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

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Meropenem Injection IP 500 mg / 1 g

IXZA® 500 / IXZA®

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COMPOSITION:
IXZA® 500
Each Vial Contains:
Meropenem IP (Sterile)
Eq. to Anhydrous Meropenem 500 mg
Sodium Carbonate IP (As buffer)
Eq. to Sodium 45.1 mg

IXZA®
Meropenem IP (Sterile)
Eq. to Anhydrous Meropenem 1000 mg
Sodium Carbonate IP (As buffer)
Eq. to Sodium 90.2 mg

ATC code: J01DH02

FOR INTRAVENOUS USE ONLY
To reduce the development of drug-resistant bacteria and maintain the effectiveness of **IXZA® 500/IXZA®** I.V. (Meropenem Injection IP) and other antibacterial drugs,**IXZA® 500/IXZA®** should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

IXZA® 500/IXZA® (Meropenem Injection IP) is a sterile, pyrogen-free, synthetic, broadspectrum, carbapenem antibiotic for intravenous administration. It is (4R,5S,6S)-3-[[(3S,5S)-5-(Dimethylcarbamoyl)-3-pyrrolidinyl]thio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1- azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid. Its empirical formula is $C_{17}H_{25}N_3O_5S$ with a molecular weight of 383.5 g/mol.

PHARMACEUTICAL DOSAGE FORM: Powder for injection
CLINICAL PHARMACOLOGY
Pharmacodynamics
Meropenem is a broad-spectrum carbapenem antibiotic. It is active against many Gram-positive and Gram-negative bacteria.

Meropenem has significant stability to hydrolysis by β-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).

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. Bactericidal concentrations (defined as a 3 log10 reduction in cell counts within 12 to 24 hours) are typically 1-2 times the bacteriostatic concentrations of meropenem, with the exception of Listeria monocytogenes, against which lethal activity is not observed.

Lists of Microorganisms
Meropenem has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections.

Aerobic Gram-positive microorganisms
Enterococcus faecalis, *Staphylococcus aureus* (beta-lactamase and non-beta-lactamase producing strains), *Staphylococcus epidermidis* (β-lactamase and non-β-lactamase-producing, methicillin-susceptible isolates only), Streptococcus agalactiae, Streptococcus pneumoniae, Streptococcus pyogenes, Viridans group streptococci.

Aerobic Gram-negative microorganisms
Aeromonas hydrophila, Campylobacter jejuni, Escherichia coli, Haemophilus influenzae (betalactamase and non-beta-lactamase producing strains), *Klebsiella pneumoniae, Neisseria meningitidis, Pseudomonas aeruginosa, Proteus mirabilis, Acinetobacter species, Citrobacter diversus, Citrobacter freundii, Enterobacter cloacae, Haemophilus influenzae* (incl. ampicillin resistant 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 fragilis, Bacteroides thetaiotaomicron, Bacteroides distasonis, Bacteroides ovatus, Bacteroides uniformis, Bacteroides ureolyticus, Bacteroides vulgatus, Clostridium difficile, Clostridium perfringens, Peptostreptococcus species, Eubacterium lentum, Fusobacterium species, Prevotella bivia, Prevotella intermedia, Prevotella melaninogenica, Porphyromonas asaccharolytic, Propionibacterium acnes.

Meropenem has significant stability to hydrolysis by β-lactamases of most categories, both penicillinases and cephalosporinases produced by Gram-positive (exept methicillin-resistant staphylococci (MRSA)) and Gram-negative bacteria.

Pharmacokinetics
At the end of a 30-minute intravenous infusion of a single dose of Meropenem 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 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. In subjects with normal renal function, the elimination half-life of Meropenem 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 µg/mL are maintained for up to 5 hours after a 500 mg dose. No accumulation of meropenem in plasma or urine was observed with regimens using 500 mg administered every 8 hours or 1g administered every 6 hours in volunteers with normal renal function.

Plasma protein binding of Meropenem is approximately 2%. There is one metabolite that is microbiologically inactive. Meropenem penetrates well into most body fluids and tissues including cerebrospinal fluid, achieving concentrations matching or exceeding those required to inhibit most susceptible bacteria. After a single intravenous dose of Meropenem, the highest mean concentrations of meropenem were found in tissues and fluids at 1 hour (0.5 to 1.5 hours) after the start of infusion.

