IMICRIT I.V. Injection (Imipenem + Cilastatin)

Composition

IMICRIT I.V. 250 mg
Each vial contains:
Imipenem IP equivalent to anhydrous imipenem .......... 250 mg
Cilastatin sodium, USP equivalent to anhydrous cilastatin .......... 250 mg
Sodium bicarbonate, USP, added as buffer

IMICRIT I.V. 500 mg
Each vial contains:
Imipenem IP equivalent to anhydrous imipenem .......... 500 mg
Cilastatin sodium, USP equivalent to anhydrous cilastatin .......... 500 mg
Sodium bicarbonate, USP, added as buffer

IMICRIT I.V. 1 g
Each vial contains:
Imipenem IP equivalent to anhydrous imipenem .......... 1 g
Cilastatin sodium IP equivalent to cilastatin ................. 1 g
Sodium bicarbonate, IP, added as buffer

Dosage Form

Powder for reconstitution and I.V. use only.

Description

IMICRIT I.V. is a potent broad-spectrum beta-lactam antibiotic. IMICRIT I.V. consists of two components: (1) imipenem, the first new class of beta-lactam antibiotics, the thienamycins; and, (2) cilastatin sodium, a competitive, reversible and specific inhibitor of renal dipeptidase, dehydropeptidase-I (which blocks the metabolism of imipenem in the kidneys and substantially increases the concentration of intact imipenem in the urinary tract). Imipenem and cilastatin sodium are present in IMICRIT I.V. in a 1:1 ratio by weight.
Pharmacology

Pharmacodynamics

The bactericidal activity of imipenem results from the inhibition of cell wall synthesis. Its greatest affinity is for penicillin-binding proteins (PBPs) 1A, 1B, 2, 4, 5 and 6 of *Escherichia coli*, and 1A, 1B, 2, 4 and 5 of *Pseudomonas aeruginosa*. The lethal effect is related to the binding to PBP 2 and PBP 1B. Imipenem has a high degree of stability in the presence of beta-lactamases, both penicillinases and cephalosporinases produced by gram-negative and gram-positive bacteria. It is a potent inhibitor of beta-lactamases from certain gram-negative bacteria that are inherently resistant to most beta-lactam antibiotics, e.g., *Pseudomonas aeruginosa*, *Serratia* spp., and *Enterobacter* spp.

Cilastatin sodium is devoid of intrinsic antibacterial activity itself and does not affect the antibacterial activity of imipenem.

Imipenem has *in vitro* activity against a wide range of gram-positive and gram-negative organisms. Imipenem has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections treated with the I.V. formulation of imipenem-cilastatin sodium:

**Gram-positive aerobes**
- *Enterococcus faecalis* (formerly *S. faecalis*)
- *Staphylococcus aureus*, including penicillinase-producing strains
- *Staphylococcus epidermidis*, including penicillinase-producing strains
- *Streptococcus agalactiae* (Group B streptococci)
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*

(NOTE: Imipenem is inactive *in vitro* against *Enterococcus faecium*. Methicillin-resistant staphylococci should be reported as resistant to imipenem.)

**Gram-negative aerobes**
- *Acinetobacter* spp.
- *Citrobacter* spp.
- *Enterobacter* spp.
- *Escherichia coli*
- *Gardnerella vaginalis*
- *Haemophilus influenzae*
- *Haemophilus parainfluenzae*
- *Klebsiella* spp.
- *Morganella morganii*
- *Proteus vulgaris*
- *Providencia rettgeri*
- *Pseudomonas aeruginosa*
- *Serratia* spp., including *S. marcescens*

(NOTE: Imipenem is inactive *in vitro* against *Stenotrophomonas maltophilia* and some strains of *Burkholderia cepacia*.)

**Gram-positive anaerobes**
- *Bifidobacterium* spp.
- *Clostridium* spp.
- *Eubacterium* spp.
- *Peptococcus* spp.
Peptostreptococcus spp.
Propionibacterium spp.
Gram-negative anaerobes
Bacteroides spp., including B. fragilis
Fusobacterium spp.
The following *In vitro* data are available, but their clinical significance is unknown.
Imipenem exhibits *In vitro* minimum inhibitory concentrations (MICs) of 4 μg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of imipenem in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials:
Gram-positive aerobes
Bacillus spp.
Listeria monocytogenes
Nocardia spp.
Staphylococcus saprophyticus
Group C streptococci
Group G streptococci
Viridans group streptococci
Gram-negative aerobes
Aeromonas hydrophila
Alcaligenes spp.
Capnocytophaga spp.
Haemophilus ducreyi
Neisseria gonorrhoeae, including penicillinase-producing strains
Pasteurella spp.
Providencia stuartii
Gram-negative anaerobes
Prevotella bivia
Prevotella disiens
Prevotella melaninogenica
Veillonella spp.
*In vitro* tests show that imipenem acts synergistically with aminoglycoside antibiotics against some isolates of Pseudomonas aeruginosa.

