PHYSICIANS CIRCULAR

I.V. Infusion

TIENAM®

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(imipenem and cilastatin sodium, MSD)

TIENAM (imipenem and cilastatin sodium, MSD) is a broad spectrum beta-lactam antibiotic supplied as intravenous infusion only. TIENAM consists of two components: (1) imipenem, the first of a new class of beta-lactam antibiotics, the thienamycins; and (2) cilastatin sodium, a specific enzyme inhibitor that blocks the metabolism of imipenem in the kidney, and substantially increases the concentration of intact imipenem in the urinary tract. Imipenem and cilastatin sodium are present in TIENAM in a 1:1 ratio by weight.

The thienamycin class of antibiotics, to which imipenem belongs, is characterized by a spectrum of potent bactericidal activity broader than that provided by any other antibiotic studied.

MICROBIOLOGY

TIENAM is a potent inhibitor of bacterial cell-wall synthesis and is bactericidal against a broad spectrum of pathogens—gram-positive and gram-negative, aerobic and anaerobic.

TIENAM shares with the newer cephalosporins and penicillins a broad spectrum of activity against gram-negative species, but is unique in retaining the high potency against gram-positive species, previously associated only with earlier narrow-spectrum beta-lactam antibiotics. The spectrum of activity of TIENAM includes *Pseudomonas aeruginosa, Staphylococcus aureus, Enterococcus faecalis* and *Bacteroides fragilis*, a diverse group of problem pathogens commonly resistant to other antibiotics.

TIENAM is resistant to degradation by bacterial beta-lactamases, which makes it active against a high percentage of organisms such as *Pseudomonas aeruginosa, Serratia* spp., and *Enterobacter* spp. which are inherently resistant to most beta-lactam antibiotics.

The antibacterial spectrum of TIENAM is broader than that of any other antibiotic studied, and includes virtually all clinically significant pathogens. Organisms against which TIENAM is usually active *in vitro* include:

Gram-Negative Aerobes

Achromobacter spp.
Acinetobacter spp. (formerly *Mima-Herellea*)
Aeromonas hydrophila
Alcaligenes spp.
Bordetella bronchicanis
Bordetella bronchiseptica
Bordetella pertussis
Brucella melitensis
*Burkholderia pseudomallei (*formerly *Pseudomonas pseudomallei)*
*Burkholderia stutzeri (*formerly *Pseudomonas stutzeri)*
Campylobacter spp.
Capnocytophaga spp.
Citrobacter spp.
Citrobacter freundii

*Citrobacter koseri (*formerly *Citrobacter diversus)*
Eikenella corrodens
Enterobacter spp.
Enterobacter aerogenes
Enterobacter agglomerans
Enterobacter cloacae
Escherichia coli
Gardnerella vaginalis
Haemophilus ducreyi
Haemophilus influenzae (including beta-lactamase-producing strains)
Haemophilus parainfluenzae
Hafnia alvei
Klebsiella spp.
Klebsiella oxytoca
Klebsiella ozaenae
Klebsiella pneumoniae
Moraxella spp.
Morganella morganii (formerly *Proteus morganii*)
Neisseria gonorrhoeae (including penicillinase-producing strains)
Neisseria meningitidis
Pasteurella spp.
Pasteurella multoacida
Plesiomonas shigelloides
Proteus spp.
Proteus mirabilis
Proteus vulgaris
Providencia spp.
Providencia alcalifaciens
Providencia rettgeri (formerly *Proteus rettgeri*)
Providencia stuartii
Pseudomonas spp.**
Pseudomonas aeruginosa
Pseudomonas fluorescens
Pseudomonas putida
Salmonella spp.
Salmonella typhi
Serratia spp.
Serratia proteamaculans (formerly *Serratia liquefaciens*)
Serratia marcescens
Shigella spp.
Yersinia spp. (formerly *Pasteurella*)
Yersinia enterocolitica
Yersinia pseudotuberculosis

****Stenotrophomonas maltophilia*** (formerly *Xanthomonas maltophilia,* formerly *Pseudomonas maltophilia*) and some strains of *Burkholderia cepacia* (formerly *Pseudomonas cepacia)* are generally not susceptible to TIENAM.

<u>Gram-Positive Aerobes</u>

Bacillus spp.
Enterococcus faecalis
Erysipelothrix rhusiopathiae
Listeria monocytogenes
Nocardia spp.
Pediococcus spp.

