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

℞ Meropenem Injection IP 1gm
Merolek®

Sterile Powder for Intravenous
Injection or Infusion
Reconstitute before use

2. Composition
Each vial contains:
Meropenem IP (Sterile)
Equivalent to anhydrous
Meropenem ..... 1 gm
Sodium Carbonate IP (as buffer)
Equivalent to Sodium ..... 90.2 mg

3. Dosage Form and Strength: Meropenem is supplied in glass vials containing sterile lyophilized powder of Meropenem IP (Sterile) equivalent to 500mg/1gm of anhydrous Meropenem & Sodium carbonate IP(as Buffer) equivalent to 45.1mg/90.2mg Sodium.

4. Clinical Particulars
4.1 Indication
Meropenem is indicated for the treatment in adults and children, of the following infections caused by single or multiple bacteria sensitive to meropenem:
- Pneumonias and Nosocomial Pneumonias
- Urinary Tract Infections (UTIs)
- Intra-abdominal Infections (IAI)
- Gynaecological Infections such as Endometriatis and Pelvic Inflammatory Disease
- Skin and Skin Structure Infections (SSSTIs)
- Meningitis
- Septicaemia & empiric treatment of presumed infection in adult patients with febrile neutropenia

Meropenem has been Proved Efficacious alone or in Combination with other Antimicrobial agents in the Treatment of Polymicrobial Infections.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and Method of Administration
The tables below provide general recommendations for dosing. 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 2 g three times daily in adults and adolescents and a dose of up to 40 mg/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, Pseudomonas aeruginosa, Acinetobacter spp.), or very severe infections. Additional considerations for dosing are needed when treating patients with renal insufficiency.

Adults and adolescents

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

Meropenem is usually given by intravenous infusion over approximately 15 to 30 minutes. Alternatively, doses up to 1 g can be given as an intravenous bolus injection over approximately 5 minutes. There are limited safety data available to support the administration of a 2 g dose in adults as an intravenous bolus injection.
Renal Impairment
The dose for adults and adolescents should be adjusted when creatinine clearance is less than 51 ml/min, as shown below. There are limited data to support the application of these dose adjustments for a unit dose of 2 g.

Creatinine clearance (ml/min)	Dose (based on "unit" dose range of 500 mg or 1 g or 2 g, 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 50 ml/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 20 mg/kg every 8 hours may be an appropriate regimen.
Children from 3 months to 11 years of age and up to 50 kg 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 20 mg/kg
Broncho-pulmonary infections in cystic fibrosis	40 mg/kg
Complicated urinary tract infections	10 or 20 mg/kg
Complicated intra-abdominal infections	10 or 20 mg/kg
Complicated skin and soft tissue infections	10 or 20 mg/kg
Acute bacterial meningitis	40 mg/kg
Management of febrile neutropenic patients	20 mg/kg

Children over 50 kg body weight
The adult dose should be administered. There is no experience in children with renal impairment. Meropenem is usually given by intravenous infusion over approximately 15 to 30 minutes. Alternatively, meropenem doses of up to 20 mg/kg may be given as an intravenous bolus over approximately 5 minutes. There are limited safety data available to support the administration of a 40 mg/kg dose in children as an intravenous bolus injection.
Reconstitution
Intravenous bolus injection 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. Chemical and physical in-use stability for a prepared solution for bolus injection has been demonstrated for 1hour at up to 25°C or 2 hours under refrigerated conditions (2-8°C).
From a microbiological point of view, unless the method of opening/ reconstitution/dilution precludes the risk of microbiological contamination, the product should be used immediately.
If not used immediately in-use storage times and conditions are the responsibility of the user.
Intravenous infusion administration
A solution for infusion is prepared by dissolving the drug product in either 0.9% sodium chloride solution for infusion or 5% dextrose solution for infusion to a final concentration of 1 to 20 mg/ml. Chemical and physical in-use stability for a prepared solution for infusion using 0.9% sodium chloride solution has been demonstrated for 2 hours at up to 25°C or 2 hours under refrigerated conditions (2-8°C) and stability for a prepared solution for infusion using 5 % dextrose solution has been demonstrated for 2 hours at up to 25° C or 4 hours under refrigerated conditions (2-8°C).
From a microbiological point of view, unless the method of opening /reconstitution/dilution precludes the risk of microbiological contamination, the product should be used immediately.
If not used immediately in-use storage times and conditions are the responsibility of the user. The constituted solutions should not be frozen.

4.3 Contraindications
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).

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

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. Before initiating therapy with meropenem, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics. If a severe allergic reaction occurs, the medicinal product should be discontinued and appropriate measures taken.

