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

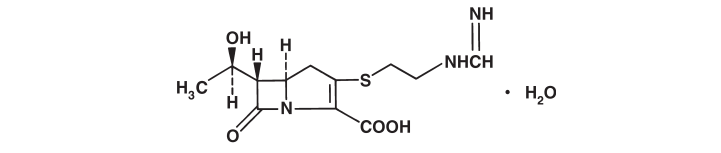
To reduce the development of drug-resistant bacteria and maintain the effectiveness of imipenem and cilastatin for injection (I.V.) and other antibacterial drugs, imipenem and cilastatin for injection (I.V.) should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

For Intravenous Injection Only

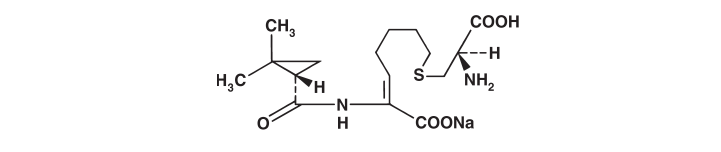
DESCRIPTION

Imipenem and Cilastatin for Injection, USP (I.V.) is a sterile formulation of imipenem (a thienamycin antibiotic) and cilastatin sodium (the inhibitor of the renal dipeptidase, dehydropeptidase I), with sodium bicarbonate added as a buffer. Imipenem and Cilastatin for Injection, USP (I.V.) is a potent broad spectrum antibacterial agent for intravenous administration.

Imipenem (N-formimidoylthienamycin monohydrate) is a crystalline derivative of thienamycin, which is produced by *Streptomyces cattleya*. Its chemical name is (5*R*,6*S*)-3-[[2-(formimidoylamino)ethyl]thio]-6-[(β)-1-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic 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 C₁₂H₁₇N₃O₅•H₂O, and its structural formula is:



Cilastatin sodium is the sodium salt of a derivatized heptenoic acid. Its chemical name is sodium (2*-*7[[[(β)-2-amino-2-carboxyethyl]thio]-2-[(*S*)-2,2-dimethylcyclopanecarboxamido]-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 C₁₆H₂₃N₂O₅Na, 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 to 8.5. There is no significant change in pH when solutions are prepared and used as directed. (see **COMPATIBILITY AND STABILITY**). 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

Adults

Intravenous Administration

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 14 to 24 mcg/mL for the 250 mg dose, from 21 to 58 mcg/mL for the 500 mg dose, and from 41 to 83 mcg/mL for the 1000 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 15 to 25 mcg/mL for the 250 mg dose, from 31 to 49 mcg/mL for the 500 mg dose, and from 56 to 88 mcg/mL for the 1000 mg dose.

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 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.).

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.

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 administered 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.

Imipenem, when administered alone, is metabolized in the kidneys by dehydropeptidase I 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, fully adequate antibacterial levels of imipenem are achieved in the urine.

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 fluids listed:

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

Imipenem-cilastatin sodium is hemodialyzable. However, usefulness of this procedure in the overdosage setting is questionable. (see **OVERDOSAGE**).

Microbiology

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

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 intravenous formulation of imipenem-cilastatin sodium as described in the **INDICATIONS AND USAGE** section. *Gram-positive aerobes:*

Enterococcus faecalis (formerly *S. faecalis*)

(NOTE: Imipenem is inactive *in vitro* against *Enterococcus faecium* [formerly

S. faecium].)

Staphylococcus aureus including penicillinase-producing strains

Staphylococcus epidermidis including penicillinase-producing strains

(NOTE: Methicillin-resistant staphylococci should be reported as resistant to imipenem.)

Streptococcus agalactiae (Group B streptococci)

Streptococcus pneumoniae

Streptococcus pyogenes

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

(NOTE: Imipenem is inactive *in vitro* against *Stenotrophomonas* [formerly *Xanthomonas*, formerly *Pseudomonas*] *malophilia* and some strains of *Burkholderia cepacia*.)

Serratia spp., including *S. marcescens*

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 mcg/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 imipenem to act synergistically with aminoglycoside antibiotics against some isolates of *Pseudomonas aeruginosa*.

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide to the physician the results of *in vitro* susceptibility tests for antimicrobial drug products used in resident hospitals as periodic reports which describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a broth dilution method(1,2) or equivalent with standardized inoculum concentrations and standardized concentrations of imipenem powder. The MIC values should be interpreted according to criteria provided in Table 1.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure requires the use of standardized inoculum concentrations (2,3). This procedure uses paper disks impregnated with 10-mcg imipenem to test the susceptibility of microorganisms to imipenem. The disk diffusion interpretive criteria should be interpreted according to criteria provided in Table 1.