Staphylococcus aureus (including penicillinase-producing strains)
Staphylococcus epidermidis (including penicillinase-producing strains)
Staphylococcus saprophyticus
Streptococcus agalactiae
Streptococcus Group C
Streptococcus Group G
Streptococcus pneumoniae
Streptococcus pyogenes
Viridans group streptococci (including alpha and gamma hemolytic strains)
Enterococcus faecium and methicillin-resistant staphylococci are not susceptible to TIENAM.

Gram-Negative Anaerobes

Bacteroides spp.
Bacteroides distasonis
Bacteroides fragilis
Bacteroides ovatus
Bacteroides thetaiotaomicron
Bacteroides uniformis
Bacteroides vulgatus
Bilophila wadsworthia
Fusobacterium spp.
Fusobacterium necrophorum
Fusobacterium nucleatum
Porphyromonas asaccharolytica (formerly *Bacteroides asaccharolyticus*)
Prevotella bivia (formerly *Bacteroides bivius*)
Prevotella disiens (formerly *Bacteroides disiens*)
Prevotella intermedia (formerly *Bacteroides intermedius*)
Prevotella melaninogenica (formerly *Bacteroides melaninogenicus*)
Veillonella spp.

Gram-Positive Anaerobes

Actinomyces spp.
Bifidobacterium spp.
Clostridium spp.
Clostridium perfringens
Eubacterium spp.
Lactobacillus spp.
Mobiluncus spp.
microaerophilic streptococcus
Peptococcus spp.
Peptostreptococcus spp.
Propionibacterium spp. (including *P. acnes*)

Other

Mycobacterium fortuitum
Mycobacterium smegmatis

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

INDICATIONS

TREATMENT

The activity of TIENAM against an unusually broad spectrum of pathogens makes it particularly useful in the treatment of polymicrobic and mixed aerobic/anaerobic infections, as well as initial therapy prior to the identification of the causative organisms. TIENAM is indicated for the treatment of the following infections due to susceptible organisms:

- Intra-abdominal infections
- Lower respiratory tract infections
- Gynecological infections
- Septicemia
- Genitourinary tract infections
- Bone and joint infections
- Skin and soft tissue infections
- Endocarditis

TIENAM is indicated for the treatment of mixed infections caused by susceptible strains of aerobic and anaerobic bacteria. The majority of these mixed infections are associated with contamination by fecal flora or flora originating from the vagina, skin and mouth. In these mixed infections, *Bacteroides fragilis* is the most commonly encountered anaerobic pathogen and is usually resistant to aminoglycosides, cephalosporins and penicillins. However, *Bacteroides fragilis* is usually susceptible to TIENAM.

TIENAM has demonstrated efficacy against many infections caused by aerobic and anaerobic gram-positive and gram-negative bacteria resistant to the cephalosporins, including cefazolin, cefoperazone, cephalothin, cefoxitin, cefotaxime, moxalactam, cefamandole, ceftazidime and ceftriaxone. Similarly, many infections caused by organisms resistant to aminoglycosides (gentamicin, amikacin, tobramycin) and/or penicillins (ampicillin, carbenicillin, penicillin-G, ticarcillin, piperacillin, azlocillin, mezlocillin) responded to treatment with TIENAM.

TIENAM is not indicated for the treatment of meningitis.

PROPHYLAXIS

TIENAM is also indicated for the prevention of certain post-operative infections in patients undergoing contaminated or potentially contaminated surgical procedures or where the occurrence of post-operative infection could be especially serious.

DOSAGE AND ADMINISTRATION

TIENAM is available as intravenous infusion only.

The dosage recommendations for TIENAM represent the quantity of imipenem to be administered. An equivalent amount of cilastatin is also present.

The total daily dosage of TIENAM 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.

INTRAVENOUS INFUSION

TREATMENT: ADULT DOSAGE SCHEDULE FOR PATIENTS WITH NORMAL RENAL FUNCTION

Doses cited in Table 1 are based on a patient with normal renal function (creatinine clearance of > 70 mL/min/1.73 m^2) and a body weight of ≥ 70 kg. A reduction in dose must be made for a patient with a creatinine clearance ≤ 70 mL/min/1.73 m^2 (see Table 2) and/or a body weight < 70 kg. The reduction for body weight is especially important for patients with much lower body weights and/or moderate/severe renal insufficiency.

