HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Imipenem and Cilastatin for Injection, USP (I.V.) safely and effectively. See full prescribing information for Imipenem and Cilastatin for Injection, USP (I.V.).

IMIPENEM AND CILASTATIN FOR INJECTION, USP, for intravenous use
Initial U.S. Approval: 1985

---------- RECENT MAJOR CHANGES ----------

Dosage and Administration (2.5) 08/2018

----------INDICATIONS AND USAGE----------

Imipenem and Cilastatin for Injection, USP for intravenous use is a combination of imipenem, a penem antibacterial, and cilastatin, a renal dehydropeptidase inhibitor, indicated for the treatment of the following serious infections caused by designated susceptible bacteria:

- Lower respiratory tract infections. (1.1)
- Urinary tract infections. (1.2)
- Intra-abdominal infections. (1.3)
- Gynecologic infections. (1.4)
- Bacterial septicemia. (1.5)
- Bone and joint infections. (1.6)
- Skin and skin structure infections. (1.7)
- Endocarditis. (1.8)

Limitations of Use:

- Imipenem and Cilastatin for Injection, USP (I.V.) is not indicated in patients with meningitis because safety and efficacy have not been established (1.9).
- Imipenem and Cilastatin for Injection, USP (I.V.) is not recommended in pediatric patients with CNS infections because of the risk of seizures (1.9).
- Imipenem and Cilastatin for Injection, USP (I.V.) is not recommended in pediatric patients weighing less than 30 kg with impaired renal function (1.9).

Usage:
To reduce the development of drug resistant bacteria and maintain the effectiveness of Imipenem and Cilastatin for Injection, USP (I.V.) and other antibacterial drugs, Imipenem and Cilastatin for Injection, USP (I.V.) should be used only to treat infections that are proven or strongly suspected to be caused by bacteria (1.10).

----------DOSAGE AND ADMINISTRATION----------

- The dosage of Imipenem and Cilastatin for Injection (I.V.) in adult patients should be based on suspected or confirmed pathogen susceptibility (2.1).
- For adult patients with normal renal function (creatinine clearance of greater than or equal to 90 mL/min), the recommended dosage regimens are: 500 mg every 6 hours OR 1,000 mg every 8 hours OR 1,000 mg every 6 hours (2.1).
- See full prescribing information for dosage recommendations in pediatric patients (2.2).
- A reduction in dose must be made for a patient with a creatinine clearance of less than 90 mL/min (2.3).
- Patients with creatinine clearances of less than 15 mL/min should not receive Imipenem and Cilastatin for Injection (I.V.) unless hemodialysis is instituted within 48 hours (2.4).
- Reconstitute Imipenem and Cilastatin for Injection, USP (I.V.) vial with appropriate diluent and dilute the reconstituted suspension with an appropriate infusion solution before administering by intravenous infusion (2.5).

----------DOSAGE FORMS AND STRENGTHS----------

For Injection: Imipenem and Cilastatin for Injection (I.V.) is a sterile powder mixture for reconstitution in single-dose vials containing:

- 250 mg imipenem (anhydrous equivalent) and 250 mg cilastatin sodium (3)
- 500 mg imipenem (anhydrous equivalent) and 500 mg cilastatin sodium (3)

----------CONTRAINDICATIONS----------

- Known hypersensitivity to any component of Imipenem and Cilastatin for Injection (I.V.) (4)

----------WARNINGS AND PRECAUTIONS ----------

- *Hypersensitivity Reactions:* Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with beta-lactams. If an allergic reaction to Imipenem and Cilastatin for Injection (I.V.) occurs, discontinue the drug immediately (5.1).
- *Seizure Potential:* Seizures and other CNS adverse reactions, such as confusional states and myoclonic activity, have been reported during treatment with Imipenem and Cilastatin for Injection (I.V.). 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 and Cilastatin for Injection (I.V.) re-examined to determine whether it should be decreased or the antibacterial drug discontinued (5.2).
- *Increased Seizure Potential Due to Interaction with Valproic Acid:* Co-administration of Imipenem and Cilastatin for Injection (I.V.), 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. The concomitant use of Imipenem and Cilastatin for Injection (I.V.) and valproic acid/divalproex sodium is generally not recommended (5.3, 7.3).
- *Clostridium difficile-Associated Diarrhea (CDAD):* has been reported with use of Imipenem and Cilastatin for Injection (I.V.) and may range in severity from mild diarrhea to fatal colitis. Evaluate if diarrhea occurs (5.4).