### Pharmacokinetics

**Adults**

An infusion of imipenem-cilastatin I.V. for injection over 20 minutes results in peak plasma levels of imipenem antimicrobial activity that range from 14 to 24 μg/mL for the 250 mg dose, from 21 to 58 μg/mL for the 500 mg dose, and from 41 to 83 μg/mL for the 1000 mg dose. At these doses, plasma levels of imipenem antimicrobial activity decline to below 1 μg/mL or less in 4 to 6 hours. Peak plasma levels of cilastatin following a 20-minute infusion of imipenem-cilastatin I.V. for injection range from 15 to 25 μg/mL for the 250 mg dose, from 31 to 49 μg/mL for the 500 mg dose, and from 56 to 88 μg/mL for the 1000 mg dose.

When administered alone, imipenem is metabolized in the kidneys by dehydropeptidase-I. Individual urinary recoveries ranged from 5% to 40%, with an average recovery of 15-20% in several studies.

The plasma half-life of each component is approximately 1 hour. The binding of imipenem to human serum proteins is
approximately 20% and that of cilastatin is approximately 40%. Approximately 70% of the administered imipenem is recovered in the urine within 10 hours, after which no further urinary excretion is detectable. Urine concentrations of imipenem in excess of 10 μg/mL can be maintained for up to 8 hours with imipenem-cilastatin I.V. for injection at the 500 mg dose. Approximately 70% of the cilastatin sodium dose is recovered in the urine within 10 hours of administration of imipenem-cilastatin I.V. for injection.

No accumulation of imipenem or cilastatin in plasma or urine has been observed with regimens administered as frequently as every 6 hours in patients with normal renal function.

In healthy elderly volunteers (65 to 75 years of age with normal renal function for their age), the pharmacokinetics of a single I.V. dose of imipenem 500 mg and cilastatin 500 mg administered over 20 minutes are consistent with those expected in subjects with slight renal impairment for which no dosage alteration is considered necessary. The mean plasma half-lives of imipenem and cilastatin are 91 ± 7.0 minutes and 69 ± 15 minutes, respectively. Multiple dosing has no effect on the pharmacokinetics of either imipenem or cilastatin, and no accumulation of imipenem or cilastatin is observed.

Imipenem, when administered alone, is metabolized in the kidneys by dehydropeptidase-I, resulting in relatively low levels in the urine. Cilastatin sodium, an inhibitor of this enzyme, effectively prevents the renal metabolism of imipenem so that when imipenem and cilastatin sodium are given concomitantly, fully adequate antibacterial levels of imipenem are achieved in the urine.

Imipenem-cilastatin sodium is hemodialyzable. However, usefulness of this procedure in the overdosage setting is questionable.

Paediatrics

Based on published studies of 178 paediatric patients ≥3 months of age (with non-central nervous system infections), the recommended dose of imipenem and cilastatin sodium I.V. for injection is 15-25 mg/kg/dose administered every 6 hours. Doses of 25 mg/kg/dose in patients, 3 months to <3 years of age, and 15 mg/kg/dose in patients, 3-12 years of age, were associated with mean trough plasma concentrations of imipenem of 1.1 ± 0.4 mcg/mL and 0.6 ± 0.2 mcg/mL following multiple 60-minute infusions, respectively; trough urinary concentrations of imipenem were in excess of 10 mcg/mL for both doses. These doses have provided adequate plasma and urine concentrations for the treatment of non-CNS infections.

In a published dose-ranging study of smaller premature infants (670-1,890 g) in the first week of life, a dose of 20 mg/kg q12h by infusion over 15-30 minutes was associated with mean peak and trough plasma imipenem concentrations of 43 mcg/mL and 1.7 mcg/mL after multiple doses, respectively. However, moderate accumulation of cilastatin sodium in neonates may occur following multiple doses of imipenem-cilastatin sodium I.V. for injection. The safety of this accumulation is unknown.

