administration. When re-constituted as instructed, each 1 g Merzel IV vial will deliver 1 g of meropenem and 90.2 mg of sodium as sodium carbonate (3.92 mEq). Each 500 mg Merzel IV vial will deliver 500 mg meropenem and 45.1 mg of sodium as sodium carbonate (1.96 mEq).

CLINICAL PHARMACOLOGY
Mechanism of Action
The bactericidal activity of meropenem results from the inhibition of cell wall synthesis. Meropenem penetrates the cell wall of most gram-positive and gram-negative bacteria to reach penicillin-binding-protein (PBP) targets. Meropenem binds to PBPs 2, 3 and 4 of *Escherichia coli* and *Pseudomonas aeruginosa*; and PBPs 1, 2 and 4 of *Staphylococcus aureus*. Bactericidal concentrations are typically 1-2 times the bacteriostatic concentrations of meropenem, with the exception of *Listeria monocytogenes*, against which lethal activity is not observed. Meropenem has significant stability to hydrolysis by β-lactamases, both penicillinases and cephalosporinases produced by gram-positive and gram-negative bacteria. Meropenem does not have *in vitro* activity against methicillin-resistant *Staphylococcus aureus* (MRSA) or methicillin resistant *Staphylococcus epidermidis* (MRSE).

Several mechanisms of resistance to carbapenems are: decreased permeability of the outer membrane of gram-negative bacteria (due to diminished production of porins) causing reduced bacterial uptake, reduced affinity of the target PBPs, increased expression of efflux pump components, and production of antibacterial drug-destroying enzymes (carbapenemases, metallo-β-lactamases). The cross-resistance is sometimes observed with isolates resistant to other carbapenems.

Antimicrobial Activity
Meropenem has been shown to be active against most isolates of the following bacteria, both *in vitro* and in clinical infections.
Gram-positive bacteria
Enterococcus faecalis (vancomycin-susceptible isolates only), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Streptococcus agalactiae, Streptococcus pneumoniae* (penicillin-susceptible isolates only), *Streptococcus pyogenes* and Viridans group streptococci.
Gram-negative bacteria
Escherichia coli, Haemophilus influenzae, Klebsiella pneumoniae, Neisseria meningitidis, Proteus mirabilis and Pseudomonas aeruginosa.
Anaerobic bacteria
Bacteroides fragilis, Bacteroides thetaiotaomicron and *Peptostreptococcus* species.

The safety and effectiveness of meropenem in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.
Gram-positive bacteria
Staphylococcus epidermidis (methicillin-susceptible isolates only).
Gram-negative bacteria
Aeromonas hydrophila, Campylobacter jejuni, Citrobacter freundii, Citrobacter koseri, Enterobacter cloacae, Hafnia alvei, Klebsiella oxytoca, Moraxella catarrhalis, Morganella morganii, Pasteurella multocida, Proteus vulgaris and *Serratia marcescens.*
Anaerobic bacteria
Bacteroides ovatus, Bacteroides uniformis, Bacteroides ureolyticus, Bacteroides vulgatus, Clostridium difficile, Clostridium perfringens, Eggerthella lenta, Fusobacterium species, *Parabacteroides distasonis, Porphyromonas asaccharolytica, Prevotella bivia, Prevotella intermedia, Prevotella melaninogenica* and *Propionibacterium acnes.*

PHARMACOKINETICS
After intravenous injection of meropenem 0.5 and 1 gm over 5 minutes, peak plasma concentration of about 45 and 112 mg/mL respectively are attained. The same doses infused over 30 minutes produce peak plasma concentration of 23 and 49 mg/mL respectively. Meropenem has a mean plasma elimination half-life of about 1 hour. This may be prolonged in patients with renal impairment and also slightly prolonged in children. Meropenem is widely distributed in the body tissues and fluids including CSF and bile. It is about 2% bound to plasma proteins. It is more stable to renal dehydropeptidase I than imipenem and is mainly excreted in the urine by tubular secretion and glomerular filtration. About 70% of a dose is recovered unchanged in the urine over a 12-hour period and urinary concentrations above 10 mg/mL are maintained for up to 5 hours after a 500 mg dose. Meropenem is reported to have one metabolite, which is inactive and excreted in the urine. Meropenem is removed by hemodialysis.

INDICATIONS AND USAGE
It is indicated in the following conditions:

Complicated skin and skin structure infections (adult patients and pediatric patients 3 months of age and older only)
Merzel IV is indicated for the treatment of complicated skin and skin structure infections due to *Staphylococcus aureus* (methicillin-susceptible isolates only), *Streptococcus pyogenes, Streptococcus agalactiae*, viridans group streptococci, *Enterococcus faecalis* (vancomycin-susceptible isolates only), *Pseudomonas aeruginosa, Escherichia coli, Proteus mirabilis, Bacteroides fragilis,* and *Peptostreptococcus* species.