----------ADVERSE REACTIONS----------

- The most frequently occurring adverse reactions (≥ 0.2%) in adults were phlebitis, nausea, diarrhea, vomiting, rash, pain injection site, fever, hypotension, seizures, erythema at injection site, dizziness, pruritus, vein induration, urticaria, somnolence (6.1).
- The most frequently occurring adverse reactions (> 1%) in pediatric patients greater than or equal to 3 months of age were diarrhea, rash, phlebitis, gastroenteritis, vomiting, IV site irritation, urine discoloration (6.1).
- The most frequently occurring adverse reactions (> 1%) in neonates to 3 months of age were convulsions, diarrhea, oliguria/anuria, oral candidiasis, rash, tachycardia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC at 1-800-551-7176 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Ganciclovir: Generalized seizures have been reported in patients who received ganciclovir. Do not co-administer unless benefit outweighs risk (7.1).
- Probenecid: Concomitant administration of Imipenem and Cilastatin for Injection (I.V.) and probenecid results in increases in the plasma level and half-life of imipenem. Concomitant administration is not recommended (7.2).
- Valproic acid/divalproex sodium: Concomitant use with Imipenem and Cilastatin for Injection (I.V.) is generally not recommended. Consider other antibacterial drugs to treat infections in patients whose seizures are well-controlled on valproic acid or divalproex sodium (5.3, 7.3).

----------USE IN SPECIFIC POPULATIONS----------

- Renal Impairment: Dosage adjustment is necessary in patients with renal impairment (2.3).
  - Adult patients with creatinine clearances of less than or equal to 30 mL/min, whether or not undergoing hemodialysis, had a higher risk of seizure activity than those without impairment of renal function (5.2).
  - Therefore, close adherence to the dosing guidelines and regular monitoring of creatinine clearance for these patients is recommended (8.6).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 8/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Lower Respiratory Tract Infections
Imipenem and Cilastatin for Injection, USP (I.V.) for intravenous use is indicated for the treatment of lower respiratory tract infections caused by susceptible strains of *Staphylococcus aureus* (penicillinase-producing isolates), *Acinetobacter* species, *Enterobacter* species, *Escherichia coli*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Klebsiella* species, *Serratia marcescens*.

1.2 Urinary Tract Infections (complicated and uncomplicated)
Imipenem and Cilastatin for Injection, USP (I.V.) is indicated for the treatment of urinary tract infections (complicated and uncomplicated) caused by susceptible strains of *Enterococcus faecalis*, *Staphylococcus aureus* (penicillinase-producing isolates), *Enterobacter* species, *Escherichia coli*, *Klebsiella* species, *Morganella morganii*, *Proteus vulgaris*, *Providencia rettgeri*, *Pseudomonas aeruginosa*.

1.3 Intra-Abdominal Infections
Imipenem and Cilastatin for Injection, USP (I.V.) is indicated for the treatment of intra-abdominal infections caused by susceptible strains of *Enterococcus faecalis*, *Staphylococcus aureus* (penicillinase-producing isolates), *Staphylococcus epidermidis*, *Citrobacter* species, *Enterobacter* species, *Escherichia coli*, *Klebsiella* species, *Morganella morganii*, *Proteus* species, *Pseudomonas aeruginosa*, *Bifidobacterium* species, *Clostridium* species, *Eubacterium* species, *Peptococcus* species, *Peptostreptococcus* species, *Propionibacterium* species, *Bacteroides* species including *B. fragilis*, *Fusobacterium* species.

1.4 Gynecologic Infections
Imipenem and Cilastatin for Injection, USP (I.V.) is indicated for the treatment of gynecologic infections caused by susceptible strains of *Enterococcus faecalis*, *Staphylococcus aureus* (penicillinase-producing isolates), *Staphylococcus epidermidis*, *Streptococcus agalactiae* (Group B streptococci), *Enterobacter* species, *Escherichia coli*, *Gardnerella vaginalis*, *Klebsiella* species, *Proteus* species, *Bifidobacterium* species, *Peptococcus* species, *Peptostreptococcus* species, *Propionibacterium* species, *Bacteroides* species including *B. fragilis*.