The average clearance (CL) and volume of distribution (Vdss) for imipenem were approximately 45% higher in paediatric patients (3 months to 14 years) as compared to adults. The AUC for imipenem following administration of 15 mg/15 mg/kg per body weight of imipenem-cilastatin sodium I.V. for injection to paediatric patients was approximately 30% higher than the exposure in adults receiving a 500 mg/500 mg dose. At the higher dose, the exposure following administration of 25 mg/25 mg/kg imipenem-cilastatin sodium I.V. for injection to children was 9% higher as compared to the exposure in adults receiving a 1,000 mg/1,000 mg dose.

**Indications**

IMICRIT I.V. is indicated for the treatment of serious infections as listed below:

- Lower respiratory tract infections (including severe pneumonia)
- Urinary tract infections (complicated and uncomplicated)
Intra-abdominal infections (including complicated infections)

- Gynaecological infections (including intra- and post-partum infections)
- Bacterial septicaemia
- Bone and joint infections
- Skin and skin structure infections (including complicated infections)
- Endocarditis
- Polymicrobial infections, including those in which S. pneumoniae (pneumonia, septicaemia), S. pyogenes (skin and skin structure), or non-penicillinase-producing S. aureus is one of the causative organisms. However, monobacterial infections due to these organisms are usually treated with narrower spectrum antibiotics, such as penicillin G.

IMICRIT I.V. may be used in the management of neutropenic patients with fever that is suspected to be due to bacterial infection. It may also be used in the treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above. Because of its broad spectrum of bactericidal activity against Gram-positive and Gram-negative aerobic and anaerobic bacteria, IMICRIT I.V. is useful for the treatment of mixed infections and as presumptive therapy prior to the identification of the causative organisms. IMICRIT I.V. is not indicated in patients with meningitis because safety and efficacy have not been established. Imipenem-cilastatin I.V. for injection has demonstrated efficacy against many infections resistant to cephalosporins, aminoglycosides and/or penicillins.

**Dosage And Administration**

**Dosage**

**Adults and Adolescents**

The total daily dosage for IMICRIT I.V. should be based on the type or severity of infection and given in equally divided doses, based on consideration of the degree of susceptibility of the pathogen(s), renal function and body weight. Adult patients with impaired renal function, as judged by creatinine clearance ≤70 mL/min/1.73 m$^2$, require adjustment of dosage as described in the succeeding section of these guidelines.

**I.V. Dosage Schedule for Adults with Normal Renal Function and Body Weight ≥70 kg**

Doses are based on a patient with normal renal function and a body weight of 70 kg. These doses should be used for a patient with a creatinine clearance of ≥71 mL/min/1.73 m$^2$ and a body weight of ≥70 kg. A reduction in dose must be made for a patient with a creatinine clearance of ≤70 mL/min/1.73 m$^2$ and/or a body weight less than 70 kg. Dosage regimens in column A of Table 1 are recommended for infections caused by fully susceptible organisms, which represent the majority of pathogenic species. Dosage regimens in column B of Table 1 are recommended for infections caused by organisms with moderate susceptibility to imipenem, primarily some strains of Pseudomonas aeruginosa.

**Table 1: I.V. Dosage Schedule of IMICRIT I.V. for Adults with Normal Renal Function and Body Weight ≥70 kg**
<table>
<thead>
<tr>
<th>Type or Severity of Infection</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fully Susceptible Organisms, Including gram-positive and gram-negative Aerobes and Anaerobes</td>
<td>250 mg q6h (total daily dose = 1.0 g)</td>
<td>500 mg q6h (total daily dose = 2.0 g)</td>
</tr>
<tr>
<td>Moderately Susceptible Organisms, Primarily Some Strains of <em>Pseudomonas aeruginosa</em></td>
<td>500 mg q8h (total daily dose = 1.5 g) or 500 mg q6h (total daily dose = 2.0 g)</td>
<td>500 mg q6h (total daily dose = 2.0 g) or 1 g q8h (total daily dose = 3.0 g)</td>
</tr>
<tr>
<td>Mild</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe, life-threatening only</td>
<td>500 mg q6h (total daily dose = 2.0 g)</td>
<td>1 g q8h (total daily dose = 3.0 g) or 1 g q6h (total daily dose = 4.0 g)</td>
</tr>
<tr>
<td>Uncomplicated urinary tract infection</td>
<td>250 mg q6h (total daily dose = 1.0 g)</td>
<td>250 mg q6h (total daily dose = 1.0 g)</td>
</tr>
<tr>
<td>Complicated urinary tract infection</td>
<td>500 mg q6h (total daily dose = 2.0 g)</td>
<td>500 mg q6h (total daily dose = 2.0 g)</td>
</tr>
</tbody>
</table>

Due to the High Antimicrobial Activity of IMICRIT I.V., it is recommended that the maximum total daily dosage not exceed 50 mg/kg/day or 4.0 g/day, whichever is lower.