Complicated intra-abdominal infections (adult and pediatric patients)
For the treatment of complicated appendicitis and peritonitis caused by viridans group streptococci, *Escherichia coli, Klebsiella pneumoniae, pseudomonas aeruginosa, Bacteroides fragilis, B. thetaiotaomicron,* and *Peptostreptococcus* species.

Bacterial meningitis (pediatric patients 3 months of age and older only)
Merzel IV is indicated for the treatment of bacterial meningitis caused by *Haemophilus influenzae, Neisseria meningitidis and penicillin-susceptible isolates of Streptococcus pneumoniae.*
Merzel IV has been found to be effective in eliminating concurrent bacteremia in association with bacterial meningitis.

Usage
To reduce the development of drug-resistant bacteria and maintain the effectiveness of Merzel IV and other antibacterial drugs, Merzel IV should only be used to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy.

DOSAGE AND ADMINISTRATION
Adult Patients
The recommended dose is 500 mg given every 8 hours for skin and skin structure infections and 1 g given every 8 hours for intra-abdominal infections. When treating complicated skin and skin structure infections caused by *P. aeruginosa*, a dose of 1 g every 8 hours is recommended.

It should be administered by intravenous infusion over approximately 15 minutes to 30 minutes. Doses of 1 g may also be administered as an intravenous bolus injection (5 mL to 20 mL) over approximately 3 minutes to 5 minutes.

Use in Adult Patients with Renal Impairment
Dosage should be reduced in patients with creatinine clearance of 50 mL/min or less. The recommended dosage schedule for adult patients with renal impairment are as;

Creatinine Clearance (mL/min)	Dose (dependent on type of infection)	Dose Interval
Greater than 50	Recommended dose (500 mg complicated skin and skin structure infections and 1 g Intra-abdominal)	Every 8 hours
26-50	Recommended dose	Every 12 hours
10-25	One-half recommended dose	Every 12 hours
Less than 10	One-half recommended dose	Every 24 hours

There is inadequate information regarding the use of meropenem IV in patients on hemodialysis or peritoneal dialysis.

Use in pediatric patients 3 months of age and older
- For pediatric patients 3 months of age and older, the dose is 10 mg/kg, 20 mg/kg or 40 mg/kg every 8 hours (maximum dose is 2 g every 8 hours), depending on the type of infection (complicated skin and skin structure infections, complicated intra-abdominal infections, intra-abdominal infection or meningitis).
- For pediatric patients weighing over 50 kg administer at a dose of 500 mg every 8 hours for complicated skin and skin structure infections, 1 g every 8 hours for complicated intraabdominal infections, and 2 g every 8 hours for meningitis.

  Administer meropenem as an intravenous infusion over approximately 15 minutes to 30 minutes or as an intravenous bolus injection (5 mL to 20 mL) over approximately 3 minutes to 5 minutes.

  There is limited safety data available to support the administration of a 40 mg/kg (up to a maximum of 2 g) bolus dose.

The recommended dosage schedule for pediatric patients 3 months of age and older with normal renal function are as;

Type of Infection	Dose (mg/kg)	Up to a Maximum Dose	Dose Interval
Complicated skin and skin structure Infections	10	500 mg	Every 8 hours
Complicated intra-abdominal Infections	20	1 g	Every 8 hours
Meningitis	20	2 g	Every 8 hours

There is no experience in pediatric patients with renal impairment. When treating complicated skin and skin structure infections caused by *P. aeruginosa*, a dose of 20 mg/kg (or 1 g for pediatric patients weighing over 50 kg) every 8 hours is recommended.

Pediatric patients less than 3 months of age
For pediatric patients (with normal renal function) less than 3 months of age, with complicated intra-abdominal infections, the meropenem dose is based on gestational age (GA) and postnatal age (PNA). Meropenem IV should be given as intravenous infusion over 30 minutes.
The recommended meropenem dosage schedule for pediatric patients less than 3 months of age with complicated intra-abdominal infections and normal renal function are as;

Age Group	Dose (mg/kg)	Dose Interval
Infants less than 32 weeks gestational age and postnatal age less than 2 weeks	20	Every 12 hours
Infants less than 32 weeks gestational age and postnatal age 2 weeks and older	20	Every 8 hours
Infants 32 weeks and older gestational age and postnatal age less than 2 weeks	20	Every 8 hours
Infants 32 weeks and older gestational age and postnatal age 2 weeks and older	30	Every 8 hours

There is no experience in pediatric patients with renal impairment.

