MEROCRIT I.V. Injection (Meropenem)

**Composition**

**MEROCRIT I.V. Baby**
Each vial contains:
Meropenem trihydrate IP equivalent to
anhydrous meropenem .................................................... 125 mg
Also contains sodium carbonate (sodium 11.275 mg)

**MEROCRIT I.V. 250 mg**
Each vial contains:
Meropenem trihydrate IP equivalent to
anhydrous meropenem .................................................... 250 mg
Also contains sodium carbonate (sodium 22.55 mg)

**MEROCRIT I.V. 0.5 g**
Each vial contains:
Meropenem trihydrate IP equivalent to
anhydrous meropenem .................................................... 500 mg
Also contains sodium carbonate (sodium 45.1 mg)

**MEROCRIT I.V. 1 g**
Each vial contains:
Meropenem trihydrate IP equivalent to
anhydrous meropenem .................................................... 1 g
Also contains sodium carbonate (sodium 90.2 mg)

**MEROCRIT I.V. 2 g**
Each vial contains:
Meropenem trihydrate IP equivalent to
anhydrous meropenem .................................................... 2 g
Also contains sodium carbonate (sodium 180.4 mg)

**Dosage Form**

Powder for reconstitution and I.V. use only.
Meropenem is a broad-spectrum carbapenem antibiotic. The bactericidal activity of meropenem results from the inhibition of cell wall synthesis. Meropenem readily penetrates the cell wall of most Gram-positive and Gram-negative bacteria to reach penicillin-binding-protein (PBP) targets. Its strongest affinities are toward PBPs 2, 3 and 4 of Escherichia coli and *Pseudomonas aeruginosa* and PBPs 1, 2, and 4 of *Staphylococcus aureus*. Meropenem has significant stability to hydrolysis by beta-lactamases of most categories, both penicillinases and cephalosporinases produced by Gram-positive and Gram-negative bacteria.

Meropenem should not be used to treat methicillin-resistant *Staphylococcus aureus* (MRSA) or methicillin-resistant *Staphylococcus epidermidis* (MRSE). *In vitro* tests show that meropenem acts synergistically with aminoglycoside antibiotics against some isolates of *Pseudomonas aeruginosa*.

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

**Gram-positive Bacteria**
- *Enterococcus faecalis* (vancomycin-sensitive isolates only)
- *Staphylococcus aureus* (methicillin-susceptible isolates only)
- *Streptococcus agalactiae*
- *Streptococcus pneumoniae* (penicillin-susceptible isolates only)
- *Streptococcus pyogenes*
- Viridans group streptococci

**Gram-negative Bacteria**
- *Escherichia coli*
- *Haemophilus influenzae*
- *Klebsiella pneumoniae*
- *Neisseria meningitidis*
- *Pseudomonas aeruginosa*
- *Proteus mirabilis*

**Anaerobic Bacteria**
- *Bacteroides fragilis*
- *Bacteroides thetaiotaomicron*
- *Peptostreptococcus* species

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

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

Gram-negative Bacteria
*Aeromonas hydrophila*
*Campylobacter jejuni*
*Citrobacter koseri* (formerly *diversus*)
*Citrobacter freundii*
*Enterobacter cloacae*
*Hafnia alvei*
*Klebsiella oxytoca*
*Moraxella catarrhalis*
*Morganella morganii*
*Pasteurella multocida*
*Proteus vulgaris*
*Serratia marcescens*

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

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**Pharmacokinetics**

At the end of a 30-minute infusion of a single dose of meropenem I.V. in healthy volunteers, mean peak plasma concentrations are approximately 23 mcg/mL (range: 14 to 26) for the 500 mg dose and 49 mcg/mL (range: 39 to 58) for the 1 g dose. A 5-minute bolus injection of meropenem I.V. in healthy volunteers results in mean peak plasma concentrations of approximately 45 mcg/mL (range: 18 to 65) for the 500 mg dose and 112 mcg/mL (range: 83 to 140) for the 1 g dose.

Following I.V. doses of 500 mg, mean plasma concentrations of meropenem usually decline to approximately 1 mcg/mL at 6 hours after administration.
No accumulation of meropenem in plasma or urine was observed with regimens using 500 mg administered every 8 hours or 1 g administered every 6 hours in healthy volunteers with normal renal function.

Meropenem penetrates well into most body fluids and tissues, including the cerebrospinal fluid (CSF), achieving concentrations matching or exceeding those required to inhibit most susceptible bacteria. Plasma protein binding of meropenem is approximately 2%.