There is no evidence that higher doses provide greater efficacy. However, patients over 12 years of age with cystic fibrosis and normal renal function have been treated with IMICRIT I.V. at doses up to 90 mg/kg/day in divided doses, not exceeding 4.0 g/day.

Infections suspected or proven to be due to less susceptible bacteria species (such as *Pseudomonas aeruginosa*) and very severe infections (e.g. in neutropenic patients with a fever) should be treated with 1000 mg/1000 mg administered every 6 hours.

**Reduced I.V. Schedule for Adults with Impaired Renal Function and/or Body Weight <70 kg**

Patients with a creatinine clearance of ≤70 mL/min/1.73 m² and/or body weight IMICRIT I.V. as indicated in tables 2 and 3 below. Creatinine clearance may be calculated from serum creatinine concentration by the following equation:
To determine the dose for adults with impaired renal function and/or reduced body weight:

1. Choose a total daily dose from Table 1, based on infection characteristics.
   1. If the total daily dose is 1.0 g, 1.5 g or 2.0 g, use the appropriate subsection of Table 2 and continue with step 3.
   2. If the total daily dose is 3.0 g or 4.0 g, use the appropriate subsection of Table 3 and continue with step 3.

2. From Tables 2 or 3, do the following:
   1. From the column titled, and body weight (kg) is
   2. Select the patient's creatinine clearance category.
   3. Where the row and column intersect, the value given is the reduced dosage regimen.

### Table 2: Reduced Dosage of IMICRIT I.V. in Adult Patients with Impaired Renal Function and/or Body Weight <70 kg

<table>
<thead>
<tr>
<th>Total Daily Dose (g/day)</th>
<th>Body Weight (kg)</th>
<th>Creatinine Clearance (ml/min/1.73 m²)</th>
<th>Reduced Dosage (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 g/day</td>
<td></td>
<td>≥71</td>
<td>Reduced dosage is</td>
</tr>
<tr>
<td></td>
<td></td>
<td>41-70</td>
<td>6-20</td>
</tr>
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<td>21-40</td>
<td>6-20</td>
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<tr>
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<td></td>
<td>≥71</td>
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<td>21-40</td>
<td>6-20</td>
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<tr>
<td>2.0 g/day</td>
<td></td>
<td>≥71</td>
<td>Reduced dosage is</td>
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<td>41-70</td>
<td>6-20</td>
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<td>21-40</td>
<td>6-20</td>
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</tbody>
</table>

### Table 3: Reduced Dosage of IMICRIT I.V. in Adult Patients with Impaired Renal Function and/or Body Weight <70 kg

<table>
<thead>
<tr>
<th>Total Daily Dose (g/day)</th>
<th>Body Weight (kg)</th>
<th>Creatinine Clearance (ml/min/1.73 m²)</th>
<th>Reduced Dosage (mg)</th>
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<td>≥71</td>
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<td>Reduced dosage (mg) is</td>
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<td>21-40</td>
<td>6-20</td>
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</tbody>
</table>

Patients with creatinine clearances of 6-20 mL/min/1.73 m$^2$ should be treated with IMICRIT I.V. 125 mg or 250 mg every 12 hours for most pathogens. There may be an increased risk of seizures when doses of 500 mg every 12 hours are administered to these patients.

Patients with creatinine clearance ≤5 mL/min/1.73 m$^2$ should not receive IMICRIT I.V. unless haemodialysis is instituted within 48 hours. There is inadequate information to recommend the usage of IMICRIT I.V. for patients undergoing peritoneal dialysis.

**Haemodialysis**

When treating patients with creatinine clearances of ≤5 mL/min/1.73 m² who are undergoing haemodialysis, use the dosage recommendations for patients with creatinine clearances of 6-20 mL/min/1.73 m². Both imipenem and cilastatin are cleared from the circulation during haemodialysis. The patient should receive IMICRIT I.V. after haemodialysis and at 12-hour intervals timed from the end of that haemodialysis session. Dialysis patients, especially those with background CNS disease, should be carefully monitored; for patients on haemodialysis, IMICRIT I.V. is recommended only when the benefit outweighs the potential risk of seizures.

**Hepatic Impairment**

No dose adjustment is recommended in patients with impaired hepatic function.