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. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of meropenem. Discontinuation of therapy with meropenem and the administration of specific treatment for Clostridium difficile should be considered. Medicinal products that inhibit peristalsis should not be given.

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.

Concomitant use with valproic acid/sodium valproate/valpromide
The concomitant use of meropenem and valproic acid/sodium valproate/valpromide is not recommended.

Paediatric population
Meropenem is licensed for children over 3 months of age. 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.

Meropenem contains sodium
Meropenem 500 mg: This medicinal product contains approximately 2.0 mEq of sodium per 500 mg dose which should be taken into consideration by patients on a controlled sodium diet.
Meropenem 1.0 g: This medicinal product contains approximately 4.0 mEq of sodium per 1.0 g dose which should be taken into consideration by patients on a controlled sodium diet.

4.5 Drug Interactions
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. The potential effect of meropenem on the protein binding of other medicinal products or metabolism has not been studied. However, the protein binding is so low that no interactions with other compounds would be expected on the basis of this mechanism. Decreases 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 increases in the anti-coagulant effects of orally administered anti-coagulant agents, including warfarin in patients who are concomitantly receiving antibacterial agents. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the antibiotic to the increase in INR (international normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after coadministration of antibiotics with an oral anti-coagulant agent.

4.6 Use in Special Population
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 excreted in 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.

4.7 Effect on Ability to Drive and Use Machines
No studies on the effect on the ability to drive and use machines have been performed. However, when driving or operating machines, it should be taken into account that headache, paraesthesiae and convulsions have been reported for meropenem.

4.8 Undesirable Effects
Meropenem-related adverse reactions most frequently reported were diarrhoea (2.3 %), rash (1.4 %), nausea/vomiting (1.4 %) and injection site inflammation (1.1%). The most commonly reported meropenem-related laboratory adverse events were thrombocytosis (1.6 %) and increased hepatic enzymes (1.5-4.3 %). Headche, paraesthesiae, convulsions and hypokalemia are the other reported adverse effects of meropenem.

In the table below all adverse reactions are listed by system organ class and frequency: very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
Table 1

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
Psychiatric disorders	Rare	Delirium
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
Skin and subcutaneous tissue disorders	Common	rash, pruritis
	Uncommon	toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme, urticaria
	Not known	Drug Reaction with Eosinophilia and Systemic Symptoms, 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 is licensed for children over 3 months of age. 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.
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Kindly report any suspected adverse reactions to pharmavigil@jbpharma.com

4.9 Overdose
Relative overdose may be possible in patients with renal impairment if the dose is not adjusted. In individuals with normal renal function, rapid renal elimination will occur. Haemodialysis will remove meropenem and its metabolite.

5. Pharmacological Properties
5.1 Mechanism of Action
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).

5.2 Pharmacodynamics
Similar to other beta-lactam antibacterial agents, the time that meropenem concentrations exceed the MIC (T>MIC) has been shown to best correlate with efficacy. In preclinical models meropenem demonstrated activity when plasma concentrations exceeded the MIC of the infecting organisms for approximately 40 % of the dosing interval. This target has not been established clinically.
Mechanism of Resistance
Bacterial resistance to meropenem may result from: (1) decreased permeability of the outer membrane of Gram-negative bacteria (due to diminished production of porins) (2) reduced affinity of the target PBPs (3) increased expression of efflux pump components, and (4) production of beta-lactamases that can hydrolyse carbapenems. Localised clusters of infections due to carbapenem-resistant bacteria have been reported in the European Union.
There is no target-based cross-resistance between meropenem and agents of the quinolone, aminoglycoside, macrolide and tetracycline classes. However, bacteria may exhibit resistance to more than one class of antibacterials agents when the mechanism involved include impermeability and/or an efflux pump(s).
The following table of pathogens listed is derived from clinical experience and therapeutic guidelines.
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 freudii
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 asaccharolyticus
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 burnetii
Mycoplasma pneumonia
Glanders and melioidosis: Use of meropenem in humans is based on in vitro B.mallei and B. pseudomallei susceptibilitymdata and on limited human data. Treating physicians should refer to national and/or international consensus documents regarding the treatment of glanders and melioidosis.

5.3 Pharmacokinetic Properties
Distribution
The average plasma protein binding of meropenem was approximately 2 % and was 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. The measured renal clearance and the effect of probenecid show that meropenem undergoes both filtration and tubular secretion.

Renal insufficiency
Renal impairment results in higher plasma AUC and longer half-life for meropenem. There were AUC increases of 2.4 fold in patients with moderate impairment (CrCL 33-74 ml/min), 5 fold in severe impairment (CrCL 4-23 ml/min) and 10 fold in haemodialysis patients (CrCL <2 ml/min) when compared to healthy subjects (CrCL >80 ml/min). The AUC of the microbiologically inactive ring opened metabolite was also considerably increased in patients with renal impairment. Dose adjustment is recommended for patients with moderate and severe renal impairment. 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.

