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

RECENT MAJOR CHANGES -Dosage and Administration (2.5)

-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:

08/2018

- 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)

 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 recomended 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).

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

----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

 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 Iminenem 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 rritation, 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
- 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: April 2019

FULL PRESCRIBING INFORMATION: CONTENTS*

administering by intravenous infusion (2.5)

INDICATIONS AND USAGE Lower Respiratory Tract Infections

- Urinary Tract Infections (complicated and uncomplicated)
- Intra-Abdominal Infections **Gynecologic Infections**
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- Bone and Joint Infections
- Skin and Skin Structure Infections Endocarditis
- Limitations of Use
- 2 DOSAGE AND ADMINISTRATION
- Dosage in Adults
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CONTRAINDICATIONS

- WARNINGS AND PRECAUTIONS
- Hypersensitivity Reactions
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- Increased Seizure Potential Due to Interaction with Valproic Acid
- Clostridium difficile-Associated Diarrhea (CDAD)
- Development of Drug-Resistant Bacteria

INDICATIONS AND USAGE Lower Respiratory Tract Infections

FULL PRESCRIBING INFORMATION

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 (nenicillinase-producing isolates) Acinetobacter species Enterobacter species Escherichia coli, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella species, Serratia

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,

1.3 Intra-Abdominal Infections

Imipenem and Cilastatin for Injection, USP (I.V.) is indicated for the treatment of intraabdominal 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 pecies, Peptococcus species, Peptostreptococcus species, Propionibacterium species, Bacteroides species including B. fragilis, Fusobacterium species.

1.4 Gynecologic Infections

Imperior and Cilastatin for Injection, USP (LV) 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, Serratía 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,

ADVERSE REACTIONS

- Postmarketing Experience DRUG INTERACTIONS
- Ganciclovir Probenecid

Valproic Acid

- **USE IN SPECIFIC POPULATIONS**
- Pregnancy 8.2 Lactation
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*Sections or subsections omitted from the full prescribing information are not listed.

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.

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).

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,

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.

DOSAGE AND ADMINISTRATION

is advisable during prolonged therapy.

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

spected or Proven Pathogen Susceptibility	Dosage of Imipenem and Cilastatin for Injection (I.V.)
ne infection is suspected or proven to be due to a ceptible bacterial species	500 mg every 6 hours OR 1,000 mg every 8 hours
ne infection is suspected or proven to be due to eterial species with intermediate susceptibility of 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

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

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)					
25 mg/kg	Every 6 hours				
25 mg/kg	Every 8 hours				
Less than 1 week of age 25 mg/kg Every 12 hours					
	15-25 mg/kg ater than or equal 25 mg/kg 25 mg/kg				

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:

(weight in kg) x (140-age in years) (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)

	Greatinine 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	500 mg every 6 hours	400 mg every 6 hours	300 mg every 6 hours	200 mg every 6 hours
infection is suspected		0	R	
or proven to be due to a susceptible bacterial species:	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)7. Patients with creatinine clearance less than 15 mL/min should not receive Imipenem and Cilastatin for Ínjection (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 patie should receive Iminenem and Cilastatin for Injection (LV) 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

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

2.6 Storage of Reconstituted Solutions

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 notency 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.).

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

Imipenem and Cilastatin for Injection (I.V.) may be administered concomitantly with other antibacterial drugs, such as aminoglycosides

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.

WARNINGS AND PRECAUTIONS

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 betalactams 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

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.

ADVERSE REACTIONS

The following serious adverse reactions are described in greater detail in the Warnings and 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

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.

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.).

Adult Patients Treated with Imipenem and Cilastatin for Injection (I.V.)