Meropenem is metabolized by hydrolysis of the beta-lactam ring, generating a microbiologically inactive metabolite.

In subjects with normal renal function, the elimination half-life of meropenem I.V. is approximately 1 hour. Approximately 70% of the administered I.V. dose is recovered as unchanged meropenem in the urine over 12 hours, after which little further urinary excretion is detectable. Urinary concentrations of meropenem in excess of 10 mcg/mL are maintained for up to 5 hours after a 500 mg dose. Faecal elimination represents only approximately 2% of the dose.

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 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 that in anuric patients.

Pharmacokinetic study with meropenem I.V. in patients with hepatic impairment has shown no effects of liver disease on the pharmacokinetics of meropenem.

Pharmacokinetic study with meropenem I.V. in elderly patients with renal impairment showed a reduction in plasma clearance of meropenem that correlates with age-associated reduction in creatinine clearance. No dose adjustment is required in elderly patients, except in cases of moderate to severe renal impairment.

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 2,000 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 (1/2, 1.6 hours). The mean meropenem clearance values were 5.8 ml/min/kg (aged 6 to 12 years), 6.2 ml/min/kg (aged 2 to 5 years), 5.3 ml/min/kg (aged 6 to 23 months) and 4.3 ml/min/kg (aged 2 to 5 months). Approximately 60% of the dose is excreted in urine over 12 hours as meropenem, with a further 12% as the 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 pharmacokinetics model showed that a dose regimen of 20 mg/kg given every 8 hours achieved 60% T>MIC for Pseudomonas aeruginosa in 95% of pre-term and 91% of full-term neonates.
**Indications**

MEROCRIT I.V. is indicated for the treatment of the following infections in adults and children above 3 months of age, when caused by susceptible bacteria:

- Pneumonia, including community-acquired pneumonia and nosocomial pneumonia
- Complicated urinary tract infections
- Complicated intra-abdominal infections (complicated appendicitis and peritonitis)
- Intra-and post-partum infections
- Complicated skin and skin structure infections
- Broncho-pulmonary infections in cystic fibrosis
- Acute bacterial meningitis

MEROCRIT I.V. has been found to be effective in eliminating concurrent bacteraemia in association with bacterial meningitis.

MEROCRIT I.V. may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.

**Dosage And Administration**

**Dosage**

Adults and Adolescents

The dosage and duration of therapy shall be established based on the type and severity of infection and the clinical response of the patient.

<table>
<thead>
<tr>
<th>Infection</th>
<th>Dose to Be Administered Every 8 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia, including community-acquired pneumonia and nosocomial pneumonia</td>
<td>500 mg or 1 g</td>
</tr>
<tr>
<td>Broncho-pulmonary infections in cystic fibrosis</td>
<td>2 g</td>
</tr>
<tr>
<td>Complicated urinary tract infections</td>
<td>500 mg or 1 g</td>
</tr>
</tbody>
</table>
Complicated intra-abdominal infections 500 mg or 1 g
Intra- and post-partum infections 500 mg or 1 g
Complicated skin and skin structure infections 500 mg or 1 g
Acute bacterial meningitis 2 g
Management of febrile neutropenic patients 1 g

A dose of up to 2 g three times daily in adults may be particularly appropriate when treating some types of infections, such as nosocomial infections due to *Pseudomonas aeruginosa* or *Acinetobacter species*.

**Renal Impairment**
Dosage should be reduced in patients with creatinine clearance less than 51 mL/min.

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

**Males:** Creatinine clearance (mL/min) = \( Weight \ (kg) \times (140 - \text{age}) \) \( \frac{72 \times \text{serum creatinine (mg/dL)}}{\text{Creatinine Clearance (mL/min)}} \)

**Females:** 0.85 \times \text{the above value}

**Recommended MEROCRIT I.V. Dosage Schedule for Adults and adolescents with Impaired Renal Function**

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Dose (based on 'unit' dose range of 500 mg, 1 g or 2 g)</th>
<th>Dosing Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>26-50</td>
<td>Recommended dose</td>
<td>Every 12 hours</td>
</tr>
<tr>
<td>10-25</td>
<td>Half of recommended dose</td>
<td>Every 12 hours</td>
</tr>
</tbody>
</table>
There are limited data to support the application of these dose adjustments for a unit dose of 2 g.

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.

