PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] MEROPENEM FOR INJECTION USP AND SODIUM CHLORIDE INJECTION USP

Meropenem for Injection

Powder for Solution, 500 mg and 1 g Meropenem, Intravenous

USP

Antibiotic

B|BRAUN

B. Braun Medical Inc.
824 Twelfth Avenue
Bethlehem, PA 18018-3524 USA

Date of Initial Authorization:
JAN 03, 2024

Imported by:
B. Braun of Canada, Ltd.
2000 Ellesmere Road, Unit 16
Scarborough, Ontario M1H 2W4

Submission Control Number: 266553

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Meropenem for Injection USP and Sodium Chloride Injection USP is indicated for treatment of the following infections when caused by susceptible strains of the designated micro-organisms:

- **Lower Respiratory Tract**
  Community-acquired pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible strains only), *Streptococcus pneumoniae*, *Escherichia coli* and *Haemophilus influenzae* (including β-lactamase-producing strains).

  Nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible strains only), *Escherichia coli*, *Haemophilus influenzae* (non-β-lactamase-producing), *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*.

- **Urinary Tract**
  Complicated urinary tract infections caused by *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Serratia marcescens*.

- **Intra-abdominal**
  Complicated intra-abdominal infections caused by *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Morganella morganii*, *Pseudomonas aeruginosa*, *Bacteroides fragilis*, *Bacteroides ovatus*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Clostridium perfringens*, and *Peptostreptococcus* species.

- **Gynecologic**
  Gynecologic infections caused by *Staphylococcus aureus* (methicillin-susceptible strains only), *Staphylococcus epidermidis* (methicillin-susceptible strains only), *Escherichia coli*, *Prevotella bivia*, and *Peptostreptococcus* species.

  Pelvic inflammatory disease caused by *Staphylococcus epidermidis* (methicillin-susceptible strains only), *Streptococcus agalactiae*, *Escherichia coli* and *Prevotella bivia*.

  Note: Meropenem for Injection has no activity against *Chlamydia trachomatis*. Additional antimicrobial coverage is required if this pathogen is expected.

- **Uncomplicated Skin and Skin Structure**
  Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible strains only), *Streptococcus agalactiae*, *Streptococcus pyogenes* and *Escherichia coli*.

- **Complicated Skin and Skin Structure**
  Complicated skin and skin structure infections, except infected burns, due to *Staphylococcus aureus* (methicillin-susceptible strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, Viridans group streptococci, *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis, Klebsiella pneumoniae, Peptostreptococcus* species*,* and *Bacteroides fragilis*.

- **Bacterial Meningitis**
  Bacterial meningitis caused by *Streptococcus pneumoniae, Haemophilus influenzae* (including β-lactamase-producing strains) and *Neisseria meningitidis*.

  Note: There is limited adult efficacy data for Meropenem for Injection in the treatment of bacterial meningitis. Support for the adult meningitis indication is largely provided by pediatric data.

- **Bacterial Septicemia**
  Bacterial septicemia caused by *Escherichia coli*.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Meropenem for Injection and other antibacterial drugs, Meropenem for Injection should be used only to treat 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. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Therapy with Meropenem for Injection may be initiated on the basis of clinical judgement before results of sensitivity testing are available. Continuation of therapy should be re-evaluated on the basis of bacteriological findings and on the patient's clinical condition. Regular sensitivity testing is recommended when treating *Pseudomonas aeruginosa* infections.

Appropriate use of meropenem should be guided by local susceptibility data accumulated for key bacterial pathogens.

Localized clusters of infections due to carbapenem-resistant bacteria have been reported in some regions.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

1.1 Pediatrics

Pediatrics (≥ 3 months of age): The safety and effectiveness of Meropenem for Injection USP and Sodium Chloride Injection USP in pediatric patients 3 months of age and older have been established. Meropenem for Injection USP and Sodium Chloride Injection USP is not recommended for use in infants under the age of 3 months (see 7.1.3 Pediatrics).

1.2 Geriatrics

Geriatrics (≥ 65 years of age): This drug is known to be substantially excreted by the kidney. No dose adjustment is required in elderly patients, except in cases of moderate to severe renal impairment (see 4.2 Recommended Dose and Dosage Adjustment).

2 CONTRAINDICATIONS

Meropenem for Injection is contraindicated:

- in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- in patients who have demonstrated anaphylactic reactions to β-lactam antibiotics.
- where the administration of sodium chloride could be clinically detrimental (see 7 WARNINGS AND PRECAUTIONS).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with β-lactam antibiotics, including Meropenem for Injection (see 7 WARNINGS AND PRECAUTIONS)

- Seizures and other adverse central nervous system (CNS) experiences have been reported during treatment (see 7 WARNINGS AND PRECAUTIONS)

- Co-administration of Meropenem for Injection with valproic acid or divalproex sodium reduces the serum concentration of valproic acid potentially increasing the risk of breakthrough seizures (see 7 WARNINGS AND PRECAUTIONS)

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Meropenem for Injection USP and Sodium Chloride Injection USP in the DUPLEX® Container is designed to deliver a 500 mg or 1 gram dose of meropenem. If a dose of Meropenem for Injection USP and Sodium Chloride Injection USP is required that does not equal 500 mg or 1 gram, this product is not recommended for use and an alternative formulation of meropenem should be considered.

Adults

The usual dose is 500 mg to 1 g by intravenous infusion every 8 hours, depending on the type and severity of infection, the known or suspected susceptibility of the pathogens and the condition of the patient (see Table 1). Doses up to 2 g every 8 hours have been used. Meropenem for Injection should be given by intravenous infusion over approximately 15 to 30 minutes.

When treating infections known or suspected to be caused by *Pseudomonas aeruginosa*, a dose of at least 1 g every 8 hours in adults (maximum approved dose is 6 g daily given in 3 divided doses) is recommended. This dose is based on pharmacokinetic/pharmacodynamic modeling and probability of target attainment simulation for susceptible strains of *Pseudomonas aeruginosa* (MIC ≤ 2 mcg / mL).

4.2 Recommended Dose and Dosage Adjustment

The recommended dose to be given for adults is as in Table 1.

Table 1: Recommended Dose in Adults

Type of Infection	Dose	Dosing Interval
Complicated urinary tract	500 mg	Every 8 hours
Uncomplicated skin and skin structure	500 mg	Every 8 hours
Complicated skin and skin structure	500 mg	Every 8 hours
Gynecologic and Pelvic Inflammatory Disease	500 mg	Every 8 hours
Lower respiratory Community-acquired pneumonia Nosocomial pneumonia	 500 mg 1 g	 Every 8 hours Every 8 hours
Complicated intra-abdominal	1 g	Every 8 hours
Meningitis	2 g	Every 8 hours
Septicemia	1 g	Every 8 hours

Impaired Renal Function

Dosage should be reduced in patients with creatinine clearance less than 51 mL / min (Table 2).

Table 2: Dosage in Patients with Creatinine Clearance Less than 51 mL / min

Creatinine Clearance (mL / min)	Dose (dependent on type of infection)	Dosing Interval
26 - 50	Recommended dose (500 mg to 2000 mg)	Every 12 hours
10 - 25	One-half recommended dose	Every 12 hours
< 10	One-half recommended dose	Every 24 hours

Meropenem is removed by hemodialysis and hemofiltration; if continued treatment with Meropenem for Injection is necessary, the dose, based on the infection type and severity, should be administered at the completion of the hemodialysis procedure to reinstitute effective treatment.

There are no data on appropriate doses in patients requiring peritoneal dialysis.

Hepatic Impairment (Adults)
No dosage adjustment is necessary in patients with hepatic dysfunction as long as renal function is normal.

Geriatrics (≥ 65 years of age)
Dosage adjustment is recommended for the elderly with an estimated or measured creatinine clearance value below 51 mL / min (see 7.1.4 Geriatrics).

Pediatrics (≥ 3 months of age)
Meropenem for Injection USP and Sodium Chloride Injection USP in the DUPLEX® Container is designed to deliver a 500 mg or 1 gram dose of meropenem. Meropenem is not to be used in pediatric patients aged less than three months.

For infants and children over 3 months of age and weighing up to 50 kg, the recommended dose of Meropenem for Injection is 10 to 40 mg / kg every 8 hours, depending on the type and severity of infection, the known or suspected susceptibility of the pathogens and the condition of the patient (see Table 3). Children weighing over 50 kg require the adult dosage. Meropenem for Injection should be given as an intravenous infusion over approximately 15 to 30 minutes.

When treating infections known or suspected to be caused by *Pseudomonas aeruginosa*, a dose of at least 20 mg / kg every 8 hours in children (maximum approved dose is 120 mg / kg daily given in 3 divided doses) is recommended. This dose is based on pharmacokinetic/pharmacodynamic modeling and probability of target attainment simulation for susceptible strains of *Pseudomonas aeruginosa* (MIC ≤ 2 mcg / mL).

Table 3: Dosage in Pediatric Patients

Type of Infection	Dose (mg / kg)	Dosing Interval
Complicated urinary tract	10	Every 8 hours
Uncomplicated skin and skin structure	10 - 20	Every 8 hours
Community acquired pneumonia	10 - 20	Every 8 hours
Complicated intra-abdominal	20	Every 8 hours
Meningitis	40	Every 8 hours

There are no data on appropriate doses for children with renal impairment.

4.3 Reconstitution

After reconstitution (activation) (per instructions in Section 4.4 Administration), the delivered doses are equivalent to 500 mg and 1 gram meropenem anhydrous (added as meropenem trihydrate).

Compatibility
Compatibility of Meropenem for Injection USP and Sodium Chloride Injection USP with other drugs has not been established. Meropenem for Injection USP and Sodium Chloride Injection USP should not be mixed with or physically added to solutions containing other drugs.