1.5 Bacterial Septicemia
Imipenem and Cilastatin for Injection, USP (I.V.) is indicated for the treatment of bacterial septicemia caused by susceptible strains of *Enterococcus faecalis*, *Staphylococcus aureus* (penicillinase-producing isolates), *Enterobacter* species, *Escherichia coli*, *Klebsiella* species, *Pseudomonas aeruginosa*, *Serratia* species, *Bacteroides* species including *B. fragilis*.

1.6 Bone and Joint Infections
Imipenem and Cilastatin for Injection, USP (I.V.) is indicated for the treatment of bone and joint infections caused by susceptible strains of *Enterococcus faecalis*, *Staphylococcus aureus* (penicillinase-producing isolates), *Staphylococcus epidermidis*, *Enterobacter* species, *Pseudomonas aeruginosa*.

1.7 Skin and Skin Structure Infections
Imipenem and Cilastatin for Injection, USP (I.V.) is indicated for the treatment of skin and skin structure infections caused by susceptible strains of *Enterococcus faecalis*, *Staphylococcus aureus* (penicillinase-producing isolates), *Staphylococcus epidermidis*, *Acinetobacter* species, *Citrobacter* species, *Enterobacter* species, *Escherichia coli*, *Klebsiella* species, *Morganella morganii*, *Proteus vulgaris*, *Providencia rettgeri*, *Pseudomonas aeruginosa*, *Serratia* species, *Peptococcus* species, *Peptostreptococcus* species, *Bacteroides* species including *B. fragilis*, *Fusobacterium* species.

1.8 Endocarditis
Imipenem and Cilastatin for Injection, USP (I.V.) is indicated for the treatment of endocarditis caused by susceptible strains of *Staphylococcus aureus* (penicillinase-producing isolates).

1.9 Limitations of Use
- Imipenem and Cilastatin for Injection, USP (I.V.) is not indicated in patients with meningitis because safety and efficacy have not been established.
- Imipenem and Cilastatin for Injection, USP (I.V.) is not recommended in pediatric patients with CNS infections because of the risk of seizures *[see Dosage and Administration (2.2), Warnings and Precautions (5.2), and Use in Specific Populations (8.4)]*.
- Imipenem and Cilastatin for Injection, USP (I.V.) is not recommended in pediatric patients less than 30 kg with impaired renal function, as no data are available *[see Use in Specific Populations (8.4), and Dosage and Administration (2.2)]*.
- Periodic assessment of organ system functions, including renal, hepatic and hematopoietic, is advisable during prolonged therapy.

1.10 Usage
To reduce the development of drug-resistant bacteria and maintain the effectiveness of Imipenem and Cilastatin for Injection, USP (I.V.) and other antibacterial drugs, Imipenem and Cilastatin for Injection, USP (I.V.) 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.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in Adults
For Intravenous Injection Only

- The dosage of Imipenem and Cilastatin for Injection (I.V.) in adult patients should be based on suspected or confirmed pathogen susceptibility as shown in Table 1 below. The dosage recommendations for Imipenem and Cilastatin for Injection (I.V.) represent the quantity of imipenem to be administered. An equivalent amount of cilastatin is also present in the solution.
- These doses should be used for patients with creatinine clearance of greater than or equal to 90 mL/min. A reduction in dose must be made for patients with creatinine clearance less than 90 mL/min as shown in Table 3 *[see Dosage and Administration (2.3)]*.
- Recommend that the maximum total daily dosage not exceed 4 g/day.
- Administer 500 mg by intravenous infusion over 20 to 30 minutes.
- Administer 1,000 mg by intravenous infusion over 40 to 60 minutes.
- In patients who develop nausea during the infusion, the rate of infusion may be slowed.

Table 1: Dosage of Imipenem and Cilastatin for Injection (I.V.) in Adult Patients with Creatinine Clearance Greater than or Equal to 90 mL/min

Suspected or Proven Pathogen Susceptibility	Dosage of Imipenem and Cilastatin for Injection (I.V.)
If the infection is suspected or proven to be due to a susceptible bacterial species	500 mg every 6 hours OR 1,000 mg every 8 hours
If the infection is suspected or proven to be due to bacterial species with intermediate susceptibility *[see Microbiology (12.4)]*	1,000 mg every 6 hours

2.2 Dosage in Pediatric Patients
Imipenem and Cilastatin for Injection (I.V.) is not recommended in pediatric patients with CNS infections because of the risk of seizures *[see Use in Specific Populations (8.4)]*.