Anaerobic Techniques

For anaerobic bacteria, the susceptibility to imipenem as MICs can be determined by standardized test methods.(2,4) The MIC values obtained should be interpreted according to criteria provided in Table 1.

The MIC and disk diffusion values obtained should be interpreted according to the following criteria:

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion Zone Diameter (mm)		
	S	I	R	S	I	R
<i>Enterobacteriaceae</i>	≤ 1	2	≥ 4	≥ 23	20 to 22	≤ 19
<i>Pseudomonas aeruginosa</i>	≤ 2	4	≥ 8	≥ 19	16 to 18	≤ 15
<i>Acinetobacter</i> spp.	≤ 4	8	≥ 16	≥ 16	14 to 15	≤ 13
<i>Staphylococcus</i> spp.*	≤ 4	8	≥ 16	≥ 16	14 to 15	≤ 13
<i>Haemophilus influenzae</i> and <i>H. parainfluenzae</i> [†]	≤ 4	-	-	≥ 16	-	-
<i>Streptococcus pneumoniae</i> [‡]	≤ 0.12	0.25 to 0.5	≥ 1	-	-	-
Anaerobes	≤ 4	8	≥ 16	-	-	-

* For oxacillin-susceptible *S. aureus* and coagulase negative staphylococci results for carbapenems, including imipenem, if tested, should be reported according to the results generated using routine interpretive criteria. For oxacillin-resistant *S. aureus* and coagulase negative staphylococci, other beta lactam agents, including carbapenems, may appear active *in vitro* but are not effective clinically. Results for beta lactam agents other than cephalosporins with anti-MRSA activity should be reported as resistant or should not be reported.

[†] For some organism/antimicrobial combinations, the absence or rare occurrence of resistant strains precludes defining any results categories other than “susceptible”. For strains yielding results suggestive of a “non-susceptible” category, organism identification and antimicrobial susceptibility test results should be confirmed.

[‡] For non-meningitis *S. pneumoniae* isolates, penicillin MICs ≤ 0.06 mcg/mL (or oxacillin zones ≥ 20 mm) indicate susceptibility to imipenem.

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound at the infection site reaches the concentrations usually achievable. A report of “Intermediate” indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound at the infection site reaches the concentrations usually achievable, and that other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory control microorganisms to ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test. Quality control microorganisms are specific strains of organisms with intrinsic biological properties. QC strains are very stable strains which will give a standard and repeatable susceptibility pattern. The specific strains used for microbiological quality control are not clinically significant. Standard imipenem powder should provide the following range of values noted in Table 2.(2)

Microorganism	Minimum Inhibitory Concentrations MIC Range (mcg/mL)	Disk Diffusion Zone Diameter (mm)
<i>Pseudomonas aeruginosa</i> ATCC 27853	1 to 4	20 to 28
<i>Escherichia coli</i> ATCC 25922	0.06 to 0.25	26 to 32
<i>Haemophilus influenzae</i> ATCC 49247	-	21 to 29
<i>Haemophilus influenzae</i> ATCC 49766	0.25 to 1	-
<i>Staphylococcus aureus</i> ATCC 29213	0.015 to 0.06	-
<i>Enterococcus faecalis</i> ATCC 29212	0.5 to 2	-
<i>Streptococcus pneumoniae</i> ATCC 49619	0.03 to 0.12	-
<i>Bacteroides fragilis</i> ATCC 25285	0.03 to 0.25* 0.03 to 0.125 [†]	-
<i>Bacteroides thetaiotaomicron</i> ATCC 29741	0.25 to 1* 0.125 to 0.5 [†]	-
<i>Eubacterium lentum</i> ATCC 43055	0.25 to 2* 0.125 to 0.5 [†]	-
* Quality control ranges for broth microdilution testing		
[†] Quality control ranges for agar dilution testing		

INDICATIONS AND USAGE

Imipenem and Cilastatin for Injection, USP (I.V.) is indicated for the treatment of serious infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

(1) **Lower respiratory tract infections.** *Staphylococcus aureus* (penicillinase-producing strains), *Acinetobacter* species, *Enterobacter* species, *Escherichia coli*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*¹, *Klebsiella* species, *Serratia marcescens*

(2) **Urinary tract infections** (complicated and uncomplicated). *Enterococcus faecalis*, *Staphylococcus aureus* (penicillinase-producing strains)¹, *Enterobacter* species, *Escherichia coli*, *Klebsiella* species, *Morganella morganii*¹, *Proteus vulgaris*¹, *Providencia rettgeri*¹, *Pseudomonas aeruginosa*