Stability and Storage
Freshly prepared solutions of Meropenem for Injection USP and Sodium Chloride Injection USP should be used. Following reconstitution (activation) in the DUPLEX® Container, the product maintains satisfactory potency for 1 hour at up to 25°C (77°F) or for 15 hours at up to 5°C (41°F). Solutions of intravenous Meropenem for Injection USP and Sodium Chloride Injection USP should not be frozen.

4.4 Administration

Important Administration Instructions

- Do not use in series connections. Such use would result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete. If administration is controlled by a pumping device, care must be taken to discontinue pumping action before the container runs dry or air embolism may result.
- Do not introduce additives into the DUPLEX® Container.
- Administer Meropenem for Injection USP and Sodium Chloride Injection USP intravenously over approximately 15 to 30 minutes.

This reconstituted solution is for intravenous use only.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

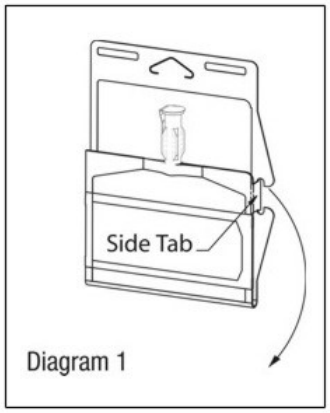
Use only if solution is clear and container and seals are intact.

DUPLEX® Container Storage

- To avoid inadvertent activation, the DUPLEX® Container should remain in the folded position until activation is intended.

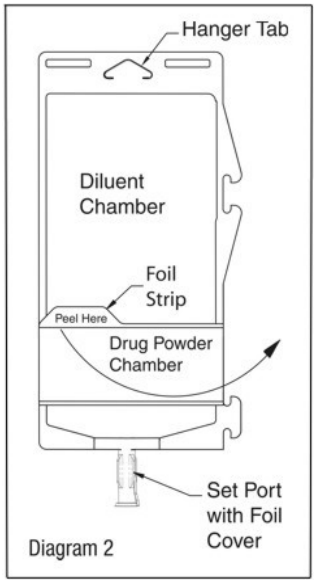
Patient Labeling and Drug Powder/Diluent Inspection

- Apply patient-specific label on foil side of container. Use care to avoid activation. Do not cover any portion of foil strip with patient label.
- Unlatch side tab and unfold DUPLEX® Container (see *Diagram 1*).



- Visually inspect diluent chamber for particulate matter.
- Use only if container and seals are intact.

- To inspect the drug powder for foreign matter or discoloration, peel foil strip from drug chamber (see *Diagram 2*).

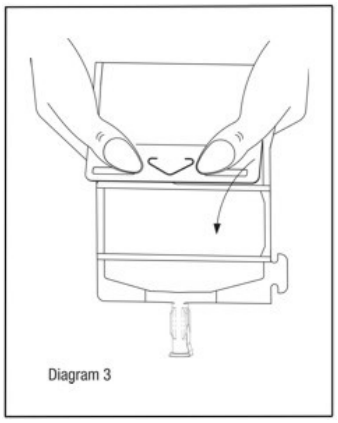


- Protect from light after removal of foil strip.

Note: If foil strip is removed, the container should be re-folded and the side tab latched until ready to activate. The product must then be used within 7 days at room temperature, but not beyond the labeled expiration date.

Reconstitution (Activation)

- Do not use directly after storage by refrigeration, allow the product to equilibrate to room temperature before patient use.
- Unfold the DUPLEX® Container and point the set port in a downward direction. Starting at the hanger tab end, fold the DUPLEX® Container just below the diluent meniscus trapping all air above the fold. To activate, squeeze the folded diluent chamber until the seal between the diluent and powder opens, releasing diluent into the drug powder chamber (see *Diagram 3*).

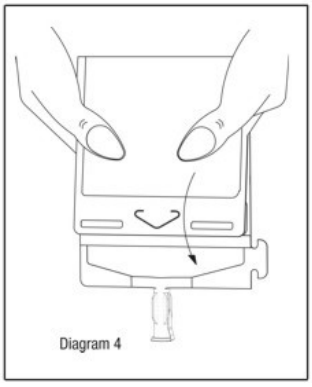


- Agitate the liquid-powder mixture until the drug powder is completely dissolved.

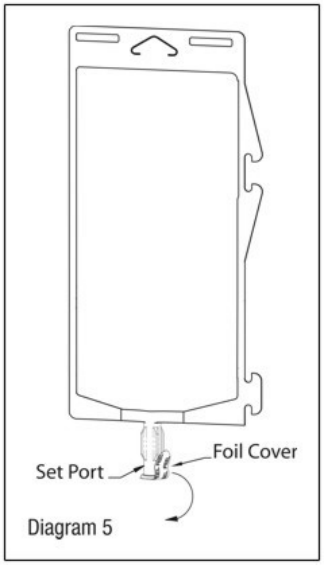
Note: Following reconstitution (activation), product must be used within 1 hour if stored at room temperature or within 15 hours if stored under refrigeration.

Administration

- Visually inspect the reconstituted solution for particulate matter.
- Point the set port in a downwards direction. Starting at the hanger tab end, fold the DUPLEX® Container just below the solution meniscus trapping all air above the fold. Squeeze the folded DUPLEX® Container until the seal between reconstituted drug solution and set port opens, releasing liquid to set port (see *Diagram 4*).



- Prior to attaching the IV set, check for minute leaks by squeezing container firmly. If leaks are found, discard container and solution as sterility may be compromised.
- Using aseptic technique, peel foil cover from the set port and attach sterile administration set (see *Diagram 5*).



- Refer to directions for use accompanying the administration set.

4.5 Missed Dose

If a dose is missed then it should be given as soon as practically possible after the scheduled time and subsequent doses should be given at 8 hour intervals from the revised dose time.

5 OVERDOSAGE

Intentional overdosing of Meropenem for Injection is unlikely, although accidental overdosing might occur particularly in patients with reduced renal function. The largest dose of meropenem administered in clinical trials has been 2 g given intravenously every 8 hours to adult patients with normal renal function and 40 mg / kg every 8 hours to children with normal renal function. At these dosages, no adverse pharmacological effects were observed.

Limited post-marketing experience indicates that if adverse events occur following overdosage, they are generally consistent with the adverse event profile described under 8 ADVERSE REACTIONS.

In the event of an overdose, Meropenem for Injection should be discontinued and general supportive treatment given until renal elimination takes place. Meropenem for Injection and its metabolite are readily dialyzable and effectively removed by hemodialysis; however, no information is available on the use of hemodialysis to treat overdosage.

The intravenous LD_{50} of meropenem in mice and rats is more than 2500 mg / kg and is approximately 2000 mg / kg in dogs.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 4: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Intravenous	Powder for solution / 500 mg or 1 g / meropenem	Drug chamber: Sodium carbonate Diluent chamber[1]: Sodium chloride, water for injection

[1] Diluent chamber contains 0.9% sodium chloride solution.

Meropenem for Injection USP and Sodium Chloride Injection USP is packaged in a sterile, nonpyrogenic, single-dose Duplex® Container with meropenem in the drug chamber and 50 mL of 0.9% sodium chloride solution in the diluent chamber.

After reconstitution (activation), each 500 mg Meropenem for Injection in the Duplex® Container will deliver 500 mg of meropenem and a total sodium content of 245.1 mg (10.7 mEq) and each 1 gram Meropenem for Injection in the Duplex® Container will deliver 1 gram of meropenem and a total sodium content of 290.2 mg (12.6 mEq).

The osmolality of the reconstituted solution of Meropenem for Injection USP and Sodium Chloride Injection USP is approximately 356 mOsmol / kg for the 500 mg dose and approximately 417 mOsmol / kg for the 1 gram dose.

The Duplex® Container is a flexible dual chamber container. After removing the peelable foil strip, activating the seals, and thoroughly mixing, the reconstituted drug product is hyperosmotic and is intended for single intravenous use. The product (diluent and drug) contact layer is a mixture of thermoplastic rubber and a polypropylene ethylene copolymer that contains no plasticizers.

The Duplex® Container is not made with natural rubber latex, PVC or Di(2-ethylhexyl)phthalate (DEHP).

Meropenem for Injection USP and Sodium Chloride Injection USP is supplied in 24-unit cases.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

As with other broad-spectrum antibiotics, prolonged use of Meropenem for Injection 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.

Meropenem for Injection should not be used to treat infections caused by methicillin-resistant staphylococci.

When treating infections known or suspected to be caused by *Pseudomonas aeruginosa,* higher doses are recommended based on pharmacokinetic/pharmacodynamic modeling and probability of target attainment simulation for susceptible strains of *Pseudomonas aeruginosa* (MIC ≤ 2 mcg / mL) (see 4 DOSAGE AND ADMINISTRATION and 15 MICROBIOLOGY). Caution may be required in critically ill patients with known or suspected *Pseudomonas aeruginosa* lower respiratory tract infections.

Each 500 mg of Meropenem for Injection and Sodium Chloride Injection delivers 245.1 mg (10.7 mEq) of sodium and each 1 gram of Meropenem for Injection and Sodium Chloride Injection delivers 290.2 mg (12.6 mEq) of sodium. At the usual recommended doses of 500 mg or 1000 mg every 8 hours, patients would receive between 735 mg/day and 870 mg/day (32 mEq and 38 mEq) of sodium.

Avoid use of Meropenem for Injection and Sodium Chloride Injection in patients with congestive heart failure, elderly patients and patients requiring restricted sodium intake.

Driving and Operating Machinery

No studies 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, paresthesia, and convulsions have been reported for Meropenem for Injection.