Dizziness

Somnolence

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%

Table 4: Incidence (%)* of Adverse Reactions Reported During Clinical Investigations of

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

0.3%

0.2%

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

Adverse Reactions

Body System

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			

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

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

Adverse Laboratory Changes

FRESENIUS KABI

451205F/Revised: April 2019

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 urobilinogei

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Cilastatin for Injection (I.V.)			
Body System	Adverse Reactions	Frequency (%)	
Local Administration Site	Phlebitis	2.2%	
	Intravenous Site Irritation	1.1%	
Gastrointestinal	Diarrhea	3.9%	
	Gastroenteritis	1.1%	
	Vomiting	1.1%	
Skin	Rash	2.2%	
Renal	Urine Discoloration	1.1%	

pediatric patients (greater than or equal to 3 months of age)

Table 7: Incidence (%)* of Adverse Reactions Reported During Clinical Investigations of Pediatric Patients Neonates to 3 Months of Age Treated with Imipenem and Cilastatin for Injection (LV)

Adverse reactions that occurred in > 1 % of Imipenem and Cilastatin for Injection (I.V.)-treated

injection (i.v.)			
Body System	Adverse Reactions	Frequency (%)	
Gastrointestinal	Diarrhea	3%	
CNS	Convulsions	5.9%	
Cardiovascular	Tachycardia	1.5%	
Skin	Rash	1.5%	
Body as a Whole	Oral Candidiasis	1.5%	
Renal	Oliguria/Anuria	2.2%	

 * Adverse reactions that occurred in > 1 % of Imipenem and Cilastatin for Injection (I.V.)-treated pediatric patients (neonates to 3 months of age)

Adverse Laboratory Changes

The following adverse laboratory changes were reported in studies of 178 pediatric patients 3 months of age: increased AST (SGOT), decreased hemoglobin/hematocrit, increased platelets, increased eosinophils, increased ALT (SGPT), increased urine protein, decreased neutrophils.

The following adverse laboratory changes were reported in studies of 135 patients (neonates to 3 months of age): increased eosinophils, increased AST (SGPT), increased serum creatinine. increased/decreased platelet count, increased/decreased bilirubin, increased ALT (SGPT), increased alkaline phosphatase, increased/decreased hematocrit.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Imipenem and Cilastatin for Injection (I.V.). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal

Table 8: Adverse Reactions Identified During Post Approval Use of Imipenem and

Body System	Adverse Reactions
Gastrointestinal	Hepatitis (including fulminant hepatitis)
	Hepatic failure
	Jaundice
	Staining of the teeth and/or tongue
Hematologic	Pancytopenia
	Bone marrow depression
	Thrombocytopenia
	Neutropenia
	Leukopenia
	Hemolytic anemia
CNS	Tremor
	Psychic disturbances including hallucinations
	Dyskinesia
	Agitation
Special Senses	Taste perversion
Skin	Stevens-Johnson syndrome
	Toxic epidermal necrolysis
Body as a whole	Drug fever
Renal	Acute renal failure
	Urine discoloration

Adverse Laboratory Changes

Adverse laboratory changes reported since the drug was marketed were: *Hematologic:* agranulocytosis.

Examination of published literature and spontaneous adverse reactions reports suggested a similar spectrum of adverse reactions in adult and pediatric patients.

DRUG INTERACTIONS

7.1 Ganciclovir

Generalized seizures have been reported in patients who received ganciclovir and Imipenem and Cilastatin for Injection (I.V.). These drugs should not be used concomitantly with Imipenem and Cilastatin for Injection (I.V.) unless the potential benefits outweigh the risks.

Concomitant administration of Imipenem and Cilastatin for Injection (I.V.) and probenecid results in increases in the plasma level and half-life of imipenem. Therefore, it is not recommended that probenecid be given concomitantly with Imipenem and Cilastatin for Injection (I.V.).

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. Although the mechanism of this interaction is unknown, data from *in* vitro and animal studies suggest that carbapenems may inhibit the hydrolysis of valproic acid's glucuronide metabolite (VPA-g) back to valproic acid, thus decreasing the serum concentrations of valproic acid [see Warnings and Precautions (5.3)]. 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.

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Available data from a small number of postmarketing cases with Imipenem and Cilastatin for Injection (I.V.) use in pregnancy are not sufficient to identify any drug-associated risks for major birth defects, miscarriage, or adverse maternal or fetal outcomes.

Developmental toxicity studies with imipenem and cilastatin sodium (alone or in combination) administered to mice, rats, rabbits, and monkeys at doses 0.4 to 2.9 times the recommended human dose (RHD), (based on body surface area), showed no drug-induced fetal malformations.