Preparation and Administration of Merzel IV Important Administration Instructions:
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

For Intravenous Bolus Administration
Re-constitute injection vials (500 mg and 1 g) with sterile Water for Injection (see table below). Shake to dissolve and let stand until clear.

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

For Infusion
- Injection vials (500 mg and 1 g) may be directly re-constituted with a compatible infusion fluid.
- Alternatively, an injection vial may be re-constituted, then the resulting solution added to an intravenous container and further diluted with an appropriate infusion fluid.

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Compatibility
Compatibility of Merzel IV with other drugs has not been established. Merzel IV should not be mixed with or physically added to solutions containing other drugs.

Stability and Storage
Freshly prepared solutions of Merzel IV should be used. However, re-constituted solutions of Merzel IV maintain satisfactory potency under the conditions described below. Solutions of intravenous Merzel IV should not be frozen.

Intravenous Bolus 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, may be stored for 3 hours at up to 25ºC or 12 hours under refrigerated conditions (2-8ºC).

Intravenous Infusion Administration
Solutions prepared for infusion (Merzel IV concentrations ranging from 1 mg/mL to 20 mg/mL) re-constituted with Sodium Chloride Injection 0.9% may be stored for 1 hour at up to 25ºC (77ºF) or 15 hours at up to 5ºC (41ºF).
Solutions prepared for infusion (Merzel IV concentrations ranging from 1 mg/mL to 20 mg/mL) re-constituted with Dextrose Injection 5% should be used immediately.

CONTRAINDICATIONS
Meropenem is contraindicated in patients with known hypersensitivity to any component of this product or to other drugs in the same class or in patients who have demonstrated anaphylactic reactions to beta (β)-lactams.

WARNINGS AND PRECAUTIONS
Hypersensitivity Reactions
Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with β-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 β-lactam. Before initiating therapy with Meropenem, it is important to inquire about previous hypersensitivity reactions to penicillins, cephalosporins, other β-lactams, and other allergens. If an allergic reaction to meropenem occurs, discontinue the drug immediately.

Seizure Potential
Seizures and other adverse CNS experiences have been reported during treatment with Meropenem. These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) or with bacterial meningitis and/or compromised renal function. Dosage adjustment is recommended in patients with advanced age and/or adult patients with creatinine clearance of 50 mL/min or less. Close adherence to the recommended dosage regimens is urged, especially in patients with known factors that predispose to convulsive activity. Continue anti-convulsant therapy in patients with known seizure disorders. If focal tremors, myoclonus, or seizures occur, evaluate neurologically, placed on anti-convulsant therapy if not already instituted, and reexamine the dosage of meropenem to determine whether it should be decreased or discontinued.

Risk of Breakthrough Seizures Due to Drug Interaction with Valproic Acid
The concomitant use of meropenem and valproic acid or divalproex sodium is generally not recommended. Co-administration of carbapenems, including meropenem, to patients receiving valproic acid or divalproex sodium results in a reduction in valproic acid concentrations. The valproic acid concentrations may drop below the therapeutic range as a result of this interaction, therefore increasing the risk of breakthrough seizures. Increasing the dose of valproic acid or divalproex sodium may not be sufficient to overcome this interaction. Consider administration of antibacterial drugs other than carbapenems to treat infections in patients whose seizures are well controlled on valproic acid or divalproex sodium. If administration of meropenem is necessary, consider supplemental anti-convulsant therapy.

***Clostridium difficile*–associated Diarrhea**
Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Meropenem, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*. *C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing isolates of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial drug use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibacterial drug use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial drug treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.

Development of Drug-Resistant Bacteria
Prescribing Meropenem in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Overgrowth of Non susceptible Organisms
As with other broad-spectrum antibacterial drugs, prolonged use of meropenem may result in overgrowth of non susceptible organisms. Repeated evaluation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

Thrombocytopenia
In patients with renal impairment, thrombocytopenia has been observed but no clinical bleeding reported.

Potential for Neuromotor Impairment
Alert patients receiving Meropenem on an outpatient basis regarding adverse events such as seizures, delirium, headaches and/or paresthesia that could interfere with mental alertness and/or cause motor impairment. Although Meropenem is well tolerated, it is advise patients not to operate machinery or motorized vehicles.

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.