Gastrointestinal

Clostridium difficile-associated disease

Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents, including Meropenem for Injection. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of *Clostridium difficile. C. difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *Clostridium difficile*. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *Clostridium difficile*. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases (see 8.5 Post-Market Adverse Reactions).

Hepatic/Biliary/Pancreatic

Patients with pre-existing liver disorders should have their liver function monitored during treatment with Meropenem for Injection.

Immune

Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with β-lactam antibiotics, including Meropenem for Injection. These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens (see 8.5 Post-Market Adverse Reactions).

There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe reactions when treated with another β-lactam antibiotic. Before initiating therapy with Meropenem for Injection, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, other β-lactam antibiotics and other allergens. If an allergic reaction to Meropenem for Injection occurs, discontinue the drug immediately. **Anaphylactic reactions require immediate treatment with epinephrine. Oxygen, intravenous steroids, antihistamines and airway management, including intubation, may be required.**

Monitoring and Laboratory Tests

Use of Meropenem for Injection may lead to the development of a positive direct or indirect Coombs test.

Neurologic

Seizures

Meropenem for Injection, like all β-lactam antibiotics, has the potential to cause seizures. Diminished renal function and central nervous system lesions may increase the risk of seizures. When Meropenem for Injection is indicated in patients with these risk factors, caution is advised. Convulsions have been observed in a temporal association with use of Meropenem for Injection.

Valproic Acid Interaction

Case reports in the literature have shown that 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. The concomitant use of meropenem and valproic acid or divalproex sodium is generally not recommended. Antibacterials other than carbapenems should be considered to treat infections in patients whose seizures are well controlled on valproic acid or divalproex sodium. If administration of Meropenem for Injection is necessary, supplemental anti-convulsant therapy should be considered. The concomitant use of valproic acid/sodium valproate and Meropenem for Injection is not recommended (see 9.4 Drug-Drug Interactions).

Renal

Dosage adjustment is recommended for patients with renal insufficiency (see 4.2 Recommended Dose and Dosage Adjustment).

Sensitivity/Resistance

Development of Drug-Resistant Bacteria

Prescribing Meropenem for Injection in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

Skin

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 generalised exanthematous pustulosis (AGEP) have

been reported in patients receiving Meropenem for Injection (see 8 ADVERSE REACTIONS). If signs and symptoms suggestive of these reactions appear, Meropenem for Injection should be withdrawn immediately and an alternative treatment should be considered.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled studies in pregnant women. Meropenem for Injection should be used during pregnancy only if the potential benefit justifies the potential risk to mother and fetus. Reproduction studies have been performed in rats and Cynomolgus monkeys at doses up to 1000 mg / kg / day (approximately 16 times the usual human 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 240 mg / kg / day and above in rats.

7.1.2 Breast-feeding

Meropenem has been reported to be excreted in human milk. Meropenem for Injection should not be given to breast-feeding women unless the potential benefit justifies the potential risk to the baby.

7.1.3 Pediatrics

Pediatrics (≥ 3 months of age):

The safety and effectiveness of Meropenem for Injection in the pediatric population 3 months of age and older have been established. Meropenem for Injection is not recommended for use in infants under the age of 3 months.

The use of Meropenem for Injection in pediatric patients with bacterial meningitis is supported by evidence from adequate and well controlled studies in the pediatric population. Use of Meropenem for Injection in pediatric patients for all other indications, as listed in the INDICATIONS section, is supported by evidence from adequate and well controlled studies in adults with additional data from pediatric pharmacokinetic studies and controlled clinical trials in pediatric patients (see 4.2 Recommended Dose and Dosage Adjustment).

Note: Inadequate data are available to support the pediatric indications for nosocomial pneumonia, septicemia and complicated skin and skin structure infections.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age):

This drug is known to be substantially excreted by the kidney. No dose adjustment is required in elderly patients, except in cases of moderate to severe renal impairment (see 4.2 Recommended Dose and Dosage Adjustment).

Each 500 mg of Meropenem for Injection and Sodium Chloride Injection delivers 245.1 mg (10.7 mEq) of sodium and each 1 gram of Meropenem for Injection and Sodium Chloride Injection delivers 290.2 mg (12.6 mEq) of sodium. At the usual recommended doses of 500 mg or 1000 mg every 8 hours, patients would receive between 735 mg/day and 870 mg/day (32 mEq and 38 mEq) of sodium. The geriatric population may respond with a blunted natriuresis to salt loading. This may be clinically important with regard to such diseases as congestive heart failure.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Meropenem for Injection is generally well tolerated. Many patients receiving Meropenem for Injection are severely ill, have multiple background diseases, physiological impairments and

receive multiple other drug therapies. In such seriously ill patients, it is difficult to establish the relationship between adverse events and Meropenem for Injection.

Serious adverse reactions include occasionally fatal hypersensitivity (anaphylactic) reactions, and severe skin reactions (erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms and acute generalised exanthematous pustulosis) which require immediate discontinuation of the drug and standard of care treatment.

The most commonly reported drug-related adverse events in the clinical trial programme were inflammation at the site of injection, diarrhea, nausea and vomiting, and rash. The most commonly reported laboratory adverse events included increased levels of ALT and AST and increased platelets.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety of meropenem has been evaluated in a clinical trial program of 3187 adults and children, in a range of bacterial infections including pneumonia, complicated urinary tract, intra-abdominal and skin/skin structure infections, gynecological infections and meningitis.

A subsequent safety review on an expanded clinical trial database of 4872 patients treated intravenously or intramuscularly with meropenem (5026 treatment exposures) was generally consistent with earlier findings.

Table 5 presents a summary of clinical trial adverse drug reactions, judged by the investigator to be related to therapy with meropenem (possibly, probably or definitely), that occurred at frequencies greater than 0.2% in the 3187 patients treated intravenously with meropenem, plus those reactions only observed in the expanded clinical trial database at frequencies greater than or equal to 0.1%.

Table 5: Meropenem Clinical Trial Adverse Drug Reactions with Frequency ≥ 0.2% (N = 3187 patients) and Frequency ≥ 0.1% only observed in the expanded clinical database (N= 4872 patients)

System Organ Class	Frequency[1]	Reaction[2]
Blood and lymphatic system disorders	Common	Thrombocythemia[3]
	Uncommon	Eosinophilia, thrombocytopenia, leucopenia, neutropenia
Gastrointestinal disorders	Common	Diarrhea (2.5%), nausea/vomiting (1.2%)
	Uncommon	Abdominal pain
General disorders and administration site conditions	Common	Fever, injection site inflammation (1.6%)
	Uncommon	Injection site phlebitis / thrombophlebitis (0.5%), injection site reaction (0.4%)
Infections and infestations	Uncommon	Oral (0.3%) and vaginal (0.7%) candidiasis, vaginitis (0.3%)
Nervous system disorders	Common	Headache
	Uncommon	Paraesthesia, convulsions
Skin and subcutaneous tissue disorders	Common	Rash (1.1%)
	Uncommon	Urticaria (0.3%), pruritis

[1] CIOMS III frequency classification: very common (≥1/10; ≥10%); common (≥1/100 to <1/10; ≥1% to <10%); uncommon (≥1/1000 to <1/100; ≥0.1% to <1%)

[2] *Medical Dictionary for Regulatory Activities* preferred term level. Incidence is provided where available.

[3] Observed in the expanded clinical trial database at ≥0.1%, n = 4872 patients (5026 meropenem treatment exposures)

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Pediatrics (≥ 3 months of age):

Drug-related increases in platelets (7%) appear to occur more frequently in pediatric patients than in adults treated with meropenem.

8.3 Less Common Clinical Trial Adverse Reactions

Blood and lymphatic system disorders: Agranulocytosis

Gastrointestinal disorders: Constipation

General disorders and administration site conditions: Chills, infection, injection site pain and injection site edema

Metabolism and nutrition disorders: Peripheral edema

Nervous system disorders: Agitation, dizziness, hallucinations, neuropathy, taste perversion

Renal and urinary disorders: Renal impairment

Skin and subcutaneous tissue disorders: Sweating

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

This information is not available for this drug product.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Adverse laboratory changes that were reported in clinical trials by the investigator as possibly, probably or definitely related to meropenem occurring in greater than 0.2% of the patients are summarised in Table 6.

Table 6: Meropenem-Related Adverse Chemical and Hematologic Laboratory Changes with Frequency ≥ 0.2% (N = 3187 patients)

Adverse Laboratory Change[1]	Frequency[2]
Chemistry:	
Alanine aminotransferase increased	Common
Alkaline phosphatase increased	Common
Aspartate aminotransferase increased	Common
Blood bilirubin increased	Uncommon
Blood urea nitrogen increased	Uncommon
Blood creatinine increased	Uncommon
Lactate dehydrogenase increased	Common
Transaminases increased	Common
Hematology:	
Eosinophil count increased	Common
Partial thromboplastin time abnormal	Uncommon
Platelet count decreased	Uncommon
Platelet count increased	Common
Prothrombin time abnormal	Uncommon
White blood cell count decreased	Uncommon

[1] *Medical Dictionary for Regulatory Activities* preferred term level
[2] CIOMS III frequency classification: very common (≥1/10; ≥10%); common (≥1/100 to <1/10; ≥1% to <10%); uncommon (≥1/1000 to <1/100; ≥0.1% to <1%)

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-approval use of meropenem. These reactions were reported voluntarily from a population of uncertain size, so it is not possible to reliably estimate their frequency. A causal relationship could not be excluded in spite of concomitant medications and/or illnesses.