(3) **Intra-abdominal infections.** *Enterococcus faecalis*, *Staphylococcus aureus* (penicillinase-producing strains)¹, *Staphylococcus epidermidis*, *Citrobacter* species, *Enterobacter* species, *Escherichia coli*, *Klebsiella* species, *Morganella morganii*¹, *Proteus* species, *Pseudomonas aeruginosa*, *Bifidobacterium* species, *Clostridium* species, *Eubacterium* species, *Peptococcus* species, *Peptostreptococcus* species, *Propionibacterium* species¹, *Bacteroides* species including *B. fragilis*, *Fusobacterium* species

(4) **Gynecologic infections.** *Enterococcus faecalis*, *Staphylococcus aureus* (penicillinase-producing strains)¹, *Staphylococcus epidermidis*, *Streptococcus agalactiae* (Group B streptococci), *Enterobacter* species¹, *Escherichia coli*, *Gardnerella vaginalis*, *Klebsiella* species¹, *Proteus* species, *Bifidobacterium* species¹, *Peptococcus* species¹, *Peptostreptococcus* species, *Propionibacterium* species¹, *Bacteroides* species including *B. fragilis*¹

(5) **Bacterial septicemia.** *Enterococcus faecalis*, *Staphylococcus aureus* (penicillinase-producing strains), *Enterobacter* species, *Escherichia coli*, *Klebsiella* species, *Pseudomonas aeruginosa*, *Serratia* species¹, *Bacteroides* species including *B. fragilis*¹

(6) **Bone and joint infections.** *Enterococcus faecalis*, *Staphylococcus aureus* (penicillinase-producing strains), *Staphylococcus epidermidis*, *Enterobacter* species, *Pseudomonas aeruginosa*

(7) **Skin and skin structure infections.** *Enterococcus faecalis*, *Staphylococcus aureus* (penicillinase-producing strains), *Staphylococcus epidermidis*, *Acinetobacter* species, *Citrobacter* species, *Enterobacter* species, *Escherichia coli*, *Klebsiella* species, *Morganella morganii*, *Proteus vulgaris*, *Providencia rettgeri*¹, *Pseudomonas aeruginosa*, *Serratia* species, *Peptococcus* species, *Peptostreptococcus* species, *Bacteroides* species including *B. fragilis*, *Fusobacterium* species¹

(8) **Endocarditis.** *Staphylococcus aureus* (penicillinase-producing strains)

(9) **Polymicrobial infections.** Imipenem and Cilastatin for Injection, USP (I.V.) is indicated for polymicrobial infections including those in which *S. pneumoniae* (pneumonia, septicemia), *S. pyogenes* (skin and skin structure), or nonpenicillinase-producing *S. aureus* is one of the causative organisms. However, nonbacterial infections due to these organisms are usually treated with narrower spectrum antibiotics, such as penicillin G.

Imipenem and Cilastatin for Injection, USP (I.V.) is not indicated in patients with meningitis because safety and efficacy have not been established.

For Pediatric Use information, see **PRECAUTIONS, Pediatric Use**, and **DOSAGE AND ADMINISTRATION** sections.

Because of its broad spectrum of bactericidal activity against gram-positive and gram-negative aerobic and anaerobic bacteria, Imipenem and Cilastatin for Injection, USP (I.V.) is useful for the treatment of mixed infections and as presumptive therapy prior to the identification of the causative organisms.

Although clinical improvement has been observed in patients with cystic fibrosis, chronic pulmonary disease, and lower respiratory tract infections caused by *Pseudomonas aeruginosa*, bacterial eradication may not necessarily be achieved.

As with other beta-lactam antibiotics, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with Imipenem and Cilastatin for Injection, USP (I.V.). During therapy of *Pseudomonas aeruginosa* infections, periodic susceptibility testing should be done when clinically appropriate.

Infections resistant to other antibiotics, for example, cephalosporins, penicillin, and aminoglycosides, have been shown to respond to treatment with Imipenem and Cilastatin for Injection, USP (I.V.).

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 or prevent 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.

CONTRAINDICATIONS

Imipenem and cilastatin for injection (I.V.) is contraindicated in patients who have shown hypersensitivity to any component of this product.

WARNINGS

(imipenem-cilastatin sodium) and *in vivo* mouse cytogenetics test (imipenem-cilastatin sodium). None of these tests showed any evidence of genetic alterations.