Imipenem and Cilastatin for Injection (I.V.) is not recommended in pediatric patients < 30 kg with renal impairment, as no data are available *[see Use in Specific Populations (8.4)]*.

Based on studies in adults, the maximum total daily dose in pediatric patients should not exceed 4 g/day *[see Dosage and Administration (2.1)]*.

The recommended dosage for pediatric patients with non-CNS infections is shown in Table 2 below:

Table 2: Recommended Imipenem and Cilastatin for Injection (I.V.) Dosage in Pediatric Patients for Non-CNS Infections

Age	Dose (mg/kg) *,†	Frequency (hours)
Greater than or equal to 3 Months of Age		
	15-25 mg/kg	Every 6 hours
Less than or equal to 3 months of age (Greater than or equal to 1,500 g body weight)		
4 weeks to 3 months of age	25 mg/kg	Every 6 hours
1 to 4 weeks of age	25 mg/kg	Every 8 hours
Less than 1 week of age	25 mg/kg	Every 12 hours

* Doses less than or equal to 500 mg should be given by intravenous infusion over 20 to 30 minutes
† Doses greater than 500 mg should be given by intravenous infusion over 40 to 60 minutes
Recommend that the maximum total daily dosage not exceed 4 g/day

2.3 Dosage in Adult Patients with Renal Impairment
Patients with creatinine clearance less than 90 mL/min require dosage reduction of Imipenem and Cilastatin for Injection (I.V.) as indicated in Table 3. The serum creatinine should represent a steady state of renal function. Use the Cockroft-Gault method described below to calculate the creatinine clearance:

$$\text{Males: } \frac{\text{(weight in kg) x (140-age in years)}}{\text{(72) x serum creatinine (mg/100 mL)}}$$

Females: (0.85) x (value calculated for males)

Table 3: Dosage of Imipenem and Cilastatin for Injection (I.V.) for Adult Patients in Various Renal Function Groups Based on Estimated Creatinine Clearance (CLcr)

	Creatinine clearance (mL/min)			
	Greater than or equal to 90	**Less than 90 to greater than or equal to 60**	**Less than 60 to greater than or equal to 30**	**Less than 30 to greater than or equal to 15**
Dosage of Imipenem and Cilastatin for Injection (I.V.)*,† If the infection is suspected or proven to be due to a susceptible bacterial species:	500 mg every 6 hours	400 mg every 6 hours	300 mg every 6 hours	200 mg every 6 hours
	OR			
	1,000 mg every 8 hours	500 mg every 6 hours	500 mg every 8 hours	500 mg every 12 hours
Dosage of Imipenem and Cilastatin for Injection (I.V.)*,† If the infection is suspected or proven to be due to bacterial species with intermediate susceptibility *[see Microbiology (12.4)]*:	1,000 mg every 6 hours	750 mg every 8 hours	500 mg every 6 hours	500 mg every 12 hours

* Administer doses less than or equal to 500 mg by intravenous infusion over 20 to 30 minutes.
† Administer doses greater than 500 mg by intravenous infusion over 40 to 60 minutes. In patients who develop nausea during the infusion, the rate of infusion may be slowed

In patients with creatinine clearances of less than 30 to greater than or equal to 15 mL/min, there may be an increased risk of seizures *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.6)]*. Patients with creatinine clearance less than 15 mL/min should not receive Imipenem and Cilastatin for Injection (I.V.) unless hemodialysis is instituted within 48 hours. There is inadequate information to recommend usage of Imipenem and Cilastatin for Injection (I.V.) for patients undergoing peritoneal dialysis.

2.4 Dosage in Hemodialysis Patients
When treating patients with creatinine clearances of less than 15 mL/min who are undergoing hemodialysis, use the dosage recommendations for patients with creatinine clearances of less than 30 to greater than or equal to 15 mL/min in Table 3 above *[see Dosage and Administration (2.3)]*. Both imipenem and cilastatin are cleared from the circulation during hemodialysis. The patient should receive Imipenem and Cilastatin for Injection (I.V.) after hemodialysis and at intervals timed from the end of that hemodialysis session. Dialysis patients, especially those with background CNS disease, should be carefully monitored; for patients on hemodialysis, Imipenem and Cilastatin for Injection (I.V.) is recommended only when the benefit outweighs the potential risk of seizures *[see Warnings and Precautions (5.2)]*.