Embryofetal development studies with imipenem/cilastatin administered to cynomolgus monkeys at doses similar to the RHD (based on body surface area) showed an increase in

The background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies within the general population.

Animal Data

Reproductive toxicity studies with imipenem and cilastatin (alone or in combination) administered to mice, rats, and rabbits showed no evidence of effects on embryofetal (mice, rats and rabbits) or pre/postnatal (rats) development.

mipenem was administered intravenously to rats (gestation days (GD) 7 to 17) and rabbits (GD 6 to 18) at doses up to 900 and 60 mg/kg/day, respectively, approximately 2.9 and 0.4 times the RHD (based on body surface area

Cilastatin was administered subcutaneously to rats (GD 6 to 17) and intravenously to rabbits (GD 6 to 18) at doses up to 1000 and 300 mg/kg/day, respectively, approximately 3.2 and 1.9 times the RHD (based on body surface area).

ipenem/cilastatin was administered intravenously to mice at doses up to 320 mg/kg/day (GD 6 to 15). In two separate studies, imipenem/cilastatin was administered to rats (GD 6 to 17 and GD 15 to day 21 postpartum) both intravenously at doses up to 80 mg/kg/day and subcutaneously at 320 mg/kg/day. The higher dose is approximately equal to the RHD (based

Imipenem/cilastatin administered intravenously to pregnant cynomolgus monkeys during organogenesis at 100 mg/kg/day, approximately 0.6 times the RHD (based on body surface area), at an infusion rate mimicking human clinical use, was not associated with fetal malformations, but there was an increase in embryonic loss relative to controls. Imipenem/cilastatin administered to pregnant cynomolgus monkeys during organogenesis at 40 mg/kg/day by bolus intravenous injection caused significant maternal toxicity including death and embryofetal loss.

8.2 Lactation Risk Summary

There are insufficient data on the presence of imipenem/cilastatin in human milk, and no data on the effects on the breastfed child, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Imipenem and Cilastatin for Injection (I.V.) and any potential adverse effects on the breastfed child from Imipenem and Cilastatin for Injection (I.V.) or from the underlying maternal condition.

8.4 Pediatric Use

Use of Imipenem and Cilastatin for Injection (I.V.) in pediatric patients is supported by evidence from adequate and well-controlled trials of Imipenem and Cilastatin for Injection (I.V.) in adults and clinical studies in pediatric patients [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)].

nipenem and Cilastatin for Injection (I.V.) is not recommended in pediatric patients with CNS infections because of the risk of seizures.

Imipenem and Cilastatin for Injection (I.V.) is not recommended in pediatric patients less than 30 kg with renal impairment, as no data are available.

Geriatric Use

Of the approximately 3,600 subjects ≥ 18 years of age in clinical studies of Imipenem and Cilastatin for Injection (I.V.), including postmarketing studies, approximately 2,800 received mipenem and Cilastatin for Injection (I.V.). Of the subjects who received Imipenem and Cilastatin for Injection (I.V.), data are available on approximately 800 subjects who were 65 and over, including approximately 300 subjects who were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. 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 dosage adjustment is required based on age [see Clinical Pharmacology (12.3)]. Dosage adjustment in the case of renal impairment is necessary [see Dosage and Administration (2.3)].

Dosage adjustment is necessary in patients with renal impairment [see Dosage and Administration (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 *[see Warnings and Precautions (5.2)]*. Therefore, close adherence to the dosing guidelines and regular monitoring of creatinine clearance for these

In the case of overdosage, discontinue Imipenem and Cilastatin for Injection (I.V.), treat symptomatically, and institute supportive measures as required. Imipenem and Cilastatin for Injection (I.V.) is hemodialyzable.

11 DESCRIPTION

Imipenem and Cilastatin for Injection, USP (I.V.) (imipenem and cilastatin) for Injection is a sterile formulation of imipenem, a penem antibacterial, and cilastatin, a renal dehydropeptida inhibitor with sodium bicarbonate added as a buffer. Imipenem and Cilastatin for Injection, USP (I.V.) is an antibacterial drug for intravenous administration.