Reproductive tests in male and female rats were performed with imipenem-cilastatin sodium at intravenous doses up to 80 mg/kg/day and at a subcutaneous dose of 320 mg/kg/day, approximately equal to the highest recommended human dose of the intravenous formulation (on a mg/m² body surface area basis). Slight decreases in live fetal body weight were restricted to the highest dosage level. No other adverse effects were observed on fertility, reproductive performance, fetal viability, growth or postnatal development of pups.

Pregnancy: Teratogenic Effects

Pregnancy Category C: Teratology studies with cilastatin sodium at doses of 30, 100, and 300 mg/kg/day administered intravenously to rabbits and 40, 200, and 1000 mg/kg/day administered subcutaneously to rats, up to approximately 1.9 and 3.2 times² the maximum recommended daily human dose (on a mg/m² body surface area basis) of the intravenous formulation of imipenem-cilastatin sodium (50 mg/kg/day) in the two species, respectively, showed no evidence of adverse effect on the fetus. No evidence of teratogenicity was observed in rabbits given imipenem at intravenous doses of 15, 30 or 60 mg/kg/day and rats given imipenem at intravenous doses of 225, 450, or 900 mg/kg/day, up to approximately 0.4 and 2.9 times² the maximum recommended daily human dose (on a mg/m² body surface area basis) in the two species, respectively.

Teratology studies with imipenem-cilastatin sodium at intravenous doses of 20 and 80, and a subcutaneous dose of 320 mg/kg/day, up to 0.5 times² (mice) to approximately equal to (rats) the highest recommended daily intravenous human dose (on a mg/m² body surface area basis) in pregnant rodents during the period of major organogenesis, revealed no evidence of teratogenicity.

Imipenem-cilastatin sodium, when administered subcutaneously to pregnant rabbits at dosages equivalent to the usual human dose of the intravenous formulation and higher (1000-4000 mg/day), caused body weight loss, diarrhea, and maternal deaths. When comparable doses of imipenem-cilastatin sodium were given to non-pregnant rabbits, body weight loss, diarrhea, and deaths were also observed. This intolerance is not unlike that seen with other beta-lactam antibiotics in this species and is probably due to alteration of gut flora.

A teratology study in pregnant cynomolgus monkeys given imipenem-cilastatin sodium at doses of 40 mg/kg/day (bolus intravenous injection) or 160 mg/kg/day (subcutaneous injection) resulted in maternal toxicity including emesis, inappetence, body weight loss, diarrhea, abortion, and death in some cases. In contrast, no significant toxicity was observed when non-pregnant cynomolgus monkeys were given doses of imipenem-cilastatin sodium up to 180 mg/kg/day (subcutaneous injection). When doses of imipenem-cilastatin sodium (approximately 100 mg/kg/day or approximately 0.6 times² the maximum recommended daily human dose of the intravenous formulation) were administered to pregnant cynomolgus monkeys at an intravenous infusion rate which mimics human clinical use, there was minimal maternal intolerance (occasional emesis), no maternal deaths, no evidence of teratogenicity, but an increase in embryonic loss relative to control groups.

No adverse effects on the fetus or on lactation were observed when imipenem-cilastatin sodium was administered subcutaneously to rats late in gestation at dosages up to 320 mg/kg/day, approximately equal to the highest recommended human dose (on a mg/m² body surface area basis).

There are, however, no adequate and well-controlled studies in pregnant women. Imipenem and cilastatin for injection (I.V.) should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Nursing Mothers

It is not known whether imipenem-cilastatin sodium is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when imipenem and cilastatin for injection (I.V.) is administered to a nursing woman.

Pediatric Use

Use of imipenem and cilastatin for injection (I.V.) in pediatric patients, neonates to 16 years of age, is supported by evidence from adequate and well-controlled studies of imipenem and cilastatin for injection (I.V.) in adults and by the following clinical studies and published literature in pediatric patients: Based on published studies of 178³ pediatric patients ≥ 3 months of age (with non-CNS infections), the recommended dose of imipenem and cilastatin for injection (I.V.) is 15 to 25 mg/kg/dose administered every six hours. 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 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. Based on studies in adults, the maximum daily dose for treatment of infections with fully susceptible organisms is 2 g per day, and of infections with moderately susceptible organisms (primarily some strains of *P. aeruginosa*) is 4 g/day. (see **DOSEAGE AND ADMINISTRATION**, Table 3). Higher doses (up to 90 mg/kg/day in older children) have been used in patients with cystic fibrosis. (see **DOSEAGE AND ADMINISTRATION**).