2.5 Reconstitution and Preparation of Imipenem and Cilastatin for Injection (I.V.) Solution for Intravenous Administration
Imipenem and Cilastatin for Injection (I.V.) Vials

- Do not use diluents containing benzyl alcohol to reconstitute Imipenem and Cilastatin for Injection (I.V.) for administration to neonates because it has been associated with toxicity in neonates. While toxicity has not been demonstrated in pediatric patients greater than three months of age, small pediatric patients in this age range may also be at risk for benzyl alcohol toxicity.
- Contents of the vials must be reconstituted by adding approximately 10 mL of the appropriate diluent to the vial. List of appropriate diluents are as follows:
  - 0.9% Sodium Chloride Injection
  - 5% Dextrose Injection
  - 5% Dextrose and 0.9% Sodium Chloride Injection
  - 5% Dextrose Injection with 0.225% or 0.45% saline solution
- Reconstituted Solutions of Imipenem and Cilastatin for Injection (I.V.) range from colorless to yellow. Variations of color within this range do not affect the potency of the product.
- The reconstituted suspension must not be administered by direct Intravenous Infusion.
- After reconstitution, shake vial well and transfer the resulting suspension to 100 mL of an appropriate infusion solution before administering by intravenous infusion.
- Repeat transfer of the resulting suspension with an additional 10 mL of infusion solution to ensure complete transfer of vial contents to the infusion solution. Agitate the resulting mixture until clear.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
- Discard unused portion.

2.6 Storage of Reconstituted Solutions
Vials (After Reconstitution)

- Imipenem and Cilastatin for Injection (I.V.), as supplied in single dose vials and reconstituted with the appropriate diluents *[see Dosage and Administration (2.5)]*, maintains satisfactory potency for 4 hours at room temperature or for 24 hours under refrigeration (5°C). Do not freeze solutions of Imipenem and Cilastatin for Injection (I.V.).

2.7 Incompatibility and Compatibility of Imipenem and Cilastatin for Injection (I.V.) with other Antibacterial Drugs
- Do not mix Imipenem and Cilastatin for Injection (I.V.) with, or physically add to, other antibacterial drugs
- Imipenem and Cilastatin for Injection (I.V.) may be administered concomitantly with other antibacterial drugs, such as aminoglycosides.

3 DOSAGE FORMS AND STRENGTHS
For Injection Imipenem and Cilastatin for Injection (I.V.) is a sterile powder mixture for reconstitution in single-dose vials containing:

- 250 mg imipenem (anhydrous equivalent) and 250 mg cilastatin sodium
- 500 mg imipenem (anhydrous equivalent) and 500 mg cilastatin sodium

4 CONTRAINDICATIONS
Imipenem and Cilastatin for Injection (I.V.) is contraindicated in patients who have shown hypersensitivity to any component of this product.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions
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 Imipenem and Cilastatin for Injection (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 Imipenem and Cilastatin for Injection (I.V.) occurs, discontinue the drug immediately. Serious anaphylactic reactions require immediate emergency treatment as clinically indicated.

5.2 Seizure Potential
Seizures and other CNS adverse experiences, such as confusional states and myoclonic activity, have been reported during treatment with Imipenem and Cilastatin for Injection (I.V.), especially when recommended dosages were exceeded *[see Adverse Reactions (6.1, 6.2)]*. These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function *[see Use in Specific Populations (8.6)]*. However, there have been reports of CNS adverse experiences in patients who had no recognized or documented underlying CNS disorder or compromised renal function.

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 and Cilastatin for Injection (I.V.) re-examined to determine whether it should be decreased or the antibacterial drug discontinued.

5.3 Increased Seizure Potential Due to Interaction with Valproic Acid
Case reports in the literature have shown that co-administration of carbapenems, including Imipenem and Cilastatin for Injection (I.V.), 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 Imipenem and Cilastatin for Injection (I.V.) and valproic acid/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 Imipenem and Cilastatin for Injection (I.V.) is necessary, supplemental anti-convulsant therapy should be considered *[see Drug Interactions (7.3)]*. Close adherence to the recommended dosage and dosage schedules is urged, especially in patients with known factors that predispose to convulsive activity.