Imipenem (N-formimidoylthienamycin monohydrate) is a crystalline derivative of thienamycin, which is produced by $Streptomyces\ cattleya$. Its chemical name is (5R,6S)-3-[[2-(formimidoylamino)ethyl]thio]-6-[(R)-1-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-(formimidoylamino)ethyl]thio]-6-[(R)-1-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-(formimidoylamino)ethyl]thio]-6-[(R)-1-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-(formimidoylamino)ethyl]thio]-6-[(R)-1-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-(formimidoylamino)ethyl]thio]-6-[(R)-1-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-(formimidoylamino)ethyl]thio]-6-[(R)-1-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-(formimidoylamino)ethyl]thio]-6-[(R)-1-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-(formimidoylamino)ethyl]thio]-6-[(R)-1-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-(formimidoylamino)ethyll[formimidoylamino]ethyll[formimidocarboxylic acid monohydrate. It is an off-white, nonhygroscopic crystalline compound with a molecular weight of 317.37. It is sparingly soluble in water and slightly soluble in methanol. Its empirical formula is $C_{12}H_{17}N_3O_4S\bullet H_2O$, and its structural formula is

Cilastatin sodium is the sodium salt of a derivatized heptenoic acid. Its chemical name is sodium (Z)-7[[(R)-2-amino-2-carboxyethyl]thio]-2-[(S)-2,2-dimethylcyclopropanecarboxamido] 2-heptenoate. It is an off-white to yellowish-white, hygroscopic, amorphous compound with a molecular weight of 380.43. It is very soluble in water and in methanol. Its empirical formula is C₁₆H₂₅N₂O₅SNa, and its structural formula is:

Imipenem and Cilastatin for Injection, USP (I.V.) is buffered to provide solutions in the pH range of 6.5 o 8.5. There is no significant change in pH when solutions are prepared and used as directed. [see How Supplied/Storage and Handling (16.1).] Each Imipenem and Cilastatin for Injection, USP (I.V.) 250 mg/250 mg vial contains imipenem USP 250 mg (anhydrous equivalent) and cilastatin sodium USP equivalent to 250 mg cilastatin and each 500 mg/500 mg vial contains imipenem USP 500 mg (anhydrous equivalent) and cilastatin sodium USP equivalent to 500 mg cilastatin. In addition, the 250 mg/250 mg vial contains 10 mg of sodium bicarbonate and the 500 mg/500 mg vial contains 20 mg of sodium bicarbonate. The sodium content of the 250 mg/250 mg vial is 18.8 mg (0.8 mEq) and the sodium content for the 500 mg/500 mg vial is 37.5 mg (1.6 mEq). Solutions of Imipenem and Cilastatin for Injection, USP (I.V.) range from colorless to yellow. Variations of color within this range do not affect the potency of the product.

CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Imipenem and Cilastatin for Injection (I.V.) is a combination of imipenem and cilastatin. Imipenem is a penem antibacterial drug [see Microbiology (12.4)]. Cilastatin sodium is a renal

12.3 Pharmacokinetics

Intravenous infusion of Imipenem and Cilastatin for Injection (I.V.) over 20 minutes results in peak plasma levels of imipenem antimicrobial activity that range from 21 to 58 mcg/mL for the 500 mg dose, and from 41 to 83 mcg/mL for the 1,000 mg dose. At these doses, plasma levels of imipenem antimicrobial activity decline to below 1 mcg/mL or less in 4 to 6 hours. Peak plasma levels of cilastatin following a 20-minute intravenous infusion of Imipenem and Cilastatin for Injection (I.V.) range from 31 to 49 mcg/mL for the 500 mg dose, and from 56 to 88 mcg/mL for the 1,000 mg dose.

The binding of imipenem to human serum proteins is approximately 20% and that of cilastatin is

Imipenem has been shown to penetrate into human tissues, including vitreous humor, aqueous humor, lung, peritoneal fluid, CSF, bone, interstitial fluid, skin, and fascia. As there are no adequate and well-controlled studies of imipenem treatment in these additional body sites, the clinical significance of these tissue concentration data is unknown.