The pharmacokinetics of Meropenem in pediatric patients 2 years of age or older are essentially similar to those in adults. The elimination half-life for meropenem was approximately 1.5 hours in pediatric patients of age 3 months to 2 years. The pharmacokinetics are linear over the dose range from 10 to 40 mg/kg. Pharmacokinetic studies with Meropenem in patients with renal insufficiency have shown that the plasma clearance of meropenem correlates with creatinine clearance. Dosage adjustments are necessary in subjects with renal impairment. Meropenem I.V. is hemodialyzable. A pharmacokinetic study with Meropenem in patients with hepatic impairment has shown no effects of liver disease on the pharmacokinetics of meropenem.

Special Populations
Patients with Renal Impairment
Following a single 500 mg dose of Meropenem, the mean AUC of Meropenem in subjects with mild (CrCl 50–79 mL/min), moderate (CrCl 31–50 mL/min), and severe renal impairment (CrCl ≤ 30 mL/min) was 1.6, 2.8, and 5.1 times that of age-matched healthy subjects with normal renal function (CrCl ≥80mL/min), respectively. Dosage adjustment is necessary in patients with moderate and severe renal impairment.

Patients with Hepatic Impairment
The pharmacokinetics of Meropenem in patients with hepatic impairment have not been established. As Meropenem does not appear to undergo hepatic metabolism, the pharmacokinetics of Meropenem are not expected to be affected by hepatic impairment.

Geriatric Patients
No dosage adjustment is recommended for elderly patients with normal (for their age) renal function.

Indications
IXZA® 500/IXZA® is indicated as single agent therapy for the treatment of the following infections when caused by susceptible isolates of the designated microorganisms:

Skin and Skin Structure Infections
Complicated skin and skin structure infections due to Staphylococcus aureus (b-lactamase and non-b-lactamase producing, methicillin susceptible isolates only), Streptococcus pyogenes, Streptococcus agalactiae, viridans group streptococci, Enterococcus faecalis (excluding vancomycin-resistant isolates), Pseudomonas aeruginosa, Escherichia coli, Proteus mirabilis, Bacteroides fragilis, and Peptostreptococcus species.

Intra-abdominal Infections
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 only) Bacterial meningitis caused by Streptococcus pneumoniae, Haemophilus influenzae (β–lactamase and non-β–lactamase-producing isolates), and Neisseria meningitidis. Also Meropenem has been found to be effective in eliminating concurrent bacteremia in association with bacterial meningitis.

CONTRAINDICATIONS
Hypersensitivity to meropenem, any component of the formulation, or other carbapenems (eg, imipenem); patients who have experienced anaphylactic reactions to other beta-lactams.

WARNINGS

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. BEFORE INITIATING THERAPY WITH IXZA® 500/IXZA®, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OTHER β-LACTAMS, AND OTHER ALLERGENS. IF ANY ALLERGIC REACTION TO IXZA® 500/IXZA®, 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 CNS adverse experiences have been reported during treatment with Meropenem. Carbapenems, including meropenem, may reduce serum valproic acid concentrations to subtherapeutic levels, resulting in loss of seizure control. Serum valproic acid concentrations should be monitored frequently after initiating carbapenem therapy. Alternative antibacterial or anticonvulsant therapy should be considered if serum valproic acid concentrations drop below the therapeutic range or a seizure occurs.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including **IXZA® 500/IXZA®**, 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. CDAD must be considered in all patients who present with diarrhea following antibiotic 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 antibiotic use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS
General
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.

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 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. There is inadequate information regarding the use of Meropenem in patients on hemodialysis. As with other broad-spectrum antibiotics, prolonged use of meropenem may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

Laboratory Tests
While Meropenem possesses the characteristic low toxicity of the beta-lactam group of antibiotics, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during prolonged therapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
Carcinogenesis studies have not been performed.
Mutagenesis
Genetic toxicity studies were performed with meropenem using the bacterial reverse mutation test, the Chinese hamster ovary HGPRT assay, cultured human

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इक्ज़ा ५०० / इक्ज़ा

lymphocytes cytogenic assay, and the mouse micronucleus test. There was no evidence of mutagenic potential found in any of these tests.