Based on studies of 135⁴ pediatric patients ≤ 3 months of age (weighing ≥ 1,500 g), the following dosage schedule is recommended for non-CNS infections:

< 1 wk of age: 25 mg/kg every 12 hrs
1 to 4 wks of age: 25 mg/kg every 8 hrs
4 wks to 3 mos. of age: 25 mg/kg every 6 hrs.

In a published dose-ranging study of smaller premature infants (670 to 1,890 g) in the first week of life, a dose of 20 mg/kg q 12 h 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 unknown.

Imipenem 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 < 30 kg with impaired renal function, as no data are available.

Geriatric Use

Of the approximately 3600 subjects ≥ 18 years of age in clinical studies of imipenem and cilastatin for injection (I.V.), including postmarketing studies, approximately 2800 received imipenem 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, Adults**). Dosage adjustment in the case of renal impairment is necessary (see **DOSEAGE AND ADMINISTRATION, Reduced Intravenous Schedule for Adults with Impaired Renal Function and/or Body Weight < 70 kg**).

ADVERSE REACTIONS

Adults

Imipenem and cilastatin for injection (I.V.) is generally well tolerated. Many of the 1,723 patients treated in clinical trials were severely ill and had multiple background diseases and physiological impairments, making it difficult to determine causal relationship of adverse experiences to therapy with imipenem and cilastatin for injection (I.V.).

Local Adverse Reactions

Adverse local clinical reactions that were reported as possibly, probably, or definitely related to therapy with imipenem and cilastatin for injection (I.V.) were:

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 and cilastatin for injection (I.V.) were nausea (2%), diarrhea (1.8%), vomiting (1.5%), rash (0.9%), fever (0.5%), hypotension (0.4%), seizures (0.4%) (see **PRECAUTIONS**), dizziness (0.3%), pruritus (0.3%), urticaria (0.2%), somnolence (0.2%).

Additional adverse systemic clinical reactions reported as possibly, probably, or definitely drug related occurring 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: *Gastrointestinal* — pseudomembranous colitis (the onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment, see **WARNINGS**), hemorrhagic colitis, hepatitis (including fulminant hepatitis), hepatic failure, jaundice, gastroenteritis, abdominal pain, glossitis, tongue papillar hypertrophy, staining of the teeth and/or tongue, heartburn, pharyngeal pain, increased salivation; *Hematologic* — pancytopenia, bone marrow depression, thrombocytopenia, neutropenia, leukopenia, hemolytic anemia; *CNS* — encephalopathy, tremor, confusion, myoclonus, paresthesia, vertigo, headache, psychic disturbances including hallucinations, dyskinesia, agitation; *Special Senses*

^[2] Based on patient body surface area of 1.6 m² (weight of 60 kg).

^[3] Two patients were less than 3 months of age.

^[4] One patient was greater than 3 months of age.

— hearing loss, tinnitus, taste perversion; *Respiratory* — chest discomfort, dyspnea, hyperventilation, thoracic spine pain; *Cardiovascular* — palpitations, tachycardia; *Skin* — Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, angioneurotic edema, flushing, cyanosis, hyperhidrosis, skin texture changes, candidiasis, pruritus vulvae; *Body as a whole* — polyarthralgia, asthenia/weakness, drug fever; *Renal* — acute renal failure, oliguria/anuria, polyuria, urine discoloration. The role of imipenem and cilastatin for injection (I.V.) in changes in renal function is difficult to assess, since factors predisposing to pre-renal azotemia or to impaired renal function usually have been present.

Adverse Laboratory Changes

Adverse laboratory changes without regard to drug relationship that were reported during clinical trials or reported since the drug was marketed were:

Hepatic: Increased ALT (SGPT), AST (SGOT), alkaline phosphatase, bilirubin, and LDH
Hemic: Increased eosinophils, positive Coombs test, increased WBC, increased platelets, decreased hemoglobin and hematocrit, agranulocytosis, increased monocytes, abnormal prothrombin time, increased lymphocytes, increased basophils
Electrolytes: Decreased serum sodium, increased potassium, increased chloride
Renal: Increased BUN, creatinine
Urinanalysis: Presence of urine protein, urine red blood cells, urine white blood cells, urine casts, urine bilirubin, and urine urobilinogen.

Pediatric Patients

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

The Most Common Clinical Adverse Experiences Without Regard to Drug Relationship (Patient Incidence > 1%)		
Adverse Experience	No. of Patients (%)	
<i>Digestive System</i>		
Diarrhea	7* (3.9)	
Gastroenteritis	2 (1.1)	
Vomiting	2* (1.1)	
<i>Skin</i>		
Rash	4 (2.2)	
Irritation, I.V. site	2 (1.1)	
<i>Urogenital System</i>		
Urine discoloration	2 (1.1)	
<i>Cardiovascular System</i>		
Phlebitis	4 (2.2)	
*One patient had both vomiting and diarrhea and is counted in each category.		