After a 1 gram dose of Imipenem and Cilastatin for Injection (I.V.), the following average levels of imipenem were measured (usually at 1 hour post dose except where indicated) in the tissues and

Table 9: Average Levels of Imipenem

Tissue or Fluid	N	Imipenem Level mcg/mL or mcg/g	Range
Vitreous Humor	3	3.4 (3.5 hours post dose)	2.88 to 3.6
Aqueous Humor	5	2.99 (2 hours post dose)	2.4 to 3.9
Lung Tissue	8	5.6 (median)	3.5 to 15.5
Sputum	1	2.1	_
Pleural	1	22	_
Peritoneal	12	23.9 S.D.±5.3 (2 hours post dose)	_
Bile	2	5.3 (2.25 hours post dose)	4.6 to 6
CSF (uninflamed)	5	1 (4 hours post dose)	0.26 to 2
CSF (inflamed)	7	2.6 (2 hours post dose)	0.5 to 5.5
Fallopian Tubes	1	13.6	_
Endometrium	1	11.1	_
Myometrium	1	5	_
Bone	10	2.6	0.4 to 5.4
Interstitial Fluid	12	16.4	10 to 22.6
Skin	12	4.4	NA
Fascia	12	4.4	NA
Metaholism			

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

The plasma half-life of each component is approximately 1 hour. 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 mcg/mL can be maintained for up to 8 hours with Imipenem and Cilastatin for Injection (I.V.) at the 500-mg dose. Approximately 70% of the cilastatin sodium dose is recovered in the urine within 10 hours of administration of Imipenem and Cilastatin for Injection (I.V.). Imipenem/cilastatin sodium is hemodialyzable [see Overdosage (10)].

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

Geriatric Patients In healthy elderly volunteers (65 to 75 years of age with normal renal function for their age), the pharmacokinetics of a single dose of imipenem 500 mg and cilastatin 500 mg administere intravenously 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 minutes and 69 ± 15 minutes, respectively. Multiple dosing has no effect on the pharmacokinetics of either imipenem or cilastatin, and no accumulation of imipenem/cilastatin is observed.

Doses of 25 mg/kg/dose in patients 3 months to < 3 years of age, and 15 mg/kg/dose in patients 3 to 12 years of age were associated with mean trough plasma concentrations of mipenem 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 dose-ranging study of smaller premature infants (670 to 1,890 g) in the first week of life, a dose of 20 mg/kg q12h by 15 to 30 minutes infusion 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 in neonates may occur following multiple doses of Imipenem and Cilastatin for Injection (I.V.). The safety of this accumulation is

12.4 Microbiology

Mechanism of Action Imipenem and Cilastatin for Injection (I.V.) is a combination of imipenem and cilastatin. 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 binding to PBP

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 which are inherently resistant to most beta-lactam antibacterials, e.g., *Pseudomonas aeruginosa, Serratia* spp., and *Enterobacter* spp.

Imipenem is inactive in vitro against Enterococcus faecium, Stenotrophomonas maltophilia and some isolates of Burkholderia cepacia. Methicillin-resistant staphylococci should be reported as resistant to imipenem.

Interaction with Other Antimicrobials

In vitro tests show imipenem to act synergistically with aminoglycoside antibacterials against some isolates of *Pseudomonas aeruginosa*.

Imipenem has been shown to be active against most isolates of the following microorganisms, both in vitro and in clinical infections [see Indications and Usage (1)].

Aerobic bacteria

Gram-positive bacteria Enterococcus faecalis Staphylococcus aureus Staphylococcus epidermidis Streptococcus agalactiae (Group B streptococci) Streptococcus pneumoniae Streptococcus pyogenes

Gram-negative bacteria Acinetobacter spp. Citrobacter spp. Enterobacter spp Escherichia coli Gardnerella vaginalis Haemophilus influenzae Haemonhilus parainfluenzae Klebsiella spp. Morganella morganii Proteus vulgaris Providencia rettgeri Pseudomonas aeruginosa

Serratia spp., including S. marcescens

Anaerobic bacteria

Gram positive bacteria *Bifidobacterium* spp. Clostridium spp. Eubacterium spp. Peptococcus spp. Peptostreptococcus spp. Propionibacterium spp.