Blood and the lymphatic system disorders
Thrombocytopenia with bleeding, hemolytic anemia

Gastrointestinal disorders
Pseudomembranous colitis

Hepatobiliary disorders
Cholestasis, hepatitis

Investigations
Hypokalemia, hypomagnesemia

Immune system disorders
Severe hypersensitivity reactions of angioedema and anaphylaxis

Psychiatric disorders
Delirium

Skin and subcutaneous tissue disorders
Severe skin reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS Syndrome), acute generalised exanthematous pustulosis, erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Other than probenecid and valproic acid, no specific drug interaction studies were conducted.

9.3 Drug-Behavioural Interactions

Not applicable.

9.4 Drug-Drug Interactions

The drugs listed in this section are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

- **Probenecid**

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 for Injection. The co-administration of probenecid with Meropenem for Injection is neither required nor recommended.

- **Valproic Acid**

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 meropenem in patients stabilized on valproic acid is not considered to be manageable and therefore should be avoided (see 7 WARNINGS AND PRECAUTIONS).

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Use of Meropenem for Injection may lead to the development of a positive direct or indirect Coombs test.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Meropenem is a broad spectrum, β-lactamase-resistant, carbapenem antibiotic for parenteral administration.

The bactericidal activity of meropenem results from the inhibition of bacterial cell wall synthesis. Meropenem readily penetrates through the cell wall of most Gram-positive and Gram-negative bacteria to reach penicillin-binding protein (PBP) targets. Its greatest affinity is for PBP 2 of *Escherichia coli*, PBP 2 and 3 of *Pseudomonas aeruginosa* and 1, 2 and 4 of *Staphylococcus aureus*.

Meropenem is stable in the presence of most serine β-lactamases (both penicillinases and cephalosporinases) produced by Gram-positive and Gram-negative bacteria.

10.2 Pharmacodynamics

The percentage of time of a dosing interval that unbound plasma concentration of meropenem exceeds the meropenem minimum inhibitory concentration (MIC) against the infecting organism has been shown to best correlate with efficacy in animal and *in vitro* models of infection.

10.3 Pharmacokinetics

The pharmacokinetics of meropenem are typical of those parenteral β-lactam antibiotics that have low protein binding and predominantly renal excretion.

Meropenem shows bi-exponential pharmacokinetics after intravenous administration in healthy adult volunteers with normal renal function. There is a rapid distribution phase followed by a terminal elimination phase with a half-life (t½) of approximately 1 hour. The pharmacokinetic parameters following three doses of meropenem are shown in Table 7 (see also Table 9).

Table 7: Pharmacokinetic Parameters of Meropenem in Healthy Volunteers Following a Single Intravenous Infusion Over 30 Minutes

Dose (mg)	Cmax (mcg / mL)	AUC∞ (mcg.h / mL)	t½ (h)	Volume of Distribution Steady State Vss (L)	Plasma Clearance Clp (mL / min)	Renal Clearance Clr (mL / min / kg)	Urinary Recovery (% dose)
500	22.5 (21)	27.1 (15)	0.97 (13)	20.2 (16)	314 (15)	3.05 (20)	73 (12)
1000	48.6 (16)	60.8 (16)	0.96 (14)	18.9 (10)	280 (16)	2.52 (15)	69 (6)
2000	115 (20)	153 (15)	1.18 (8)	15.8 (20)	205 (18)	1.73 (12)	65.4 (18)

mean (coefficient of variation)

Absorption

The area under the serum concentration time curve (AUC) of meropenem increases approximately 5.5-fold over the dose range of 500 mg to 2 g. There are no marked changes in the pharmacokinetic parameters. However, there is a reduction in renal clearance with higher doses probably due to the saturation of tubular clearance. These changes in kinetic parameters are not important in otherwise healthy adults.

There were no important changes in the pharmacokinetics of meropenem when administered as a 5 minute infusion, compared with a 30 minute infusion. Peak plasma concentrations of meropenem were doubled after the bolus infusion, but from 1 hour after dosing, plasma concentrations for both rates of administration were similar.

After multiple dose administration in healthy subjects, there was no accumulation of meropenem and no change in the pharmacokinetics of meropenem as a consequence of repeated administration (Table 8).

Table 8: Pharmacokinetic Parameters of Meropenem in Healthy Volunteers Following Multiple Dose (1000 mg) Intravenous Infusion*

Day	Cmax (mcg / mL)	AUC∞ (mcg.h / mL)	t½ (h)	Plasma Clearance (Clp) (mL / min)	Urinary Recovery (% dose)
1	42.4 (13)	71.6 (15)	0.96 (9)	227 (14)	59.4 (6)
4	34.1 (57)	60.4 (25)	0.48 (23)	293 (29)	62.6 (21)
7	40.5 (14)	61.3 (17)	1.11 (32)	279 (17)	53.2 (19)

mean (coefficient of variation)
*25 infusions over 60 min at intervals of 6 h for 7 days

Distribution:

At the end of a 30 minute intravenous infusion of a single dose of meropenem in healthy, male volunteers, mean peak plasma concentrations are approximately 23 mcg / mL for the 500 mg dose, 49 mcg / mL for the 1 g dose and 115 mcg / mL for the 2 g dose. The plasma concentration-time data for meropenem after a single 30 minute infusion are presented in Table 9.

A 5 minute intravenous bolus injection of meropenem in healthy, male volunteers results in mean peak plasma levels of approximately 52 mcg / mL for the 500 mg dose and 112 mcg / mL for the 1 g dose.

Tissue Concentrations
Meropenem penetrates into body tissues in sufficient concentrations to treat most commonly occurring pathogens at the principal sites of infection.

However, it does not penetrate readily into cerebrospinal fluid or aqueous humor in the absence of inflammation at the sites. In children and adults with bacterial meningitis, meropenem concentrations in the cerebrospinal fluid, after intravenous administration of recommended doses, are in excess of those required to inhibit susceptible bacteria.

Note: See Table 10 for Meropenem Concentrations in Select Tissues and Body fluids. See 15 MICROBIOLOGY for susceptibility breakpoints.

Table 9: Plasma concentration-time values during and following single 30 minute infusion doses of meropenem in volunteers

	500 mg	1000 mg	2000 mg
Time (h)	Mean Conc. ± SD (mcg / mL)	Mean Conc. ± SD (mcg / mL)	Mean Conc. ± SD (mcg / mL)
Pre-dose	ND	ND	ND
0.083	5.43 ± 3	12.9 ± 3.62	-
0.167	-	-	48.4 ± 18.23
0.25	13.9 ± 2.74	28.6 ± 3.74	-
0.5	22.5 ± 4.86	48.6 ± 7.81	115.2 ± 23.5
0.75	15.5 ± 0.97	33.8 ± 1.99	78.8 ± 10.2
1	10.8 ± 1.46	24.6 ± 3.03	58.3 ± 8.93
1.5	6.84 ± 0.91	14.8 ± 2.17	36.9 ± 7.45
2	3.68 ± 0.81	11.1 ± 3.88	25.1 ± 4.62
2.5	2.92 ± 0.8	6.22 ± 1.4	-
3	1.95 ± 0.67	4.49 ± 1.02	12.5 ± 3.25

Table 9: Plasma concentration-time values during and following single 30 minute infusion doses of meropenem in volunteers (continued)			
	500 mg	1000 mg	2000 mg
Time (h)	Mean Conc. ± SD	Mean Conc. ± SD	Mean Conc. ± SD
3.5	1.28 ± 0.58	2.47 ± 1.07	-
4	0.91 ± 0.41	2.35 ± 1.07	-
4.5	0.57 ± 0.31	1.54 ± 0.86	-
5	0.40 ± 0.19	0.99 ± 0.63	3.33 ± 1.2
6	0.27 ± 0.15	0.60 ± 0.36	1.83 ± 0.65
7	0.14 ± 0.09	0.30 ± 0.23	1.03 ± 0.46
8	-	-	0.63 ± 0.32
10	-	-	0.21 ± 0.13

ND: Not detectable, - Not measured

Table 10: Meropenem Concentrations in Selected Tissues or Body Fluids (Highest Concentrations Reported)

Tissue	Dose (g)	Number of Samples	Mean [mcg / mL or mcg / (g)]*	Range [mcg / mL or mcg / (g)]
Endometrium	0.5	7	4.2	1.7 - 10.2
Myometrium	0.5	15	3.8	0.4 - 8.1
Ovary	0.5	8	2.8	0.8 - 4.8
Cervix	0.5	2	7	5.4 - 8.5
Fallopian tube	0.5	9	1.7	0.3 - 3.4
Skin	0.5	22	3.3	0.5 - 12.6
Skin	1	10	5.3	1.3 - 16.7
Colon	1	2	2.6	2.5 - 2.7
Bile	1	7	14.6 (3 h)	4 - 25.7
Gall bladder	1	1	-	3.9
Interstitial fluid	1	5	26.3	20.9 - 37.4
Peritoneal fluid	1	9	30.2	7.4 - 54.6
Lung	1	2	4.8 (2 h)	1.4 - 8.2
Bronchial mucosa	1	7	4.5	1.3 - 11.1
Muscle	1	2	6.1 (2 h)	5.3 - 6.9
Fascia	1	9	8.8	1.5 - 20
Heart valves	1	7	9.7	6.4 - 12.1
Myocardium	1	10	15.5	5.2 - 25.5
CSF (inflamed)	20 mg / kg**	8	1.1 (2 h)	0.2 - 2.8
	40 mg / kg***	5	3.3 (3 h)	0.9 - 6.5
CSF (uninflamed)	1	4	0.2 (2 h)	0.1 - 0.3

* at 1 hour unless otherwise noted mean (coefficient of variation)
** in children of age 5 months to 8 years
*** in children of age 1 month to 15 years

Metabolism and Excretion:

Meropenem is cleared predominantly by renal excretion, with a combination of glomerular filtration and active tubular secretion.