**Paediatric**

For paediatric patients ≥3 months of age, the recommended dose for non-CNS infections is 15-25 mg/kg/dose administered every 6 hours. Based on studies in adults, the maximum daily dose for treatment of infections with fully susceptible organisms is 2.0 g per day; for infections with moderately susceptible organisms (primarily some strains of Pseudomonas aeruginosa), it is 4.0 g/day. Higher doses (up to 90 mg/kg/day in older children) have been used in patients with cystic fibrosis.

Paediatric patients ≥1 year of age with very severe infections (e.g., in neutropenic patients with a fever) should be treated with 25 mg/kg administered every 6 hours.

For paediatric patients who are ≤3 months of age (weighing ≥1,500 g), the following dosage schedule is recommended.
for non-CNS infections:
<1 week of age: 25 mg/kg every 12 hours
1 to 4 weeks of age: 25 mg/kg every 8 hours
4 weeks to 3 months of age: 25 mg/kg every 6 hours

Renal Impairment
Clinical data are insufficient to recommend dosing for paediatric patients with renal impairment (serum creatinine >2 mg/dl).

IMICRIT I.V. is not recommended in
1. paediatric patients with CNS infections because of the risk of seizures; and,
2. paediatric patients

Method of Preparation
The following table is provided for convenience in reconstituting IMICRIT I.V. for infusion.

Table 4: Reconstituting IMICRIT I.V. for Infusion

<table>
<thead>
<tr>
<th>Dose of IMICRIT I.V. (mg of Imipenem)</th>
<th>Volume of Diluent Added (ml)</th>
<th>Approximate Concentration of Imipenem (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>250</td>
<td>50</td>
<td>5</td>
</tr>
<tr>
<td>500</td>
<td>100</td>
<td>5</td>
</tr>
<tr>
<td>1000</td>
<td>250</td>
<td>4</td>
</tr>
</tbody>
</table>

Reconstitution of Vial
Procedure for IMICRIT I.V. 250 mg
The contents of the vials must be suspended and transferred to 50 mL of an appropriate infusion solution. A suggested procedure is to add approximately 10 mL from the appropriate infusion solution (see Compatibility and Stability) to the vial. Shake well and transfer the resulting suspension to the infusion solution container. Repeat with an additional 10 mL of infusion solution to ensure the complete transfer of the vial contents to the infusion solution. The resulting mixture should be agitated until clear.

Procedure for IMICRIT I.V. 500 mg
The contents of the vials must be suspended and transferred to 100 mL of an appropriate infusion solution. A suggested procedure is to add approximately 10 mL from the appropriate infusion solution (see Compatibility and Stability) to the vial. Shake well and transfer the resulting suspension to the infusion solution container. Repeat with an additional 10 mL of infusion solution to ensure the complete transfer of the vial contents to the infusion solution. The resulting mixture should be agitated until clear.

Procedure for IMICRIT I.V. 1 g
The contents of the vial must be suspended and transferred to 250 mL of an appropriate compatible infusion solution. A suggested procedure is to add approximately 20 mL from the appropriate compatible infusion solution (see Compatibility and Stability) to the vial. Shake well and transfer the resulting suspension to the compatible infusion solution container. Repeat with an additional 20 mL of compatible infusion solution to ensure complete the transfer of the vial contents to the compatible infusion solution. The resulting mixture should be agitated until clear.

Benzyl alcohol as a preservative has been associated with toxicity in neonates. While toxicity has not been demonstrated
in paediatric patients >3 months of age, small paediatric patients in this age range may also be at risk for benzyl alcohol toxicity. Therefore, diluents containing benzyl alcohol should not be used when IMICRIT I.V. is constituted for administration to paediatric patients in this age range.

CAUTION: THE SUSPENSION IS NOT FOR DIRECT INFUSION.

Method of Administration

Adults and Adolescents

The dosage recommendations for IMICRIT I.V. represent the quantity of imipenem to be administered. An equivalent amount of cilastatin is also present in the solution. Each 250 mg or 500 mg dose should be given by I.V. administration over 20-30 minutes. 1,000 mg dose should be infused over 40-60 minutes. In patients who develop nausea during the infusion, the rate of infusion may be slowed.

Paediatric

Doses less than or equal to 500 mg should be given by I.V. infusion over 15-30 minutes.

Doses greater than 500 mg should be given by I.V. infusion over 40-60 minutes. In patients who develop nausea during the infusion, the rate of infusion may be slowed.

Compatibility and Stability

Before Reconstitution

The dry powder should be stored at a temperature below 25ºC (77ºF).

Reconstituted Solutions

Solutions of IMICRIT I.V. range from colourless to yellow. Variations of colour within this range do not affect the potency of the product. However, IMICRIT I.V. may be administered concomitantly with other antibiotics, such as aminoglycosides.