<u>Gram-negative bacteria</u> <u>Bacteroides spp., including B. fragilis</u>

The following in vitro data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for imipenem against isolates of similar genus or organism group. However, the efficacy of imipenem in treating clinical infections

due to these bacteria has not been established in adequate and well-controlled clinical trials.

Aerobic bacteria

Gram-positive bacteria *Bacillus* spp. Listeria monocytogene Nocardia spp. Staphylococcus saprophyticus Group G streptococci Viridans group streptococc

Gram-negative bacteria Aeromonas hydrophila Alcaligenes spp. Capnocytophaga spp Haemophilus ducrevi Neisseria gonorrhoeae Pasteurella spp. Providencia stuartii

Anaerobic bacteria

Prevotella bivia Prevotella disiens Prevotella melaninogenica Veillonella spp.

For specific information regarding susceptibility test methods, interpretive criteria, and associated test methods and quality control standards recognized by FDA for this drug, please see: https://www.fda.gov/STIC

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals have not been performed to evaluate carcinogenic potential of imipenem/cilastatin. A variety of bacterial and mammalian tests were performed to evaluate genetic toxicity. The tests used were: V79 mammalian cell mutagenesis assay (cilastatin sodium alone and imipenem alone), Ames test (cilastatin sodium alone and imipenem alone), unscheduled DNA synthesis assay (iminenem/cilastatin sodium) and in vivo mouse cytogenetics test (imipenem/cilastatin sodium). None of these tests showed any evidence of genetic

Impairment of fertility or reproductive performance was not observed in male and female rats given imipenem/cilastatin at intravenous doses up to 80 mg/kg/day and at a subcutaneous dose of 320 mg/kg/day. In rats, a dose of 320 mg/kg/day was approximately equal to the highest recommended human dose based on body surface area.

HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Imipenem and Cilastatin for Injection, USP (I.V.) is supplied as a sterile powder mixture in single dose vials containing imipenem (anhydrous equivalent) and cilastatin sodium as follows:

Product No.	NDC No.		
349025	63323-349-25	250 mg imipenem equivalent and 250 mg cilastatin equivalent and 10 mg sodium bicarbonate as a buffer	Packaged in carton of 25.
342025	63323-322-25	500 mg imipenem equivalent and 500 mg cilastatin equivalent and 20 mg sodium bicarbonate as a buffer	Packaged in carton of 25.

16.2 Storage and Handling Before Reconstitution

Imipenem and Cilastatin for Injection, USP (I.V.) sterile powder should be stored at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]

PATIENT COUNSELING INFORMATION

Advise patients that allergic reactions, including serious allergic reactions, could occur and that serious reactions require immediate treatment. They should report any previous hypersensitivity reactions to Imipenem and Cilastatin for Injection (I.V.), other carbapenems,

Counsel patients that antibacterial drugs including Imipenem and Cilastatin for Injection (I.V.) should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Imipenem and Cilastatin for Injection (I.V.) is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Imipenem and Cilastatin for Injection (I.V.) or other antibacterial drugs

Counsel patients to inform their physician:

 if they have central nervous system disorders such as stroke or history of seizures. Seizures have been reported during treatment with Imipenem and Cilastatin for Injection (LV) and with closely related antibacterial drugs

if they are taking valproic acid or sodium valproate. Valproic acid concentrations in the blood may drop below the therapeutic range upon co-administration with Imipenem and Cilastatin for Injection (I.V.). If treatment with Impenem and Cilastatin for Injection (I.V.) is necessary and continued, alternative or supplemental anti-convulsant medication to t and/or treat seizures may be needed

 Advise patients that diarrhea is a common problem caused by antibacterial drugs and usually resolves when the drug is discontinued. Sometimes, frequent watery or bloody diarrhea may occur and may be a sign of a more serious intestinal infection. If severe watery or bloody diarrhea develops, patients should contact their healthcare provider.

Manufactured for:

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Made in Italy www.fresenius-kabi.com/us

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