At doses of 500 mg, mean plasma levels of meropenem decline to 1 mcg / mL or less, 6 hours after administration.

In vitro studies demonstrate that meropenem is stable to human renal dehydropeptidase. This finding is supported by the urinary excretion of meropenem which is typically 60% to 70% of the administered dose. Thus, there is no requirement to co-administer an inhibitor of dehydropeptidase-1 with meropenem.

Meropenem plasma protein binding is low, approximately 2%. Therefore the renal filtration rate should approximate the glomerular filtration rate (GFR). However, renal clearance values are generally in excess of the measured or calculated value for GFR: the difference is due to active tubular secretion of meropenem.

The hydrolysis of the β-lactam bond can occur either chemically in solution or biologically under the influence of enzymes. The reduction in the non-renal clearance of meropenem that occurs as renal function declines suggests that the kidney may be a site of metabolism. The trend to reduction in the non-renal clearance of meropenem seen when meropenem was co-administered with probenecid implies that the proximal renal tubule may be involved in the metabolism of meropenem.

The only identified metabolite of meropenem is ICI 213 689 which is produced by hydrolysis of the β-lactam bond and is bacteriologically inactive. In healthy subjects, the apparent elimination half-life of ICI 213 689 was longer than that of meropenem at approximately 2.3 hours (range 1.8 to 2.8 hours). The AUC for ICI 213 689 was approximately 10% of the AUC for meropenem, showing that exposure to the circulating metabolite is small in subjects with normal renal function.

The administration of probenecid with meropenem did not alter the urinary half-life of ICI 213 689. Exposure to ICI 213 689 does not appear to change on repeated meropenem administration and there are no major changes in the excretion of ICI 213 689 after repeated meropenem administration in persons with normal renal function.

In subjects with normal renal function, the elimination half-life of meropenem is approximately one hour. Urinary concentrations of meropenem in excess of 10 mcg / mL are maintained for at least 5 hours at the 500 mg dose. The metabolism and excretion of meropenem were studied by means of administration of [^{14}C]-labelled meropenem. Radioactivity was very rapidly excreted with 95.4% of the dose recovered in the urine at 8 hours after dosing. This rapid excretion is consistent with the observed lack of accumulation on multiple dosing. Overall, 99% of the dose was recovered in the urine, with an additional 2.1% recovered in the feces.

Multiple dosing with meropenem in normal volunteers caused increases, decreases or no change in the fecal flora, depending on the organism. Changes were small and were reversed after cessation of meropenem administration. Meropenem is present in bile at concentrations of up to 25 mcg / mL. This biliary excretion of a small proportion of the dose as active antibiotic could account for both the minor disturbance of fecal flora and the fecal recovery of radioactivity.

Special Populations and Conditions

- **Pediatrics (≥ 3 months of age):** The pharmacokinetics of meropenem in infants and children over age 2 are essentially similar to those in adults, except that the half-life is approximately double to 1.75 hours in the youngest age group (3 to 5 months). The elimination half-life for meropenem was approximately 1.5 hours in children of age 3 months to 2 years. The pharmacokinetics for children are linear for doses of 10, 20 and 40 mg / kg and the peak plasma concentrations and AUC values are similar to those seen in healthy adult volunteers after 500 mg, 1 g and 2 g doses, respectively.

  The prolongation of half-life and increased volume of distribution of meropenem in the younger subjects is consistent with the reduced renal function and increased extra cellular fluid volume in infants of this age. An 8-hour dosing interval is considered acceptable even in the 3 to 5 month age group (Table 11).

  In general, meropenem dosing on a mg / kg basis is appropriate in infants and children.

Table 11: Pharmacokinetic Parameters of Meropenem in Children

Age	Dose (mg / kg)	Cmax (mcg / mL)	AUC∞ (mcg•h / mL)	t½ (h)	Volume of Distribution (V_{ss})* (L / kg)	Plasma Clearance (Cl_p)* (mL / min / kg)	Urinary Recovery (% dose)
3-5 Months	10	26.3 (18)	38.8 (30)	1.4 (31)	0.401 (10)	4.6 (35)	64.9 (15)
	20	53.4 (33)	90 (29)	1.7 (30)	0.449 (12)	4 (30)	37.5 no CV %
	40	125 (48)	228 (80)	2.3 (59)	0.48 (24)	4.3 (8)	21.6 no CV %
6-23 Months	10	28.8 (33)	34.9 (56)	1.1 (49)	0.358 (33)	5.7 (37)	62.8 (31)
	20	64 (25)	75 (24)	1.3 (37)	0.356 (29)	4.3 (34)	47.4 (29)
	40	84.9 (21)	122 (27)	1.5 (35)	0.524 (18)	5.8 (26)	39.6 (62)
2-5 Years	10	29.2 (28)	33.1 (24)	1.1 (35)	0.353 (23)	5.3 (29)	54.5 (24)
	20	51.6 (18)	60.6 (22)	1 (4)	0.375 (16)	5.8 (24)	55.3 (16)
	40	79 (18)	91.9 (27)	1.1 (47)	0.501 (31)	7.7 (28)	52.6 (32)
6-12 Years	10	32.1 (40)	35.3 (50)	0.9 (30)	0.314 (23)	5.7 (39)	67.2 (7)
	20	58.6 (29)	64.4 (38)	0.8 (43)	0.315 (22)	6.3 (42)	60.4 (10)
	40	79.7 (7)	93 (19)	1 (24)	0.414 (16)	6.4 (8)	50.3 (12)

mean (coefficient of variation)

* V_{ss}, Cl_p normalized for body weight

- **Geriatrics (≥ 65 years of age):** In the elderly, there are changes in the pharmacokinetics of meropenem and ICI 213 689 that reflect the age-associated reduction in renal function (Table 12). Dosage reduction, dependent upon renal function, may be necessary.

Table 12: Comparison of Pharmacokinetic Parameters between Healthy Elderly and Healthy Younger Patients (500 mg infused over 30 min)

Patients (age, years)	Creatinine Clearance (mL / min)	GFR* (mL / min)	Cmax (mcg / mL)	AUC∞ (mcg.h / mL)	t½ (h)	Volume of Distribution at Steady State (L)	Urinary Recovery (% dose)	Renal Clearance Clr (mL / min / kg)
Young (10)	120 (7)	99 (15)	35.6 (17)	39.5 (12)	0.81 (20)	13.8	68.2 (12)	2.18 (20 - 35) (20)
Elderly (65 - 80)	68 (17)	72 (17)	37 (17)	58.3 (17)	1.29 (14)	14.5 (17)	67.3 (7)	1.51 (11)

mean (coefficient of variation)

* glomerular filtration rate

- **Hepatic Insufficiency:** A study in patients with alcoholic cirrhosis has shown no effects of liver disease on the pharmacokinetics of meropenem.
- **Renal Insufficiency:** Meropenem is excreted predominantly by the kidney and changes in renal function alter meropenem pharmacokinetics.

  Pharmacokinetic studies of 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 (see 4.2 Recommended Dose and Dosage Adjustment). A pharmacokinetic study with meropenem in elderly patients with renal insufficiency has shown that a reduction in plasma clearance of meropenem correlates with age-associated reduction in creatinine clearance.

  The reduction in meropenem clearance correlates well with creatinine clearance and is consistent across studies. Even in renally impaired subjects, there is no alteration in the pharmacokinetics of meropenem due to multiple dosing, when it is dosed appropriately. The metabolite accumulates with repeated doses: the clinical importance of this observation is unknown. The physiological reduction in renal function due to age and renal impairment due to disease produce a similar effect on the clearance of meropenem (Table 13).

Table 13: Pharmacokinetic Parameters for Meropenem in Patients with Renal Insufficiency

Creatinine Clearance (mL / min)	Dose (g)	Dosing Interval (h)	Cmax (mcg / mL)	AUC∞ (mcg.h / mL)	t½ (h)	Renal Clearance Clr (mL / min / kg)	Urinary Recovery (% dose)
Day 1							
51-70	1	8	60.9 (25)	115 (21)	1.59 (26)	1.05 (29)	58.1 (18)
26 - 50	1	12	75.9 (22)	207 (27)	2.12 (29)	0.53 (62)	55.1 (36)
10 - 25	0.5	12	32 (34)	143 (17)	4.61 (33)	0.2 (33)	32.1 (52)
0	0.5	24	41 (28)	320 (30)	6.56 (16)		
Day 4							
51 - 70	1	8	60 (31)	115 (23)	1.45 (23)	0.69 (81)	nd
26 - 50	1	12	90.6 (32)	229 (31)	2.33 (27)	0.37 (36)	nd
10 - 25	0.5	12	40.6 (25)	188 (34)	4.87 (38)	0.19 (41)	nd
0	0.5	24	50.7 (38)	306 (26)	7.04 (54)		

mean (coefficient of variation); nd = not determined

10.4 Detailed Pharmacology

Meropenem failed to cause any changes of biological significance in the following series of general pharmacology tests.

Autonomic Pharmacology *In Vitro*

In vitro data suggest that meropenem does not possess potent histaminergic, acetylcholinergic, alpha-adrenergic or beta-adrenergic activity when tested at 1×10^{-3} M. A weak increase in resting tone was observed in the rat fundic strip indicating a possibility of 5-hydroxytrypt- aminergic activity.

Sympathetic Function *In Vivo*
Single intravenous administrations of meropenem (300 mg / kg) to anaesthetized cats produced weak effects of short duration on the nictitating membrane. This suggested weak sympatholytic activity which would account for the transient fall in blood pressure observed.

Gastrointestinal Pharmacology
No effect upon gastrointestinal motility was seen in mice following a single intravenous administration of meropenem (300 mg / kg).