IMICRIT I.V. 250 mg and IMICRIT I.V. 500 mg, reconstituted with 0.9% Sodium Chloride Injection, maintains satisfactory potency for 4 hours at room temperature or for 24 hours under refrigeration (2º to 8ºC).

IMICRIT I.V. 1 g, reconstituted with 0.9% Sodium Chloride Injection or 5% dextrose solution, maintains satisfactory potency for 4 hours at room temperature or for 24 hours under refrigeration (2º to 8ºC).

Solutions of IMICRIT I.V. should not be frozen.

Imipenem-cilastatin I.V. for injection may also be reconstituted with the diluents mentioned below:

5% or 10% Dextrose Injection

5% Dextrose Injection with 0.225% or 0.45% saline solution

In exceptional circumstances, 5% glucose may also be used.

Imipenem-cilastatin I.V. for injection should not be mixed with, or physically added to, other antibiotics.

Contraindications

Imipenem/cilastatin is contraindicated in patients who have shown a hypersensitivity to any component of this product or to any other carbapenem antibacterial agent and other beta-lactam agents. It is contraindicated in case of severe hypersensitivity (e.g. anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial agent (e.g. penicillins or cephalosporins).

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 apt to occur in persons with a history of sensitivity to multiple allergens. There have been reports of patients with a history of penicillin hypersensitivity who have experienced severe
hypothesis reactions when treated with another beta-lactam. Before initiating therapy with imipenem/cilastatin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, other beta-lactams and other allergens. If an allergic reaction occurs, imipenem/cilastatin should be discontinued. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen, I.V. steroids, and airway management, including intubation, may also be administered as indicated.

Antibiotic-associated colitis, *Clostridium difficile*-associated diarrhoea (CDAD) and pseudomembranous colitis have been reported with imipenem/cilastatin and with nearly all other anti-bacterial agents and may range from mild to life-threatening in severity.

Discontinuation of therapy with imipenem/cilastatin and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

In case of CDAD, appropriate fluid and electrolyte management, protein supplementation, and surgical evaluation should be instituted as clinically indicated.

It is not recommended for the therapy of meningitis.

CNS-adverse experiences such as confusional states, myoclonic activity and seizures have been reported during treatment with imipenem-cilastatin I.V. for injection, especially when the recommended dosages were exceeded. These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function. However, there have been reports of CNS-adverse experiences in patients who had no recognized or documented underlying CNS disorder or compromised renal function.

Special awareness should be made to neurological symptoms or convulsions in children with known risk factors for seizures, or on concomitant treatment with medicinal products lowering the seizures threshold.

When the recommended doses were exceeded, adult patients with creatinine clearances of ≤20 mL/min/1.73 m², whether or not undergoing haemodialysis, had a higher risk of seizure activity than those without impairment of renal function. Therefore, close adherence to the dosing guidelines for these patients is recommended.

Patients with creatinine clearances of ≤5 mL/min/1.73 m² should not receive imipenem/cilastatin unless haemodialysis is instituted within 48 hours. For patients on haemodialysis, imipenem/cilastatin is recommended only when the benefit outweighs the potential risk of seizures. Close adherence to the recommended dosage and dosage schedules is urged, especially in patients with known factors that predispose to convulsive activity. Anticonvulsant therapy should be continued in patients with known seizure disorders. If focal tremors, myoclonus or seizures occur, patients should be evaluated neurologically, placed on anticonvulsant therapy if not already instituted, and the dosage of imipenem/cilastatin re-examined to determine whether it should be decreased or the antibiotic discontinued.

Hepatic function should be closely monitored during treatment with imipenem/cilastatin due to the risk of hepatic toxicity (such as increase in transaminases, hepatic failure and fulminant hepatitis).

Use in patients with liver disease: patients with pre-existing liver disorders should have liver function monitored during treatment with imipenem/cilastatin. There is no dose adjustment necessary.

A positive direct or indirect Coombs test may develop during treatment with imipenem/cilastatin. As with other antibiotics, prolonged use of imipenem/cilastatin may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Prescribing imipenem/cilastatin 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.

While imipenem/cilastatin possesses the characteristic low toxicity of the beta-lactam group of antibiotics, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during prolonged therapy.
Drug interactions

Generalized seizures have been reported in patients who received ganciclovir and imipenem-cilastatin I.V. for injection. These drugs should not be used concomitantly unless the potential benefits outweigh the risks. Since concomitant administration of imipenem-cilastatin I.V. for injection and probenecid results in only minimal increases in plasma levels of imipenem and plasma half-life, it is not recommended that probenecid be given with imipenem/cilastatin.