Impairment of fertility
Reproductive studies were performed with meropenem in rats at doses up to 1000 mg/kg/day, and cynomolgus monkeys at doses 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). There was no reproductive toxicity seen.

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 in rats. 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.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Meropenem is administered to a nursing woman.

Pediatric Use
The safety and effectiveness of Meropenem have been established for pediatric patients[3] ≥3 months of age.

Geriatric Use
A pharmacokinetic study with Meropenem in elderly patients with renal insufficiency has shown a reduction in plasma clearance of meropenem that correlates with age-associated reduction in creatinine clearance. Meropenem is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. 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.

ADVERSE REACTIONS
Local Adverse Reactions
Local adverse reactions that were reported irrespective of the relationship to therapy with Meropenem were as follows:
Inflammation at the injection site 2.4%
Injection site reaction..... 0.9%
Phlebitis/thrombophlebitis..... 0.8%
Pain at the injection site 0.4%
Edema at the injection site 0.2%

Systemic adverse reactions
1% to 10%:
Cardiovascular: Peripheral vascular disorder
Central nervous system: Headache , pain
Dermatological: Rash , pruritus
Endocrine & metabolic: Hypoglycemia
Gastrointestinal: Diarrhea , nausea/vomiting , constipation ,oral moniliasis in pediatric patients, glossitis
Hematological: Anemia
Respiratory: Apnea , pharyngitis, pneumonia
Miscellaneous: Sepsis , shock
<1%: Abdominal enlargement, abdominal pain, agitation/delirium, alkaline phosphatase increased, ALT/AST increased, anemia (hypochromic), anorexia, anxiety, asthma, back pain, bilirubin increased, bradycardia, BUN increased, chest pain, chills, cholestatic jaundice/jaundice, confusion, cough, creatinine increased, depression, diaphoresis, dizziness, dyspepsia, dyspnea, dysuria, eosinophilia, epistaxis (0.2%), fever, flatulence, gastrointestinal hemorrhage (0.5%), hallucinations, heart failure, hemoglobin/ hematocrit decreased, hemoperitoneum (0.2%), hepatic failure, hyper-/hypotension, hypervolemia, hypokalemia, hypoxia, ileus, insomnia, intestinal obstruction, LDH increased, leukocytosis, melena (0.3%), MI, nervousness, paresthesia, pelvic pain, peripheral edema, platelets decreased/increased, pleural effusion, prothrombin time decreased, pulmonary edema, pulmonary embolism, renal failure, respiratory disorder, seizure, skin ulcer, somnolence, syncope, tachycardia, urinary incontinence, urticaria, vaginal moniliasis, weakness, WBC decreased, whole body pain.

Postmarketing and/or case reports: Agranulocytosis, angioedema, erythema multiforme, hemolytic anemia, leukopenia, neutropenia, positive Coombs test, Stevens-Johnson syndrome, toxic epidermal necrolysis.

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 half-life (38%) and in the extent of systemic exposure (56%). Therefore, the coadministration of probenecid with meropenem is not recommended.

A clinically significant reduction in serum valproic acid concentration has been reported in patients receiving carbapenem antibiotics and may result in loss of seizure control. Although the mechanism of this interaction is not fully understood, data from in vitro and animal studies suggest that carbapenem antibiotics may inhibit valproic acid glucuronide hydrolysis. Serum valproic acid concentrations should be monitored frequently after initiating carbapenem therapy. Alternative antibacterial or anticonvulsant therapy should be considered if serum valproic acid concentrations drop below the therapeutic range or a seizure occurs.

DOSAGE AND ADMINISTRATION
Adults
The recommended dose of **IXZA® 500/IXZA®** is 500 mg given every 8 hours for skin and skin structure infections and 1 g given every 8 hours for intra-abdominal infections. **IXZA® 500/IXZA®** should be administered by intravenous infusion over approximately 15 to 30 minutes. Doses of 1 g may also be administered as an intravenous bolus injection (5 to 20 mL) over approximately 3-5 minutes.