In studies of 135 patients (newborn to 3 months of age), the following adverse events were noted:

The Most Common Clinical Adverse Experiences Without Regard to Drug Relationship (Patient Incidence > 1%)		
Adverse Experience	No. of Patients (%)	
<i>Digestive System</i>		
Diarrhea	4 (3%)	
Oral Candidiasis	2 (1.5%)	
<i>Skin</i>		
Rash	2 (1.5%)	
<i>Urogenital System</i>		
Oliguria/anuria	3 (2.2%)	
<i>Cardiovascular System</i>		
Tachycardia	2 (1.5%)	
<i>Nervous System</i>		
Convulsions	8 (5.9%)	

Patients (≥ 3 Months of Age) With Normal Pretherapy but Abnormal During Therapy Laboratory Values			
Laboratory Parameter	Abnormality	No. of Patients With Abnormalities/No. of Patients With Lab Done (%)	
Hemoglobin	Age < 5 mos.:	< 10 g %	19/129 (14.7)
	6 mos. to 12 yrs.:	< 11.5 g %	
Hematocrit	Age < 5 mos.:	< 30 vol %	23/129 (17.8)
	6 mos. to 12 yrs.:	< 34.5 vol %	
Neutrophils	≥ 1000/mm ³ (absolute)	4/123 (3.3)	
	≥ 7%	15/117 (12.8)	
Platelet Count	≥ 500 ths/mm ³	16/119 (13.4)	
Urine Protein	≥ 1	8/97 (8.2)	
Serum Creatinine	> 1.2 mg/dL	0/105 (0)	
BUN	> 22 mg/dL	0/108 (0)	
AST (SGOT)	> 36 IU/L	14/78 (17.9)	
ALT (SGPT)	> 30 IU/L	10/93 (10.8)	

Patients (< 3 Months of Age) With Normal Pretherapy but Abnormal During Therapy Laboratory Values			
Laboratory Parameter	No. of Patients With Abnormalities* (%)		
Eosinophil Count ↑	11 (9%)		
Hematocrit ↓	3 (2%)		
Hematocrit ↑	1 (1%)		
Platelet Count ↑	5 (4%)		
Platelet Count ↓	2 (2%)		
Serum Creatinine ↑	5 (5%)		
Bilirubin ↑	3 (3%)		
Bilirubin ↓	1 (1%)		
AST (SGOT) ↑	5 (6%)		
ALT (SGPT) ↑	3 (3%)		
Serum Alkaline Phosphate ↑	2 (3%)		
*The denominator used for percentages was the number of patients for whom the test was performed during 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 pediatric patients.

To report SUSPECTED ADVERSE EVENTS, contact FDA at 1-800-FDA-1088 or www.fda.gov.

OVERDOSAGE

The acute intravenous toxicity of imipenem-cilastatin sodium in a ratio of 1:1 was studied in mice at doses of 751 to 1359 mg/kg. Following drug administration, ataxia was rapidly produced and clonic convulsions were noted in about 45 minutes. Deaths occurred within 4 to 56 minutes at all doses.

The acute intravenous toxicity of imipenem-cilastatin sodium was produced within 5 to 10 minutes in rats at doses of 771 to 1583 mg/kg. In all dosage groups, females had decreased activity, bradypnea, and ptosis with clonic convulsions preceding death; in males, ptosis was seen at all dose levels while tremors and clonic convulsions were seen at all but the lowest dose (771 mg/kg). In another rat study, female rats showed ataxia, bradypnea, and decreased activity in all but the lowest dose (550 mg/kg); deaths were preceded by clonic convulsions. Male rats showed tremors at all doses and clonic convulsions and ptosis were seen at the two highest doses (1130 and 1734 mg/kg). Deaths occurred between 6 and 88 minutes with doses of 771 to 1734 mg/kg.

In the case of overdosage, discontinue imipenem and cilastatin for injection (I.V.), treat symptomatically, and institute supportive measures as required. Imipenem-cilastatin sodium is hemodialyzable. However, usefulness of this procedure in the overdosage setting is questionable.

DOSEAGE AND ADMINISTRATION

Adults

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. Each 125 mg, 250 mg, or 500 mg dose should be given by intravenous administration over 20 to 30 minutes. Each 750 mg or 1000 mg dose should be infused over 40 to 60 minutes. In patients who develop nausea during the infusion, the rate of infusion may be slowed.