Intravenous administration (one dose of 100 mg / kg) to male beagle dogs (with Heidenhain pouches) had no effect on stimulated gastric acid secretion and is therefore unlikely to cause acid hypersecretion.

Cardiovascular Function
In conscious male beagle dogs, a single intravenous dose of meropenem (300 mg / kg) did not produce significant changes in blood pressure, heart rate, ECG (P-R interval), cardiac output, central venous pressure or total peripheral resistance. Cardiac force decreased slightly but this was thought not to have any biological significance. No behavioural side effects were noted in this study.

Intravenous dosing at 300 mg / kg on two consecutive days to spontaneously hypertensive rats did not produce significant changes in blood pressure or heart rate on day 1. On day 2, a fall in mean arterial blood pressure, which was of borderline significance, was seen 2 hours after dosing. The effect was not seen at further time points and was thought to be biologically insignificant.

Renal Pharmacology
In fasted male rats, orally loaded with physiological saline, a single intravenous dose of meropenem (300 mg / kg) did not cause diuretic or natriuretic activity or biologically significant changes in urinary chloride or potassium levels. Hence, there was no evidence of effect upon the renal function of the rat.

However, chronic administration of meropenem was associated with increased kidney size.

Central Nervous System Pharmacology
Meropenem (given as a single intravenous dose of 300 mg / kg) did not elicit biologically significant changes in central nervous system function in rats or mice. The drug did not modify neuromuscular co-ordination or affect gross behaviour or body temperature. In mice there was no significant change in sodium barbital-induced sleeping time or in the current required to elicit tonic extensor seizures.

Spontaneous EEG and arousal response in rabbits was unaltered following an intravenous dose of meropenem (1000 mg / kg). Imipenem (300 mg / kg) evoked a response in 4/7 rabbits and cefazolin, dosed at 300 or 1000 mg / kg, evoked responses in 1/7 and 6/7 rabbits, respectively.

Intravenous administration of a single dose of meropenem (50 to 400 mg / kg) to mice failed to elicit any biologically significant potentiation of metrazole-induced convulsions. Conversely, imipenem alone (200 mg / kg) or in combination with cilastatin (400 mg / kg + 400 mg / kg), did produce a significant potentiation of seizures ($p < 0.05$).

Metabolic Homeostasis
A single intravenous administration of meropenem (100 or 300 mg / kg) to rabbits did not cause biologically significant changes in glucose metabolism or lipid metabolism where triglycerides, phospholipids or cholesterol were involved. A decrease in free fatty acid metabolism was recorded in animals given 300 mg / kg; the change was not statistically significant.

Hemostasis
In male rats, dosed intravenously (once) with meropenem (300 mg / kg), there was no significant effect on platelet aggregation.

Meropenem (3×10^{-3} M) did not have any influence on rabbit platelet aggregation in the presence of added adenosine diphosphate (ADP) or collagen.

There was no change in prothrombin time in beagle dogs dosed daily with meropenem (21 and 70 mg / kg, intravenously for 14 days). Changes were observed in values for partial thromboplastin-time-with-kaolin on days 5 and 14 in animals dosed at 70 mg / kg. These changes were small and similar to variations seen pre-dosing.

A single intravenous administration of meropenem (up to 300 mg / kg) to rabbits had no influence on recalcification time, prothrombin time, activated partial thromboplastin time or thrombin time.

Meropenem (3×10^{-3} M or 3×10^{-4} M) did not cause haemolysis of rat blood.

Respiratory Function
Single doses of meropenem (up to 300 mg / kg, intravenously), had no significant effect on airway resistance, dynamic compliance or histamine induced bronchoconstriction in guinea pigs.

Immune Function
Meropenem (300 mg / kg, given intravenously on each of eight days) showed no immunosuppressive properties in mice sensitized with oxazalone.

11 STORAGE, STABILITY AND DISPOSAL

Store the unactivated unit at 20°C to 25°C (68°F to 77°F). [See USP Controlled Room Temperature.] Protect from freezing.

For storage conditions after reconstitution, please reference 4.3 Reconstitution.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Meropenem

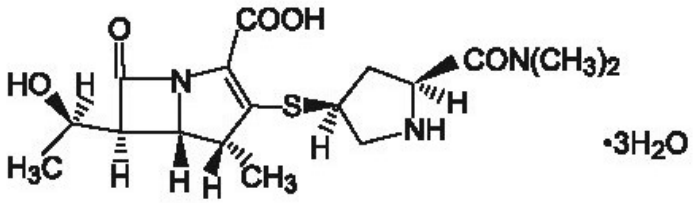
Chemical name: (-)-(4R,5S,6S)-3-[[(3S,5S)-5-(dimethylcarbamoyl)-3-pyrrolidinyl]thio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3,2,0]hept-2-ene-2-carboxylic acid

Molecular formula and molecular mass: $C_{17}H_{25}N_3O_5S \bullet 3H_2O$

437.52 g/mol (trihydrate)

383.46 g/mol (anhydrate)

Structural formula:



Physicochemical properties: Meropenem Trihydrate is a white to light yellow, crystalline powder which is soluble in 5% sodium bicarbonate solution, sparingly soluble in water, very slightly soluble in absolute ethanol and practically insoluble in ether.

The pH of a 1% w/v solution in water ranges from 4 to 6. The pKa values are 2.9 and 7.4. The melting point is difficult to determine because decomposition and colour changes occur before melting. The n-octanol: water partition coefficient is small ($< 1 \times 10^{-3}$).

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

The clinical trial studies supporting the use of Meropenem for the approved indications are not provided in the product monograph.

14.2 Study Results

See 14.1.

14.3 Comparative Bioavailability Studies

Not applicable.

15 MICROBIOLOGY

The *in vitro* susceptibility to meropenem of a given isolate should be determined by standard methods. Interpretations of *in vitro* test results should be made in accordance with local infectious diseases and clinical microbiology guidelines. Meropenem has been shown to be active against the following microorganisms (List 1) in clinical infections as described in the 1 INDICATIONS. *In vitro* data from clinical isolates collected over the period 2005 to 2011 indicate that the following species remain susceptible to meropenem.

List 1

Aerobic and facultative Gram-positive microorganisms

Staphylococcus aureus (methicillin- susceptible strains only)
Staphylococcus epidermidis (methicillin- susceptible strains only)
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes
Viridans group streptococci

Aerobic and facultative Gram-negative microorganisms

Citrobacter freundii
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae (including β-lactamase-producing strains)
Klebsiella oxytoca
Klebsiella pneumoniae
Morganella morganii
Neisseria meningitidis
Proteus mirabilis
Pseudomonas aeruginosa
Serratia marcescens

Gram-positive anaerobes

Clostridium perfringens
Peptostreptococcus species

Gram-negative anaerobes

Bacteroides fragilis
Bacteroides ovatus
Bacteroides thetaiotaomicron
Bacteroides vulgatus
Prevotella bivia

The published medical microbiology literature describes *in vitro* meropenem-susceptibilities of many other bacterial species. However, the clinical significance of *in vitro* findings should be obtained from local infectious diseases and clinical microbiology experts and local professional guidelines. The clinical safety and efficacy of meropenem have not been established for treatment of infections caused by the organisms presented in List 2.

List 2

Aerobic and facultative Gram-positive microorganisms

Streptococcus anginosus

Aerobic and facultative Gram-negative microorganisms

Enterobacter aerogenes

MICs and MBCs are little affected by changes in inoculum concentration from 10^4 to 10^8 cfu / mL or when conducted in broth adjusted in pH over the range of 5 - 7 or in test medium supplemented with 50% human serum. At pH 8, only *P. aeruginosa* showed increased MICs and MBCs.

Meropenem post-antibiotic effects ≥ 0.5 h were obtained with 87% of all strains tested including Enterobacteriaceae strains, Gram-positive aerobes, *B. fragilis* and *in vivo* in neutropenic mice infected with *P. aeruginosa*.

In vitro tests show meropenem to act synergistically with aminoglycoside antibiotics against some isolates of *Pseudomonas aeruginosa* and some of the Enterobacteriaceae. Meropenem and vancomycin act synergistically against some enterococci and coagulase-positive and coagulase-negative staphylococcal strains, including those resistant to methicillin. These *in vitro* tests show meropenem does not act antagonistically with aminoglycosides or vancomycin against Gram-negative and Gram-positive aerobes, respectively.

Assessment of Resistance
Meropenem is active against many bacteria which are resistant to other antibiotics. Meropenem was active against bacteria with known mechanisms of resistance, e.g. *S. aureus, S. epidermidis, N. gonorrhoeae* or *M. catarrhalis* which produce β-lactamase; *H. influenzae* which are resistant to ampicillin or produce β-lactamases and *S. pneumoniae* which are resistant to penicillin. Meropenem has excellent activity against strains of *Staphylococci, Enterobacteriaceae* and *P. aeruginosa* expressing plasmid or chromosomally-encoded β-lactamases. It is unaffected when tested against strains of Enterobacteriaceae harbouring transferable (plasmid-mediated) β-lactamases which hydrolyze ceftazidime, cefotaxime and other third generation cephalosporins.

Serial passage in meropenem did not select resistant *S. aureus*. While 10 serial passages in meropenem elevated the MIC of one strain each of *K. pneumoniae*, *E. cloacae* or *S. marcescens*, 2 further studies failed, using point mutation, to select Enterobacteriaceae with elevated MICs.

Bacterial resistance to meropenem may result from one or more factors: (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 β-lactamases that can hydrolyse carbapenems.

Susceptibility Test Methods
When available, the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques
Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of meropenem powder. The MIC values should be interpreted according to the criteria in Table 15.