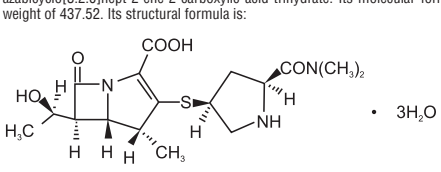
Adult patients
Pharmacokinetic studies performed in patients have not shown significant pharmacokinetic differences versus healthy subjects with equivalent renal function. A population model developed from data in 79 patients with intra-abdominal infection or pneumonia, showed a dependence of the central volume on weight and the clearance on creatinine clearance and age.

Paediatrics
The pharmacokinetics in infants and children with infection at doses of 10, 20 and 40 mg/kg showed Cmax values approximating to those in adults following 500, 1000 and 2000 mg doses, respectively. Comparison showed consistent pharmacokinetics between the doses and half-lives similar to those observed in adults in all but the youngest subjects (<6 months t1/2 1.6 hours). The mean meropenem clearance values were 5.8 ml/min/kg (6-12 years), 6.2 ml/min/kg (2-5 years), 5.3 ml/min/kg (6-23 months) and 4.3 ml/min/kg (2-5 months). Approximately 60 % of the dose is excreted in urine over 12 hours as meropenem with a further 12 % as metabolite. Meropenem concentrations in the CSF of children with meningitis are approximately 20 % of concurrent plasma levels although there is significant inter-individual variability. The pharmacokinetics of meropenem in neonates requiring anti-infective treatment showed greater clearance in neonates with higher chronological or gestational age with an overall average half-life of 2.9 hours. Monte Carlo simulation based on a population PK model showed that a dose regimen of 20 mg/kg 8 hourly achieved 60 % T>MIC for P. aeruginosa in 95 % of pre-term and 91 % of full term neonates.

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.

6. Non-Clinical Properties
6.1 Animal Toxicology or Pharmacology
Animal studies indicate that meropenem is well tolerated by the kidney. Histological evidence of renal tubular damage was seen in mice and dogs only at doses of 2000 mg/kg and above after a single administration and above and in monkeys at 500 mg/kg in a 7-day study. Meropenem is generally well tolerated by the central nervous system. Effects were seen in acute toxicity studies in rodent at doses exceeding 1000 mg/kg. The IV LD50 of meropenem in rodents is greater than 2000 mg/kg. The intravenous formulation was well tolerated in animal studies. The sole metabolite of meropenem had a similar profile of toxicity in animal studies.

7. Description
Meropenem for Injection, is a sterile, pyrogen-free, synthetic, carbapenem antibacterial 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 trihydrate. Its molecular formula is C17 H25 N3 O5 S3H2 O with a molecular weight of 437.52. Its structural formula is:



8. Pharmaceutical Particulars
8.1 Incompatibilities
This medicinal product must not be mixed with other medicinal products.

8.2 Shelf Life: Please see manufacturing date and expiry date printed on the pack.
After reconstitution: The reconstituted solutions for intravenous injection or infusion should be used immediately. The time interval between the beginning of reconstitution and the end of intravenous injection or infusion should not exceed one hour.

8.3 Packaging Information: Meropenem is available in glass vials containing 500 mg / 1 gram of meropenem.

8.4 Storage and Handling Instructions:
Storage: Store below 25°C. Protect from moisture.
Keep out of reach of children.

9. Patient Counselling Information
Counsel patients that diarrhea is a common problem caused by antibacterial drugs which usually ends when the antibacterial drug is discontinued. Sometimes after starting treatment with antibacterial drugs, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibacterial drug. If this occurs, patients should contact their physician as soon as possible. Counsel patients to inform their physician if they are taking valproic acid or divalproex sodium. Valproic acid concentrations in the blood may drop below the therapeutic range upon coadministration with meropenem. If treatment with meropenem is necessary and continued, alternative or supplemental anti-convulsant medication to prevent and/or treat seizures may be needed. Patients receiving meropenem on an outpatient basis must be alerted of adverse events such as seizures, delirium, headaches and/or paresthesias that could interfere with mental alertness and/or cause motor impairment. Until it is reasonably well established that meropenem is well tolerated, patients should not operate machinery or motorized vehicles.

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J. B. CHEMICALS & PHARMACEUTICALS LTD.
Neelam Centre, 'B' Wing, Hind Cycle Road, Worli, Mumbai - 400 030, India.

Note: This prescribing information is applicable for India Market only

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