Case reports in the literature have shown that co-administration of carbapenems, including imipenem, to patients receiving valproic acid or divalproex sodium results in a reduction in valproic acid concentrations. In some cases, breakthrough seizures have occurred. The concomitant use of imipenem and valproic acid/divalproex sodium is generally not recommended.

Simultaneous administration of antibiotics with warfarin may augment its anti-coagulant effects. There have been many reports of increases in the anti-coagulant effects of orally administered anti-coagulant agents, including warfarin in patients who are concomitantly receiving antibacterial agents. The risk may vary with 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.

Concomitant administration of imipenem/cilastatin and probenecid resulted in minimal increase in the plasma levels and plasma half-life of imipenem. The urinary recovery of active (non-metabolized) imipenem decreased to approximately 60% of the dose when imipenem/cilastatin was administered with probenecid. Concomitant administration of imipenem/cilastatin and probenecid doubled the plasma level and half life of cilastatin, but had no effect on urine recovery of cilastatin.

Renal impairment

Please refer DOSAGE AND ADMINISTRATION.

Hepatic impairment

Please refer DOSAGE AND ADMINISTRATION.

Pregnancy

Pregnancy Category C

Imipenem/cilastatin should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and the foetus.

Lactation

Imipenem and cilastatin are excreted into the mother's milk in small quantities. If the use of this drug is deemed necessary, the benefit of breast feeding for the child should be weighed against the possible risk for the child.

Paediatric use

Please refer DOSAGE AND ADMINISTRATION.

Geriatric Use

No dosage adjustment is required based on age. Dosage adjustment in the case of renal impairment is necessary.

Undesirable Effects

Adults

Imipenem/cilastatin is generally well tolerated.
Local Adverse Reactions
Adverse local clinical reactions that were reported as possibly, probably or definitely related to therapy with imipenem-cilastatin I.V. for injection were as follows:

Phlebitis/thrombophlebitis - 3.1%
Pain at the injection site - 0.7%
Erythema at the injection site - 0.4%
Vein induration - 0.2%
Infused vein infection - 0.1%

Systemic Adverse Reactions
The most frequently reported systemic adverse clinical reactions that were reported as possibly, probably or definitely related to imipenem-cilastatin I.V. for injection were nausea (2.0%), diarrhoea (1.8%), vomiting (1.5%), rash (0.9%), fever (0.5%), hypotension (0.4%), seizures (0.4%), dizziness (0.3%), pruritus (0.3%), urticaria (0.2%), and somnolence (0.2%). Rarely, incidences of anaphylactic reactions have also been reported.

Other Adverse Reactions
The other adverse events reported as possibly, probably or definitely drug-related occurring in less than 0.2% patients included the following:

Gastrointestinal
Pseudomembranous colitis, haemorrhagic colitis, hepatitis (including fulminant hepatitis), hepatic failure, jaundice, gastroenteritis, abdominal pain, glossitis, tongue papillar hypertrophy, staining of teeth and/or tongue, heartburn, pharyngeal pain and increased salivation.

Blood and Lymphatic System
Pancytopenia, eosinophilia, bone marrow depression, thrombocytopenia, neutropenia, leucopenia, thrombocytosis and haemolytic anaemia.

Central Nervous System
Encephalopathy, tremor, confusion, myoclonus, paresthesia, vertigo, headache and psychic disturbances, including hallucinations. Very rarely, aggravation of myasthenia gravis has also been reported.

Special Senses
Hearing loss, tinnitus and taste perversion.

Respiratory Tract
Chest discomfort, dyspnoea, hyperventilation and thoracic spine pain.

Cardiovascular
Palpitations and tachycardia.

Skin-related
Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, anginoneurotic oedema, flushing, cyanosis, hyperacidosisis, skin texture changes, candidiasis and pruritus vulvae.

Renal
Acute renal failure, oliguria/anuria, polyuria and urine discolouration.
The role of imipenem-cilastatin I.V. for injection in changes in renal function is difficult to assess, since factors predisposing to pre-renal azotaemia or to impaired renal function usually have been present.

Others
Polyarthralgia, flushing, asthenia/weakness and drug fever.

Adverse Laboratory Changes
The adverse laboratory changes without regard to drug relationship that were reported during clinical trials or postmarketing surveillance included the following:
Hepatic
Increased serum transaminases, alkaline phosphatase, bilirubin and LDH.