Diffusion Techniques
Quantitative methods that require measurement of zone diameters provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 10 mcg of meropenem to test the susceptibility of microorganisms to meropenem. Results should be interpreted according to the criteria in Table 14.

Anaerobic Techniques
For anaerobic bacteria, the susceptibility to meropenem as MICs should be determined by standardized test methods. The MIC values obtained should be interpreted according to the criteria in Table 14.

Table 14: Interpretive Criteria for Meropenem

Pathogen	Minimum Inhibitory Concentrations (mcg / mL)			Disk Diffusion (zone diameters in mm)		
	S	I	R	S	I	R
Enterobacteriaceae+	≤ 1	2	≥ 4	≥ 23	20 - 22	≤ 19
Pseudomonas aeruginosa+	≤ 2	4	≥ 8	≥ 19	16 - 18	≤ 15
*Haemophilus influenzae**	≤ 0.5	--	--	≥ 20	--	--
*Streptococcus pneumoniae**‡	≤ 0.25	0.5	≥ 1	--	--	--
*Streptococcus agalactiae**‡ and *Streptococcus pyogenes**‡	≤ 0.5	--	--	--	--	--
Anaerobes §	≤ 4	8	≥ 16	--	--	--

S = Susceptible, I = Intermediate, R = Resistant
+Interpretive criteria for Enterobacteriaceae and *P. aeruginosa* are based on a dosage regimen of 1g every 8h
* If isolates yield MIC results that are undefined in the above table, they should be submitted to a reference laboratory for further testing
‡ No Disk diffusion (zone diameter) interpretative criteria have been established for testing *Streptococcus pneumoniae*, *Streptococcus agalactiae*, and *Streptococcus pyogenes*. Use results from dilution techniques (MICs)
§ MIC values using either Brucella blood or Wilkins Chalgren agar (former reference medium) are considered equivalent, based upon published in vitro literature and a multicenter collaborative trial for these antimicrobial agent
Source: CLSI 2013

Susceptibility of staphylococci to meropenem may be deduced from testing penicillin and either cefoxitin or oxacillin.

Susceptibility – Quality Control
Standardized susceptibility test procedures require the use of quality control micro-organisms to control the technical aspects of the test procedures. Standard meropenem powder should provide the following range of values noted in Table 15.

Table 15: Acceptable Quality Control Ranges for Susceptibility Testing (CLSI 2013)

Species	Disk diffusion (10 mcg)	MIC (mcg / mL)
S. aureus ATCC 25923	29 - 37	-
S. aureus ATCC 29213	-	0.03 - 0.12
E. coli ATCC 25922	28 - 34	0.008 - 0.06
P. aeruginosa ATCC 27853	27 - 33	0.25 - 1
H. influenzae ATCC 49247	20 - 28	-
H. influenzae ATCC 49766	-	0.03 - 0.12
S. pneumoniae ATCC 49619	28 - 35	0.06 - 0.25
Bacteroides fragilis ATCC 25285	-	0.03 - 0.25 [a,#]
Bacteroides thetaiotaomicron ATCC 29741	-	0.125 - 0.5[#]

agar dilution MIC
[a] broth dilution MIC

References:

1. CLSI. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically: Approved Standard—Ninth Edition. CLSI document M07-A9, Wayne, PA: Clinical and Laboratory Standards Institute; 2012.
2. CLSI. Performance Standards for Antimicrobial Susceptibility Testing: Twenty-Third Informational Supplement. CLSI document M100-S23, Wayne, PA: Clinical and Laboratory Standards Institute; 2013.
3. Walkty A, Baxter M, Adam H, Karlowsky JA, Legace-Wiens P, Hoban DJ and Zhanel GG. Antimicrobial susceptibility of Pseudomonas aeruginosa isolates obtained from patients in Canadian hospitals: CANWARD 2008-2011.
4. Zhanel GG, Adam HJ, Low DE, et al. Antimicrobial susceptibility of 22 746 pathogens from Canadian Hospitals: results of the CANWARD 2007-11 study. J Antimicrob Chemother 2013; 68 Suppl 1: i7-i22.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Table 16: Acute Toxicity

Species	Sex	LD_{50} (mg / kg Intravenous)	95% Confidence Interval
Mouse	M	2650	2190 – 3210
Mouse	F	2950	2460 – 3540
Rat	M	2850	2550 – 3190
Rat	F	3200	2670 – 3840
Rabbit	F	>400	--
Dog	M/F	approx. 2000	--

Short-term Toxicity

Groups of six male and six female Alpk:APfSD (Wistar derived) rats were administered meropenem in a dose of 250 mg / kg / day intravenously for 28 days and no important effects were observed on body weight gain, food consumption, hematology, blood chemistry and compound-related pathology. Groups of 12 male and female Alpk:APfSD rats were administered meropenem at doses of 120, 240 and 1000 mg / kg / day intravenously for three months. At 1000 mg / kg / day, reduced body weight, minimal reversible degenerative changes in the kidney and an increase in relative adrenal weight were observed. Groups of 3 male and 3 female Beagle dogs were administered meropenem at doses of 120, 240 and 500 mg / kg / day intravenously for three months. Slight reduction in red cell indices, associated with a small increase in red cell osmotic fragility in the absence of effects on deformability occurred at 500 mg / kg / day. This was not associated with morphological changes. Increases in plasma alkaline phosphatase, triglycerides and relative kidney weight occurred at 240 and 500 mg / kg / day.

Long-term Toxicity

Groups of 24 male and 24 female Alpk:APfSD rats were administered meropenem at doses of 60, 240 and 1000 mg / kg / day for 6 months. Decreases in ovary weight and increases in adrenal, caecum and spleen weight and ALT occurred at all doses. Clinical observations and decreases in AST occurred at 1000 mg / kg / day. These changes were associated with either changes in the immune activity or microbial status of the animals due to the antibiotic activity of meropenem and the tissue damage and inflammation resulting from the repeated intravenous route of administration over the six month period. Groups of either three or four Beagle dogs were administered meropenem at a dose of 1, 20, 60, 240 or 500 mg / kg / day for 6 months. Increases in liver weight and serum alkaline phosphatase occurred at doses over 20 mg / kg / day; however, no pathological changes or functional abnormalities were observed.

Genotoxicity : No evidence of mutagenic potential was found in any of the five tests conducted: reverse mutation and induced mutation frequency tests in *S. typhimurium* and *E. coli*, gene mutation in cultured mammalian cells, *in vitro* cytogenetics and the micronucleus test in mice. All *in vitro* studies were conducted with and without a metabolic activation system (S-9). All doses were the highest possible based on preliminary studies except for the micronucleus test which was conducted up to a dose which was lethal in acute toxicity studies (up to 2500 mg / kg intravenously).

Reproductive and Developmental Toxicity:

Fertility Studies

Four groups of 22 male and 22 female Alpk:APfSD rats were administered meropenem at doses of 0, 240, 500 or 1000 mg / kg / day intravenously. Males were exposed for 11 weeks prior to and throughout the pairing period. Females were exposed for two weeks prior to pairing through to day eight of pregnancy. There was no effect on mating, pregnancy or fetal viability.

Pregnant animals, dosed on two consecutive days at 300 mg / kg, showed normal weight gain with no evidence of abnormal vaginal cytology or bleeding. The fertility of the rats was unaffected. One dead foetus was found in a total of 55 suggesting that the drug had no abortifacient effect. Four days of dosing to males failed to produce significant changes in seminal vesicle weights at necropsy on day five.

Teratology Studies

Four groups of 36 mated female Alpk:APfSD rats were dosed on days 6 - 17 of pregnancy with 0, 240, 500 or 750 mg / kg / day of meropenem, intravenously. Twenty-four were killed on day 20 of pregnancy and the remaining littered and reared their young to day 21 postpartum. There was no evidence of embryotoxicity or teratogenicity and no effects on the functional ability of F1 generation animals.

The teratogenic potential of meropenem in the rabbit could not be studied because of severe diarrhea therefore the cynomolgus monkey was used as an alternative species. Four groups of 12-16 female monkeys received meropenem at doses of 0, 120, 240 or 360 mg / kg / day, intravenously, from day 20 to 50 post coitum. One skeletal malformation in one foetus at 360 mg / kg, involving proximal fusion of the first and second rib on the left side, was considered to be incidental. There was no evidence of maternal toxicity, embryo toxicity or teratogenicity. Meropenem was shown to cross the placenta.

Perinatal and Postnatal Studies

Four groups of 22 mated, female rats were dosed from days 17 of pregnancy through to day 21 of lactation with 0, 240, 500 and 1000 mg / kg / day of meropenem, intravenously. All females were allowed to litter and rear their young until day 21 postpartum.

Twenty-two male and female offspring per group were selected on day 35 postpartum and retained for F1 cross. All F1 female uterine contents were examined on day 20 of pregnancy. There was a reduction in food consumption during pregnancy in the F0 females from all dose groups and an increase in body weight gain during lactation in the F0 females given 500 and 1000 mg / kg / day only. There was a reduction in body weights during maturation in the F1 females that were offspring of the group given 1000 mg / kg / day. There were no effects on successful pregnancy, parturition or lactation of the F0 dams or the survival behaviour or reproductive performance of the F1 generation.

Special Toxicology:

Immunogenic and Allergic Potential

Immunogenic and allergenic potential is a characteristic of β-lactam antibiotics. Tests of immunogenic potential have demonstrated that meropenem does not induce IgE anaphylaxis inducing antibodies although IgG antibody production was forced by concomitant administration

of Freund's complete adjuvant. There is consistency in the production of IgG antibodies under these conditions in studies in rabbits and guinea pigs. A lack of response in the passive cutaneous anaphylaxis test in guinea pigs may be due to the different induction regime employed. The induction of IgG by meropenem and cross-reactivity (in studies with synthetic protein conjugates), is similar to that found with other antibiotics. Meropenem has a weak allergenic potential and showed no contact sensitization.