The total daily dosage for imipenem and cilastatin for injection (I.V.) should be based on the type or severity of infection and given in equally divided doses based on consideration of 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 m², require adjustment of dosage as described in the succeeding section of these guidelines.

Intravenous Dosage Schedule for Adults with Normal Renal Function and Body Weight ≥ 70 kg

Doses cited in Table 3 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 m² 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 m² and/or a body weight less than 70 kg. (see Tables 4 and 5).

Dosage regimens in column A of Table 3 are recommended for infections caused by fully susceptible organisms which represent the majority of pathogenic species. Dosage regimens in column B of Table 3 are recommended for infections caused by organisms with moderate susceptibility to imipenem, primarily some strains of *P. aeruginosa*.

TABLE 3 INTRAVENOUS DOSAGE SCHEDULE FOR ADULTS WITH NORMAL RENAL FUNCTION AND BODY WEIGHT ≥ 70 kg		
Type or Severity of Infection	A Fully susceptible organisms including gram-positive and gram-negative aerobes and anaerobes	B Moderately susceptible organisms, primarily some strains of <i>P. aeruginosa</i>
Mild	250 mg q 6 h (TOTAL DAILY DOSE = 1 g)	500 mg q 6 h (TOTAL DAILY DOSE = 2 g)
Moderate	500 mg q 8 h (TOTAL DAILY DOSE = 1.5 g) or 500 mg q 6 h (TOTAL DAILY DOSE = 2 g)	500 mg q 6 h (TOTAL DAILY DOSE = 2 g) or 1 g q 8 h (TOTAL DAILY DOSE = 3 g)
Severe, life threatening only	500 mg q 6 h (TOTAL DAILY DOSE = 2 g)	1 g q 8 h (TOTAL DAILY DOSE = 3 g) or 1 g q 6 h (TOTAL DAILY DOSE = 4 g)
Uncomplicated urinary tract infection	250 mg q 6 h (TOTAL DAILY DOSE = 1 g)	250 mg q 6 h (TOTAL DAILY DOSE = 1 g)
Complicated urinary tract infection	500 mg q 6 h (TOTAL DAILY DOSE = 2 g)	500 mg q 6 h (TOTAL DAILY DOSE = 2 g)

Due to the high antimicrobial activity of imipenem and cilastatin for injection (I.V.), it is recommended that the maximum total daily dosage not exceed 50 mg/kg/day or 4 g/day, whichever is lower. There is no evidence that higher doses provide greater efficacy. However, patients over twelve years of age with cystic fibrosis and normal renal function have been treated with imipenem and cilastatin for injection (I.V.) at doses up to 90 mg/kg/day in divided doses, not exceeding 4 g/day.

Reduced Intravenous Schedule for Adults with Impaired Renal Function and/or Body Weight < 70 kg

Patients with creatinine clearance of ≤ 70 mL/min/1.73 m² and/or body weight less than 70 kg require dosage reduction of imipenem and cilastatin for injection (I.V.) as indicated in the tables below. Creatinine clearance may be calculated from serum creatinine concentration by the following equation:

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Tcc (Females) = 0.85 x above value

To determine the dose for adults with impaired renal function and/or reduced body weight:

- Choose a total daily dose from Table 3 based on infection characteristics.
- a) If the total daily dose is 1 g, 1.5 g, or 2 g, use the appropriate subsection of Table 4 and continue with step 3.

b) If the total daily dose is 3 g or 4 g, use the appropriate subsection of Table 5 and continue with step 3.
- From Table 4 or 5:
 - Select the body weight on the far left which is closest to the patient's body weight (kg).
 - Select the patient's creatinine clearance category.
 - Where the row and column intersect is the reduced dosage regimen.