**Paediatric**

*Children below 3 Months of Age*
The safety and efficacy of meropenem in children below 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:

<table>
<thead>
<tr>
<th>Infection</th>
<th>Dose to Be Administered Every 8 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia, including community-acquired pneumonia and nosocomial pneumonia</td>
<td>10 or 20 mg/kg</td>
</tr>
<tr>
<td>Broncho-pulmonary infections in cystic fibrosis</td>
<td>40 mg/kg</td>
</tr>
<tr>
<td>Complicated urinary tract infections</td>
<td>10 or 20 mg/kg</td>
</tr>
<tr>
<td>Complicated intra-abdominal infections</td>
<td>10 or 20 mg/kg (maximum dose up to 1 g)</td>
</tr>
</tbody>
</table>
Complicated skin and soft tissue infections 10 or 20 mg/kg (maximum dose up to 500 mg)

Acute bacterial meningitis 40 mg/kg (maximum dose up to 2 g)

Management of febrile neutropenic patients 20 mg/kg

Children Over 50 kg Body Weight
The adult dose should be administered.

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 nosocomial infections due to *Pseudomonas aeruginosa* or *Acinetobacter species*.

Renal Impairment
There is no experience in children with renal impairment.

Method of Preparation
Constitute injection vials (125 mg, 250 mg, 500 mg, 1 g and 2 g) with sterile water for injection. Shake to dissolve. Constituted solutions are clear and colourless or pale yellow.

<table>
<thead>
<tr>
<th>Vial Size</th>
<th>Amount of Diluent Added (mL)</th>
<th>Approximate Withdrawable Volume (mL)</th>
<th>Approximate Average Concentration (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>125 mg</td>
<td>2.5</td>
<td>2.5</td>
<td>50</td>
</tr>
<tr>
<td>250 mg</td>
<td>5</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>500 mg</td>
<td>10</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>1 g</td>
<td>20</td>
<td>20</td>
<td>50</td>
</tr>
<tr>
<td>2 g</td>
<td>30</td>
<td>30</td>
<td>67</td>
</tr>
</tbody>
</table>

Method of Administration
I.V. Bolus Injection
In adult patients, doses up to 1 g can be given as an I.V. bolus injection (5 to 20 mL) over approximately 3 - 5 minutes.
There are limited safety data available to support the administration of a 2 g dose in adults as an I.V. bolus injection.

Similarly, in paediatric patients, meropenem doses of up to 20 mg/kg may be given as an I.V. bolus injection (5 to 20 mL) over approximately 3 - 5 minutes. There are limited safety data available to support the administration of a 40 mg/kg (up to a maximum of 2 g) in children as an I.V. bolus injection dose.

<table>
<thead>
<tr>
<th>Application</th>
<th>Diluent</th>
<th>Mg/ml</th>
<th>Proposed Storage Condition (in hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Bolus injection</td>
<td>Water for Injection</td>
<td>50</td>
<td>15-25 ºC 4º C</td>
</tr>
</tbody>
</table>

**I.V. Infusion**
MEROCRIT I.V. for infusion may be constituted with the compatible infusion fluids (50 to 200 mL).

Alternatively, an injection vial may be constituted and, then, the resulting solution added to an I.V. container and further diluted with an appropriate infusion fluid.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Application</th>
<th>Diluent</th>
<th>Mg/ml</th>
<th>Proposed Storage Condition (in hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IV Infusion</td>
<td>0.9% Sodium chloride</td>
<td>1-20</td>
<td>15-25 ºC 4º C</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>5% Glucose</td>
<td>1-20</td>
<td>3  8</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>10% Glucose</td>
<td>1-20</td>
<td>1  2</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>5% Glucose &amp; 0.9% Sodium chloride</td>
<td>1-20</td>
<td>2  4</td>
</tr>
</tbody>
</table>

MEROCRIT I.V. is usually given by I.V. infusion over approximately 15 to 30 minutes.
WARNING: Do not use flexible container in series connections.

Compatibility of MEROCRIT I.V. with other drugs has not been established. MEROCRIT I.V. should not be mixed with or physically added to solutions containing other drugs.

Freshly prepared solutions of MEROCRIT I.V. should be used whenever possible. Solutions of MEROCRIT I.V. should not be frozen.

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

### Contraindications

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

### Warnings And Precautions

#### General

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

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

Studies 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, thereby increasing the risk of breakthrough seizures. 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. If administration of meropenem I.V. is necessary, supplemental anticonvulsant therapy should be considered.