As decomposition products of some antibiotics have an immunogenic potential, "aged" formulations of meropenem reconstituted in water (24h in solution at 25ºC) were examined. As with fresh meropenem, IgG antibody production was demonstrated in the PHA (Phytohemagglutinin) test and there were no reactions in the active systemic anaphylaxis or passive cutaneous tests.

Nephrotoxic Potential

No tubular necrosis was caused by meropenem in acute rabbit studies or in six month studies with rats and dogs or after co-administration with furosemide/glycerol to rats. There was mild/moderate fat accumulation and mild tubular necrosis in the Cynomolgus monkey at 500 mg / kg but there was no histological change at 180 mg / kg of meropenem.

17 SUPPORTING PRODUCT MONOGRAPHS

1. Meropenem for Injection (500 mg and 1g vials), Control No. 228648, Product Monograph, Fresenius Kabi Canada Ltd. (June 25, 2019).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

MEROPENEM FOR INJECTION USP AND SODIUM CHLORIDE INJECTION USP

Meropenem for Injection

Read this carefully before you start taking **MEROPENEM FOR INJECTION USP AND SODIUM CHLORIDE INJECTION USP** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **MEROPENEM FOR INJECTION USP AND SODIUM CHLORIDE INJECTION USP.**

Serious Warnings and Precautions

- Serious and sometimes fatal allergic reactions have occurred in patients taking Meropenem for Injection. These reactions are more likely to occur in patients who have ever had an allergic reaction to other antibiotics including penicillin, carbapenems or other cephalosporins. See **What are possible side effects from using Meropenem for Injection USP and Sodium Chloride Injection USP?**
- Seizures and other neurologic reactions have been reported in patients taking Meropenem for Injection. These reactions are more likely to occur in patients with kidney problems or brain lesions.
- Meropenem for Injection can decrease the effectiveness of valproic acid or divalproex sodium. This can increase the risk of seizures.

What is MEROPENEM FOR INJECTION USP AND SODIUM CHLORIDE INJECTION USP used for?

Meropenem for Injection USP is used to treat bacterial infections of the:

- Lungs
- Bladder
- Kidneys
- Abdomen
- Skin
- Brain (meningitis)
- Female reproductive organs. This includes infections that occur during childbirth
- Blood

Antibacterial drugs like Meropenem for Injection treat only bacterial infections. They do not treat viral infections. Although you may feel better early in treatment, Meropenem for Injection should be used exactly as directed. Misuse or overuse of Meropenem for Injection could lead to the growth of bacteria that will not be killed by Meropenem for Injection (resistance). This means that Meropenem for Injection may not work for you in the future.

How does MEROPENEM FOR INJECTION USP AND SODIUM CHLORIDE INJECTION USP work?

Meropenem for Injection prevents the formation of the bacterial cell wall. This causes the bacteria to die and there is a reduction in the infection.

What are the ingredients in MEROPENEM FOR INJECTION USP AND SODIUM CHLORIDE INJECTION USP?

Medicinal ingredients: Meropenem

Non-medicinal ingredients: Sodium Carbonate, Sodium Chloride, Water for Injection

MEROPENEM FOR INJECTION USP AND SODIUM CHLORIDE INJECTION USP comes in the following dosage forms:

Powder for solution: 500 mg and 1 g

Solution (Diluent): approximately 50 mL of 0.9% Sodium Chloride Injection USP

Do not use MEROPENEM FOR INJECTION USP AND SODIUM CHLORIDE INJECTION USP if:

- you are allergic to Meropenem or any of the other ingredients of Meropenem for Injection.
- you are allergic to a class of antibiotics called β-lactam antibiotics. This can include penicillins, carbapenems or other cephalosporins.
- Taking sodium chloride can result in experiencing harmful side effects.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take MEROPENEM FOR INJECTION USP AND SODIUM CHLORIDE INJECTION USP. Talk about any health conditions or problems you may have, including if you:

- have ever had an allergic reaction to any other antibiotic including penicillins, carbapenems or other cephalosporins;
- are taking carbapenems or valproic acid;
- have any problems with your kidneys or liver;
- have suffered diarrhea as a result of taking other antibiotics;
- have history of seizures;
- have congestive heart failure;
- require restricted sodium intake;
- are pregnant or trying to become pregnant;
- are breast-feeding or planning to breastfeed.

Other warnings you should know about:

- **While being treated with Meropenem for Injection:**
  - Tell your healthcare professional right away if you develop a severe skin rash or blisters
  - Your injection must not be mixed with or added to solutions with other drugs.
  - Meropenem for Injection is not recommended for children under 3 months of age.
  - Meropenem for Injection should only be given to the patient it has been prescribed to.
  - You should only stop receiving Meropenem for Injection when your healthcare professional tells you.

Driving and using machines

- Meropenem for Injection has caused side effects such as headache and involuntary muscle movements, shaking or seizures that can result in loss of consciousness. Do not drive or operate machinery if you have these symptoms.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with MEROPENEM FOR INJECTION USP AND SODIUM CHLORIDE INJECTION USP:

- probenecid (for gout)
- sodium valproate (for seizures)

How to take MEROPENEM FOR INJECTION USP AND SODIUM CHLORIDE INJECTION USP:

Meropenem for Injection will be given to you by your healthcare professional. Meropenem for Injection should only be given to the patient it has been prescribed to.

Usual dose:

The usual dose is 500 mg to 1 g by intravenous injection every 8 hours. Your injection must not be mixed with or added to solutions with other drugs.

Intravenous injection: your healthcare professional will give the injection to you in your vein.

This product should not be used for doses other than 500 mg or 1 g.

The exact dose you are given will be decided by your healthcare professional. It will vary depending on the type of infection that you have, where the infection is in the body and the severity of the infection.

Adults
The dose for adults is usually 500 mg to 1 g given every 8 hours. For meningitis (infection of the brain), the dose is 2 grams given every 8 hours.

Children
The dose for children over 3 months old and up to 12 years of age is decided using the weight of the child. The usual dose range is 10 to 40 mg of Meropenem for Injection for each kilogram of body weight given every 8 hours. Meropenem for Injection is not recommended for children under 3 months of age.

The dose of Meropenem for Injection may need to be reduced if your kidneys are not working properly.

Your injections should normally be given at the same times each day. You should only stop receiving Meropenem for Injection when your healthcare professional tells you.

Overdose:

Contact a healthcare professional right away if you are accidentally given more Meropenem for Injection than your dose.

If you think you, or a person you are caring for, have taken too much MEROPENEM FOR INJECTION USP AND SODIUM CHLORIDE INJECTION USP, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you think an injection was missed during your treatment, talk to your healthcare professional.

What are possible side effects from using MEROPENEM FOR INJECTION USP AND SODIUM CHLORIDE INJECTION USP?

These are not all the possible side effects you may have when taking Meropenem for Injection USP and Sodium Chloride Injection USP. If you experience any side effects not listed here, tell your healthcare professional.

Common side effects include: inflammation at site of injection, nausea, vomiting, diarrhea, skin rash, headache, fever and tingling.

Other side effects include: itchiness, abdominal pain, sore veins where Meropenem for Injection is injected, fungal infections of the mouth or the vagina, unexpected breathlessness and/or red/brown urine, fatigue, loss of energy, weakness, shortness of breath, aches, flu-like symptoms, infections, bleeding, bruising, sore mouth and gums, mouth ulcer, constipation, chills, swelling in lower legs or hands, agitation, dizziness, hallucinations, damage to nerves causing weakness pain or tingling, pain to affected areas, change in taste, sweating, yellowing of skin (jaundice), darkening or other changes in urine, irregular heartbeat.

Convulsions have been reported occasionally.

Do not be alarmed by this list of possible events. You may not have any of them.

If you notice any side effects whilst using Meropenem for Injection please inform your healthcare professional.

Tell your healthcare professional immediately if you develop a severe skin rash or blisters.

If you experience symptoms such as severe diarrhea (bloody or watery) with or without fever, abdominal pain, or tenderness, you may have *Clostridium difficile* colitis (bowel inflammation). If this occurs, stop taking Meropenem for Injection and contact your healthcare professional immediately.

Meropenem for Injection can cause abnormal blood test results. Your doctor may do blood tests before you start Meropenem for Injection and while you take it. Your doctor will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help***
	Only if severe	**In all cases**	
COMMON			
N/A			
UNCOMMON			
Hypersensitivity (Allergic reactions): severe rash with or without high fever, with itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body, shortness of breath, wheezing or trouble breathing			√
Seizures		√	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help*
	Only if severe	In all cases	
***Clostridium difficile*-associated disease (CDAD)** (inflammation of the colon): severe diarrhea (bloody or watery), abdominal pain, fever		√	
RARE			
Delirium (Change in mental abilities): confusion, disorientation		√	
NOT KNOWN			
Severe Cutaneous Adverse Reaction (SCAR): severe skin reaction that may also affect other organs: fever, sudden onset of severe rash or blistering or peeling skin, enlarged lymph nodes.			√

***If you think you have these side effects, it is important that you seek medical advice from your healthcare professional immediately.**

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

The healthcare professional will store and dispose of the medication. The unactivated unit should be stored at room temperature (20°C to 25°C). Do not freeze.

Keep out of reach and sight of children.

If you want more information about MEROPENEM FOR INJECTION USP AND SODIUM CHLORIDE INJECTION USP:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html, or by calling 1-800-227-2862.

This leaflet was prepared by B. Braun Medical Inc.

Date of Preparation: January 3, 2024