TABLE 4 REDUCED INTRAVENOUS DOSAGE OF IMPENEM AND CILASTATIN FOR INJECTION (I.V.) IN ADULT PATIENTS WITH IMPAIRED RENAL FUNCTION AND/OR BODY WEIGHT < 70 kg			
And Body Weight (kg) is:	If TOTAL DAILY DOSE from TABLE 3 is:		
	1 g/day	1.5 g/day	2 g/day
	and creatinine clearance (mL/min/1.73 m ²) is: ≥ 71 41 to 70 21 to 40 6 to 20	and creatinine clearance (mL/min/1.73 m ²) is: ≥ 71 41 to 70 21 to 40 6 to 20	and creatinine clearance (mL/min/1.73 m ²) is: ≥ 71 41 to 70 21 to 40 6 to 20
≥ 70	then the reduced dosage regimen (mg) is: 250 q 6 h 250 q 8 h 250 q 12 h	then the reduced dosage regimen (mg) is: 500 q 6 h 250 q 8 h 250 q 12 h	then the reduced dosage regimen (mg) is: 500 q 6 h 250 q 8 h 250 q 12 h
60	250 q 8 h 125 q 6 h 250 q 12 h	250 q 6 h 250 q 8 h 250 q 12 h	500 q 8 h 250 q 6 h 250 q 12 h
50	125 q 6 h 125 q 8 h 125 q 12 h	250 q 6 h 250 q 8 h 250 q 12 h	250 q 6 h 250 q 8 h 250 q 12 h
40	125 q 6 h 125 q 8 h 125 q 12 h	250 q 6 h 125 q 8 h 125 q 12 h	250 q 6 h 250 q 8 h 250 q 12 h
30	125 q 8 h 125 q 12 h	125 q 6 h 125 q 8 h 125 q 12 h	250 q 8 h 125 q 6 h 125 q 12 h

TABLE 5 REDUCED INTRAVENOUS DOSAGE OF IMPENEM AND CILASTATIN FOR INJECTION (I.V.) IN ADULT PATIENTS WITH IMPAIRED RENAL FUNCTION AND/OR BODY WEIGHT < 70 kg			
And Body Weight (kg) is:	If TOTAL DAILY DOSE from TABLE 3 is :		
	3 g/day	4 g/day	
	and creatinine clearance (mL/min/1.73 m ²) is: ≥ 71 41 to 70 21 to 40 6 to 20	and creatinine clearance (mL/min/1.73 m ²) is: ≥ 71 41 to 70 21 to 40 6 to 20	
≥ 70	then the reduced dosage regimen (mg) is: 1000 q 8 h 500 q 6 h 500 q 12 h	then the reduced dosage regimen (mg) is: 1000 q 8 h 750 q 6 h 500 q 12 h	
60	750 q 8 h 500 q 6 h 500 q 12 h	1000 q 8 h 750 q 6 h 500 q 12 h	
50	500 q 6 h 500 q 8 h 250 q 12 h	750 q 8 h 500 q 6 h 500 q 12 h	
40	500 q 8 h 250 q 6 h 250 q 12 h	500 q 6 h 500 q 8 h 250 q 12 h	
30	250 q 6 h 250 q 8 h 250 q 12 h	500 q 8 h 250 q 6 h 250 q 12 h	

Patients with creatinine clearances of 6 to 20 mL/min/1.73 m² should be treated with imipenem and cilastatin for injection (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 m² 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.

Hemodialysis

When treating patients with creatinine clearances of ≤ 5 mL/min/1.73 m² who are undergoing hemodialysis, use the dosage recommendations for patients with creatinine clearances of 6 to 20 mL/min/1.73 m². (see **Reduced Intravenous Dosage Schedule for Adults with Impaired Renal Function and/or Body Weight < 70 kg**). 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 12 hour 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 **PRECAUTIONS**).

Pediatric Patients

See **PRECAUTIONS, Pediatric Patients**.

For pediatric patients ≥ 3 months of age, the recommended dose for non-CNS infections is 15 to 25 mg/kg/dose administered every six hours. Based on studies in adults, the maximum daily dose for treatment of infections with fully susceptible organisms is 2 g per day, and of infections with moderately susceptible organisms (primarily some strains of *P. aeruginosa*) is 4 g/day. Higher doses (up to 90 mg/kg/day in older children) have been used in patients with cystic fibrosis.

For pediatric patients ≤ 3 months of age (weighing ≥ 1,500 g), the following dosage schedule is recommended for non-CNS infections:

< 1 wk of age: 25 mg/kg every 12 hrs
1 to 4 wks of age: 25 mg/kg every 8 hrs
4 wks to 3 mos. of age: 25 mg/kg every 6 hrs.

Doses less than or equal to 500 mg should be given by intravenous infusion over 15 to 30 minutes. Doses greater than 500 mg should be given by intravenous infusion over 40 to 60 minutes.

Imipenem 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 < 30 kg with impaired renal function, as no data are available.

PREPARATION OF SOLUTION

Vials

Contents of the vials must be suspended and transferred to 100 mL of infusion solution prior to intravenous infusion.

A suggested procedure is to add approximately 10 mL from the appropriate infusion solution (see list of diluents under **COMPATIBILITY AND STABILITY**) to the vial. Shake well and transfer the resulting suspension to the infusion solution container.

Benzyl alcohol as a preservative 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. Therefore, diluents containing benzyl alcohol should not be used when imipenem and cilastatin for injection (I.V