Haematological
Increased eosinophils, lymphocytes, positive Coombs test, WBC, platelets, monocytes and basophils, decreased haemoglobin and haematocrit, and agranulocytosis. There are also reports of abnormal prothrombin time.

Electrolytes
Decreased serum sodium, increased potassium and increased chloride.

Renal
Increased BUN and creatinine.

Urinalysis
Presence of urine protein, urine red blood cells, urine WBCs, urine casts, urine bilirubin and urine urobilinogen.

Paediatrics
In studies of 178 paediatric patients, ≥3 months of age, the following adverse events were noted:

Table 5: Most common clinical adverse experiences without regard to drug relationship (Patient Incidence >1%)

| Adverse Experience | No. of Patients (%)
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Digestive System</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>7* (3.9)</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2* (1.1)</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>4 (2.2)</td>
</tr>
<tr>
<td>Irritation, I.V. site</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Urogenital System</td>
<td></td>
</tr>
<tr>
<td>Urine discolouration</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Cardiovascular System</td>
<td></td>
</tr>
<tr>
<td>Phlebitis</td>
<td>4 (2.2)</td>
</tr>
</tbody>
</table>

*One patient had both vomiting and diarrhoea and is counted in each category.
In studies of 135 patients (newborn to 3 months of age), the following adverse events were noted:

Table 6: The most common clinical adverse experiences without regard to drug relationship (Patient Incidence >1%)

| Adverse Experience | No. of Patients (%)
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Digestive System</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea Oral</td>
<td>4 (3.0%)</td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td>2 (1.5%)</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>2 (1.5%)</td>
</tr>
<tr>
<td>Urogenital System</td>
<td></td>
</tr>
<tr>
<td>Oliguria/anuria</td>
<td>3 (2.2%)</td>
</tr>
<tr>
<td>Cardiovascular System</td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>2 (1.5%)</td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
</tr>
<tr>
<td>Convulsions</td>
<td>8 (5.9%)</td>
</tr>
</tbody>
</table>

Table 7: Patients (≥3 months of age) with normal pre-therapy but abnormal during therapy laboratory values

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Abnormality</th>
<th>No. of Patients with Abnormalities/No. of Patients with Lab Done (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory Parameter</td>
<td>No. of Patients with Abnormalities* (%)</td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>---------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Eosinophil count ↑</td>
<td>11 (9.0%)</td>
<td></td>
</tr>
<tr>
<td>Haematocrit ↓</td>
<td>3 (2.0%)</td>
<td></td>
</tr>
<tr>
<td>Haematocrit ↑</td>
<td>1 (1.0%)</td>
<td></td>
</tr>
<tr>
<td>Platelet count ↑</td>
<td>5 (4.0%)</td>
<td></td>
</tr>
<tr>
<td>Platelet count ↓</td>
<td>2 (2.0%)</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine ↑</td>
<td>5 (5.0%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 8: Patients (<3 months of age) with normal pre-therapy but abnormal during therapy laboratory values
Bilirubin↑ 3 (3.0%)
Bilirubin↓ 1 (1.0%)
1 (1.0%) 5 (6.0%)
ALT (SGPT)↑ 3 (3.0%)
Serum alkaline phosphate↑ 2 (3.0%)

* The denominator used for percentages was the number of patients for whom the test was performed during treatment or post-treatment and, therefore, varies by test.

Examination of published literature and spontaneous adverse event reports suggested a similar spectrum of adverse events in adult and paediatric patients.

### Overdosage

Symptoms of overdose that can occur are consistent with the adverse reaction profile; these may include seizures, confusion, tremors, nausea, vomiting, hypotension, bradycardia. In case of overdose, discontinue imipenem/cilastatin, treat symptomatically and institute supportive measures as required. Imipenem-cilastatin I.V. for injection is haemodialysable. However, the usefulness of this procedure in the overdosage setting is questionable.

### Incompatibility

IMICRIT I.V. should not be mixed with or physically added to other antibiotics. However, IMICRIT I.V. may be administered concomitantly with other antibiotics, such as aminoglycosides. This medicinal product is chemically incompatible with lactate and should not be reconstituted in diluents containing lactate. However, it can be administered into an I.V. system through which a lactate solution is being infused.

### Storage And Handling Instructions

The dry powder should be stored below 25°C (77°F). Do not expose to temperatures above 50°C.

### Packaging Information

IMICRIT I.V. 250 mg: Vial of 20 mL
IMICRIT I.V. 500 mg: Vial of 30 mL
IMICRIT I.V. 1 g: Vial of 30 mL

Last reviewed: October 2013
Last updated: October 2013

**IMICRIT I.V. Injection**

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