Antibiotic-associated colitis, *Clostridium difficile*-associated diarrhoea (CDAD) and pseudomembranous colitis have been reported with nearly all anti-bacterial agents, including meropenem, and may range in severity from mild to life threatening (including fatal colitis). 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. In case of CDAD, appropriate fluid and electrolyte management, protein supplementation, and surgical evaluation should be instituted as clinically indicated. Medicinal products that inhibit peristalsis should not be given.

Patients receiving meropenem I.V. on an outpatient basis may develop adverse events such as seizures, headaches and/or paresthesias that could interfere with mental alertness and/or cause motor impairment. Until it is reasonably well established that meropenem I.V. is well tolerated, patients should not operate machinery or motorized vehicles.

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

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

Hepatic function should be closely monitored during treatment with meropenem due to the risk of hepatic toxicity (hepatic dysfunction with cholestasis and cytolysis).

Prescribing meropenem I.V. in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

As with other broad-spectrum antibiotics, prolonged use of meropenem may result in the overgrowth of non-susceptible organisms. Repeated evaluation of the patient is essential. If super-infection does occur during therapy, appropriate measures should be taken.

While meropenem I.V. possesses the characteristic low toxicity of the beta-lactam group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and haematopoietic, is advisable during prolonged therapy.

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.

A positive direct or indirect Coombs' test may develop during treatment with meropenem.

### Drug interactions

Probenecid competes with meropenem for active tubular secretion, resulting in increased elimination half-life and plasma concentrations of meropenem. Therefore, the co-administration of probenecid with meropenem I.V. is not recommended.

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. However, if administration of meropenem I.V. is necessary, then supplemental anti-convulsant therapy should be considered.

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 the international normalized ratio (INR) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of antibiotics with an oral anti-coagulant agent.

Renal impairment

Please refer DOSAGE AND ADMINISTRATION. There is no experience in paediatric patients with renal impairment. Dosage adjustment is necessary in patients with creatinine clearance 50 mL/min or less.

Hepatic impairment

No dosage adjustment is necessary in patients with impaired hepatic function. There is no experience in paediatric patients with hepatic impairment.

Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Meropenem I.V. should be used during pregnancy only if clearly needed.

Lactation

It is not known whether meropenem is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when meropenem I.V. is administered to a nursing mother.

Paediatric use

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

Geriatric use

Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function. No dose adjustment is required for the elderly with normal renal function or creatinine clearance values above 50 mL/min.

Undesirable Effects

Local I.V. Injection Site Reactions
Inflammation at the injection site (2.4%), thrombophlebitis (0.8%), injection site reaction (0.9%), pain at the injection site (0.4%), and oedema at the injection site (0.2%).

Systemic Adverse Reactions
Systemic adverse reactions that were reported irrespective of the relationship to meropenem I.V. occurring in >1.0% of the patients were diarrhoea (4.8%), nausea/vomiting (3.6%), headache (2.3%), rash (1.9%), sepsis (1.6%), constipation (1.4%), apnoea (1.3%), shock (1.2%) and pruritus (1.2%).

Additional systemic adverse reactions that were reported irrespective of relationship to therapy with meropenem I.V. and occurring in ≤1.0% but >0.1% of the patients are listed below:
Bleeding events seen were gastrointestinal haemorrhage (0.5%), melena (0.3%), epistaxis (0.2%) and haemoperitoneum (0.2%), adding up to 1.2%.

Skin and Appendages
Sweating, skin ulcers and urticaria.

Gastrointestinal
Abdominal pain, oral moniliasis, anorexia, cholestatic jaundice/jaundice, flatulence, ileus, hepatic failure, dyspepsia and intestinal obstruction. Pseudomembranous colitis has also been reported.

Central Nervous System
Paraesthesia, insomnia, agitation/delirium, confusion, dizziness, seizures, nervousness, hallucinations, somnolence, anxiety, depression and asthenia. Convulsions have been reported although a casual relationship with meropenem I.V. has not been established.

Respiratory
Dyspnoea, pleural effusion, asthma, cough increased and lung oedema.

Cardiovascular
Heart failure, heart arrest, tachycardia, hypertension, myocardial infarction, pulmonary embolus, bradycardia, hypotension and syncope.
Blood and Lymphatic System
Anaemia, hypochromic anaemia, hypervolaemia, thrombocythaemia, eosinophilia and thrombocytopenia.

Urogenital System
Dysuria, kidney failure, vaginal moniliasis and urinary incontinence.

Infections and Infestations
Oral and vaginal candidiasis.

Body as a Whole
Chest pain, fever, back pain, abdominal enlargement, chills and pelvic pain.

Metabolic/Nutritional
Hypoxia and peripheral oedema.