5.4 *Clostridium difficile*-Associated Diarrhea (CDAD)
Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Imipenem and Cilastatin for Injection (I.V.), and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD.

Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial drug use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial drug use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial drug treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.

5.5 Development of Drug-Resistant Bacteria
As with other antibacterial drugs, prolonged use of Imipenem and Cilastatin for Injection (I.V.) 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 and Cilastatin for Injection (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.

6 ADVERSE REACTIONS
The following serious adverse reactions are described in greater detail in the Warnings and Precautions section.

- Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*
- Seizure Potential *[see Warnings and Precautions (5.2)]*
- Increased Seizure Potential Due to Interaction with Valproic Acid *[see Warnings and Precautions (5.3)]*
- *Clostridium difficile*-Associated Diarrhea (CDAD) *[see Warnings and Precautions (5.4)]*
- Development of Drug-Resistant Bacteria *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adult Patients
During clinical investigations 1,723 patients were treated with Imipenem and Cilastatin for Injection (I.V.). Table 4 shows the incidence of adverse reactions reported during the clinical investigations of adult patients treated with Imipenem and Cilastatin for Injection (I.V.).

Table 4: Incidence (%)* of Adverse Reactions Reported During Clinical Investigations of Adult Patients Treated with Imipenem and Cilastatin for Injection (I.V.)

Body System	Adverse Reactions	Frequency (%)
Local Administration site	Phlebitis/ thrombophlebitis	3.1%
	Pain at the injection site	0.7%
	Erythema at the injection site	0.4%
	Vein induration	0.2%
Gastrointestinal	Nausea	2%
	Diarrhea	1.8%
	Vomiting	1.5%
Skin	Rash	0.9%
	Pruritus	0.3%
	Urticaria	0.2%
Vascular	Hypotension	0.4%
Body as a Whole	Fever	0.5%
Nervous system	Seizures	0.4%
	Dizziness	0.3%
	Somnolence	0.2%

* Adverse reactions with an incidence ≥ 0.2% of Imipenem and Cilastatin for Injection (I.V.) -treated adult patients.

Additional adverse reactions reported in less than 0.2% of the patients or reported since the drug was marketed are listed within each body system in order of decreasing severity *[see Table 5]*.

Table 5: Additional Adverse Reactions Occurring in Less than 0.2% of Adult Patients Listed within Each Body System in Order of Decreasing Severity

Body System	Adverse Reactions
Gastrointestinal	Pseudomembranous Colitis (the onset of Pseudomembranous colitis symptoms), Hemorrhagic Colitis
	Gastroenteritis
	Abdominal Pain
	Glossitis
	Tongue Papillar
	Hypertrophy
	Heartburn
	Pharyngeal Pain
	Increased Salivation
CNS	Encephalopathy
	Confusion
	Myoclonus
	Paresthesia
	Vertigo
	Headache
Special Senses	Hearing Loss
	Tinnitus
Respiratory	Chest Discomfort
	Dyspnea
	Hyperventilation
	Thoracic Spine Pain
Cardiovascular	Palpitations
	Tachycardia
Skin	Erythema Multiforme
	Angioneurotic Edema
	Flushing
	Cyanosis
	Hyperhidrosis
	Skin Texture Changes
	Candidiasis
	Pruritus Vulvae
Local Administration site	Infused vein infection
Body as a Whole	Polyarthralgia
	Asthenia/Weakness
Renal	Oliguria/Anuria
	Polyuria

Adverse Laboratory Changes
The following adverse laboratory changes were reported during clinical trials:
Hepatic: Increased alanine aminotransferase (ALT or SGPT), aspartate aminotransferase (AST or SGOT), alkaline phosphatase, bilirubin, and lactate dehydrogenase (LDH)
Hemic: Increased eosinophils, positive Coombs test, increased WBC, increased platelets, decreased hemoglobin and hematocrit, increased monocytes, abnormal prothrombin time, increased lymphocytes, increased basophils
Electrolytes: Decreased serum sodium, increased potassium, increased chloride
Renal: Increased BUN, creatinine
Urinalysis: Presence of urine protein, urine red blood cells, urine white blood cells, urine casts, urine bilirubin, and urine urobilinogen.

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IMIPENEM AND CILASTATIN
FOR INJECTION, USP (I.V.)

IMIPENEM AND CILASTATIN
FOR INJECTION, USP (I.V.)

451205G/Revised: August 2020

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