ADVERSE REACTIONS
The reported adverse effects of meropenem are; hypersensitivity reactions, seizure potential, risk of breakthrough seizures due to drug interaction with valproic acid, *Clostridium difficile* – associated diarrhea, development of drug-resistant bacteria, overgrowth of non-susceptible organisms, thrombocytopenia, potential for neuromotor impairment, severe cutaneous reactions, inflammation at the injection site, injection site reaction, phlebitis, thrombophlebitis, pain at the injection site and edema at the injection site, diarrhea, nausea, vomiting, headache, rash, sepsis, constipation, apnea, shock, pruritus, gastrointestinal hemorrhage, melena, epistaxis, hemoperitoneum, pain, abdominal pain, chest pain, fever, back pain, abdominal enlargement, chills, pelvic pain, heart failure, heart arrest, tachycardia, hypertension, myocardial infarction, pulmonary embolus, bradycardia, hypotension, syncope, oral moniliasis, anorexia, cholestatic jaundice, jaundice, flatulence, ileus, hepatic failure, dyspepsia, intestinal obstruction, anemia, hypochromic anemia, hypervolemia, peripheral edema, hypoxia, insomnia, agitation, delirium, confusion, dizziness, seizure, nervousness, paresthesia, hallucinations, somnolence, anxiety, depression, asthenia, dyspnea, pleural effusion, asthma, cough increased, lung edema, urticaria, sweating, skin ulcer, dysuria, kidney failure, vaginal moniliasis, urinary incontinence, increased alanine transaminase (ALT), increased aspartate transaminase (AST), increased alkaline phosphatase, increased lactate dehydrogenase (LDH), increased bilirubin, increased platelets, increased eosinophils, decreased platelets, decreased hemoglobin, decreased hematocrit, decreased white blood cell (WBC), shortened prothrombin time and shortened partial thromboplastin time, leukocytosis, hypokalemia, increased creatinine and increased blood urea nitrogen (BUN), presence of red blood cells, anemia, pharyngitis, accidental injury, gastrointestinal disorder, hypoglycemia, peripheral vascular disorder, pneumonia, glossitis, convulsion, hyperbilirubinemia (conjugated), agranulocytosis, neutropenia, leukopenia, a positive direct or indirect Coombs test, hemolytic anemia, angioedema, drug rash with eosinophilia, systemic symptoms (DRESS syndrome), toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis and erythema multiforme.

DRUG INTERACTIONS
Probenecid: Probenecid competes with meropenem for active tubular secretion, resulting in increased plasma concentrations of meropenem. Co-administration of probenecid with meropenem is not recommended.

Valproic Acid: Co-administration of carbapenems, including meropenem, to patients receiving valproic acid or divalproex sodium results in a reduction in valproic acid concentrations. The valproic acid concentrations may drop below the therapeutic range as a result of this interaction, therefore increasing the risk of breakthrough seizures.

USE IN SPECIFIC POPULATIONS
Pregnancy
There are insufficient human data to establish whether there is a drug-associated risk of major birth defects or miscarriages with meropenem in pregnant women.

Nursing Mothers
Meropenem has been reported to be excreted in human milk. Caution should be exercised when Meropenem is administered to a nursing woman.

Pediatric Use
The safety and effectiveness of Meropenem has been established for pediatric patients 3 months of age and older with complicated skin and skin structure infections and bacterial meningitis, and for pediatric patients of all ages with complicated intra-abdominal infections.

Geriatric Use
Meropenem is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with renal impairment. 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.

Patients with Renal Impairment
Dosage adjustment is necessary in patients with creatinine clearance 50 mL/min or less.

OVERDOSAGE
Intentional overdosing of Meropenem is unlikely, although accidental overdosing might occur if large doses are given to patients with reduced renal function. If adverse events occur following overdosage, they are consistent with the adverse event profile described in the Adverse Reactions section and are generally mild in severity and resolve on withdrawal or dose reduction. Consider symptomatic treatments. In individuals with normal renal function, rapid renal elimination takes place. Meropenem and its metabolite are readily dialyzable and effectively removed by hemodialysis; however, no information is available on the use of hemodialysis to treat overdosage.

DOSAGE AND INSTRUCTIONS
To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30ºC. Keep in a dry place. Protect from light.

PRESENTATION
Merzel 500mg IV Injection
1 vial of 500 mg meropenem and 1 ampoule of 10mL solvent.

Merzel 1g IV Injection
1 vial of 1 g meropenem and 2 ampoules with10mL solvent each.

مرزِل™
(میروپنم)

خوراک و ہدایات:
صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔
بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔

Manufactured by:
BIO-NEXT PHARMACEUTICALS
Plot No. 50, St. No. S-10,
RCCI Industrial Estate Rawat,
Islamabad-Pakistan.

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