Adverse Laboratory Changes
Adverse laboratory changes that were reported irrespective of a relationship to meropenem I.V. and occurring in >0.2% of the patients were as follows:

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

Haematologic
Leucocytosis, hypokalaemia, increased platelets and eosinophils, decreased platelets, haemoglobin, haematocrit and white blood cells. There have been reports of reduction in the prothrombin time and partial thromboplastin time.

Renal
Increased creatinine and increased blood urea nitrogen (BUN).

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

Urinalysis
Presence of red blood cells.

Complicated Skin and Skin Structure Infections
In a study of complicated skin and skin structure infections, the adverse reactions were similar to those listed above. The other adverse events with an incidence of >1% reported were as follows: pharyngitis, accidental injury, gastrointestinal disorder, hypoglycaemia, peripheral vascular disorder and pneumonia.

Paediatric Patients
The types of clinical adverse events seen in these patients are similar to the adults, with the most common adverse events reported as possibly, probably or definitely related to meropenem I.V.

Meropenem I.V. was studied in 515 paediatric patients (≥3 months to <13 years of age) with serious bacterial infections (excluding meningitis) at dosages of 10 to 20 mg/kg every 8 hours. The rates of occurrence of the adverse events were as follows: diarrhoea (3.5%); rash (1.6%); and, nausea and vomiting (0.8%).
Meropenem I.V. was studied in 321 paediatric patients (≥3 months to <17 years of age) with meningitis at a dosage of 40 mg/kg every 8 hours. The rates of occurrence of the adverse events were as follows: diarrhoea (4.7%); rash (mostly diaper-area moniliasis) (3.1%); oral moniliasis (1.9%); and, glossitis (1.0%).

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

Adverse Laboratory Changes
Laboratory changes seen in the paediatric studies, including the meningitis studies, were similar to those reported in the adult studies.

There is no experience in paediatric patients with renal impairment.

### Postmarketing Experience

The following adverse reactions have been observed during postmarketing surveillance studies with meropenem I.V.: agranulocytosis, neutropenia, leucopenia, positive direct or indirect Coombs' test, haemolytic anaemia, toxic epidermal necrolysis, Stevens-Johnson syndrome, angio-oedema and erythema multiforme.

### Overdosage

Relative overdose may be possible in patients with renal impairment if the dose is not adjusted. The largest dose of meropenem I.V. administered in clinical trials has been 2 g, given every 8 hours. At this dosage, no adverse pharmacological effects or increased safety risks have been observed.

Limited post-marketing experience indicates that if adverse events occur following overdosage, they are consistent with the adverse event profile and are generally mild in severity and resolve on withdrawal or dose reduction. Treatment of overdosage should be symptomatic. In individuals with normal renal function, rapid renal elimination will occur. Meropenem and its metabolite are readily dialysable and effectively removed by haemodialysis; however, no information is available on the use of haemodialysis to treat overdosage.

### Incompatibility

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

### Storage And Handling Instructions

Before opening
Store in a cool, dry place. Protect from light.
Reconstituted solution

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Application</th>
<th>Diluent</th>
<th>Mg/ml</th>
<th>Proposed Storage Condition (in hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15-25 ºC</td>
</tr>
<tr>
<td>1.</td>
<td>IV Bolus injection</td>
<td>Water for Injection</td>
<td>50</td>
<td>4</td>
</tr>
<tr>
<td>2.</td>
<td>IV Infusion</td>
<td>0.9% Sodium chloride</td>
<td>1-20</td>
<td>8</td>
</tr>
<tr>
<td>3.</td>
<td></td>
<td>5% Glucose</td>
<td>1-20</td>
<td>3</td>
</tr>
<tr>
<td>4.</td>
<td></td>
<td>10% Glucose</td>
<td>1-20</td>
<td>1</td>
</tr>
<tr>
<td>5.</td>
<td></td>
<td>5% Glucose &amp; 0.9% Sodium chloride</td>
<td>1-20</td>
<td>2</td>
</tr>
</tbody>
</table>

*Solutions of Meropenem I.V. should not be Frozen.*

Packaging Information

MEROCRIT I.V. Baby: Vial of 15 mL
MEROCRIT I.V. 250 mg: Vial of 15 mL
MEROCRIT I.V. 0.5 g: Vial of 20 mL
MEROCRIT I.V. 1 g: Vial of 30 mL
MEROCRIT I.V. 2 g: Vial of 30 mL

Last updated: October 2013
Last reviewed: October 2013