Adult patients with normal renal function	
Indication	**Dosing**
Complicated skin and skin structure infections (CSSSIs)	500mg q8h
Complicated appendicitis and peritonitis	1 g q8h

Use in Adults with Renal Impairment
Dosage should be reduced in patients with Creatinine clearance less than 51 mL/min.

Adult patients with impaired renal function		
Creatinine clearance (mL/min)	**Dose (dependent on infection type)**	**Dosing interval**
≥ 51	Recommended dose (500 mg CSSSIs and 1 g complicated appendicitis and peritonitis)	q8h
26-50	Recommended dose	q12h
10-25	One-half recommended dose	q12h
<10	One-half recommended dose	q24h

Use in Pediatric Patients
For pediatric patients from 3 months of age and older, the **IXZA®500/IXZA®**dose is 10, 20 or 40 mg/kg every 8 hours (maximum dose is 2 g every 8 hours), depending on the type of infection (See dosing table below.) Pediatric patients weighing over 50 kg, **IXZA®500/IXZA®** should be administered at a dose of 500 mg every 8 hours for complicated skin and skin structure infections, 1 g every 8 hours for intra-abdominal infections and 2 g every 8 hours for meningitis. **IXZA® 500/IXZA®** should be given as intravenous infusion over approximately 15 to 30 minutes or as an intravenous bolus injection (5 to 20 mL) over approximately 3-5 minutes.
Recommended **IXZA® 500/IXZA®** Dosage Schedule for Pediatrics with Normal Renal Function

Type of Infection	Dose (mg/kg)	Up to a Maximum Dose	Dosing Interval
Complicated skin and skin structure Intra-abdominal	10	500 mg	Every 8 hours
	20	1 g	Every 8 hours
Meningitis	40	2 g	Every 8 hours

There is no experience in pediatric patients with renal impairment.
Use in Adults with Hepatic Insufficiency:
No dosage adjustment is necessary in patients with impaired hepatic function.

Use in Elderly Patients
No dosage adjustment is required for elderly patients with creatinine clearance values above 50 mL/min. Clearance values above 50 mL/min.

PREPARATION OF SOLUTION
For Intravenous Bolus Administration
Constitute injection vials (500 mg and 1g) with sterile water for Injections IP. (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
Infusion vials (500 mg and 1g) may be directly constituted with a compatible infusion fluid. 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. (See Compatibility And Stability)

Compatibility and Stability
Compatibility of Meropenem with other drugs has not been established. Meropenem should not be mixed with or physically added to solutions containing other drugs.
Freshly prepared solutions of Meropenem should be used whenever possible. However, constituted solutions of Meropenem maintain satisfactory potency at temperature 15-25°C (59- 77°F) or under refrigeration at 4°C (39°F) as described below. Solutions of intravenous Meropenem should not be frozen.

Intravenous Bolus Administration
Meropenem injection vials constituted with sterile water for Injections IP for bolus administration (up to 50 mg/mL of Meropenem) may be stored for up to 2 hours at temperature 15-25°C (59-77°F) or for up to 12 hours at 4°C (39°F).

Intravenous Infusion Administration
Stability in Infusion Vials: Meropenem infusion vials constituted with Sodium Chloride Injection 0.9% (Meropenem concentrations ranging from 2.5 to 50 mg/mL) are stable for up to 2 hours at temperature 15-25°C (59-77°F) or for up to 18 hours at 4°C (39°F). Infusion vials of Meropenem constituted with Dextrose Injection 5% (Meropenem concentrations ranging from 2.5 to 50 mg/mL) are stable for up to 1 hour at temperature 15-25°C (59-77°F) or for up to 8 hours at 4°C (39°F).

NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Shelf Life: Please refer carton / label.

Storage: Store below 25°C, protect from light and moisture.
Keep out of reach of children.

How supplied
IXZA® is available as vial of Meropenem injection IP 1g along with 20mL sterile water for injections IP for reconstitution.

IXZA®500 is available as vial of Meropenem injection IP 500mg along with 10mL sterile water for injections IP for reconstitution.

Marketed by:
Biocon Biologics India Limited
Biocon House, Semicon Park,
Electronics City, Phase - II,
Bengaluru - 560 100, India.

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