Most infections respond to a daily dose of 1-2 g administered in 3-4 divided doses. For the treatment of moderate infection, a 1g b.i.d. dosage regimen may also be used. In infections due to less susceptible organisms, the daily dosage of TIENAM I.V. may be increased to a maximum of 4 g/day or 50 mg/kg/day, whichever is lower.

Each dose of ≤ 500 mg of TIENAM I.V. should be given by intravenous infusion over 20 to 30 minutes. Each dose > 500 mg should be infused over 40 to 60 minutes. In patients who develop nausea during the infusion, the rate of infusion may be slowed.

TABLE 1. I.V. DOSAGE SCHEDULE FOR ADULTS WITH NORMAL RENAL FUNCTION AND BODY WEIGHT ≥ 70 KG*

SEVERITY OF INFECTION	DOSE (mg of imipenem)	DOSAGE INTERVAL	TOTAL DAILY DOSAGE
Mild	250 mg	6 hrs	1 g
Moderate	500 mg 1000 mg	8 hrs 12 hrs	1.5 g 2 g
Severe - Fully susceptible	500 mg	6 hrs	2 g
Severe and/or Life-threatening - Due to less susceptible organisms (primarily some strains of *P. aeruginosa*)	1000 mg 1000 mg	8 hrs 6 hrs	3 g 4 g

*****A further proportionate reduction in dose administered must be made for patients with a body weight < 70 kg.

Due to high antimicrobial activity of TIENAM, it is recommended that the maximum total daily dosage not exceed 50 mg/kg/day or 4 g/day, whichever is lower. However, cystic fibrosis patients with normal renal function have been treated with TIENAM at doses up to 90 mg/kg/day in divided doses, not exceeding 4 g/day.
TIENAM has been used successfully as monotherapy in immunocompromised cancer patients for confirmed or suspected infections such as sepsis.

TREATMENT: ADULT DOSAGE SCHEDULE FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

To determine the reduced dose for adults with impaired renal function:

1. The total daily dose is chosen from Table 1 based on infection characteristics.

2. From Table 2 the appropriate reduced dosage regimen is selected based on the daily dose from Table 1 and the patient's creatinine clearance category. (For infusion times see TREATMENT: ADULT DOSAGE SCHEDULE FOR PATIENTS WITH NORMAL RENAL FUNCTION.)

TABLE 2. REDUCED DOSAGE OF TIENAM I.V. IN ADULTS WITH IMPAIRED RENAL FUNCTION AND BODY WEIGHT ≥ 70 kg*

Total Daily Dose from Table 1	Creatinine Clearance (mL/min/1.73 m^2) 41-70	21-40	6-20
1.0g/day	250 q8h	250 q12h	250 q12h
1.5g/day	250 q6h	250 q8h	250 q12h
2.0g/day	500 q8h	250 q6h	250 q12h
3.0g/day	500 q6h	500 q8h	500 q12h
4.0g/day	750 q8h	500 q6h	500 q12h

*A further proportionate reduction in dose administered must be made for patients with a body weight < 70 kg.

When the 500 mg dose is used in patients with creatinine clearances of 6 - 20 mL/min/1.73m^2 there may be an increased risk of seizures.

Patients with creatinine clearances of ≤ 5 mL/min/1.73 m^2 should not receive TIENAM I.V. unless hemodialysis is instituted within 48 hours.

Hemodialysis

When treating patients with creatinine clearances of ≤ 5 mL/min/1.73 m^2 who are undergoing hemodialysis, use the dosage recommendations for patients with creatinine clearances of 6 - 20 mL/min/1.73 m^2 (see TREATMENT: ADULT DOSAGE SCHEDULE FOR PATIENTS WITH IMPAIRED RENAL FUNCTION).

Both imipenem and cilastatin are cleared from the circulation during hemodialysis. The patient should receive TIENAM 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, TIENAM I.V. is recommended only when the benefit outweighs the potential risk of seizures (see PRECAUTIONS).

Currently there are inadequate data to recommend use of TIENAM I.V. for patients on peritoneal dialysis. Renal status of elderly patients may not be accurately portrayed by measurement of BUN or creatinine alone. Determination of creatinine clearance is suggested to provide guidance for dosing in such patients.

PROPHYLAXIS: ADULT DOSAGE SCHEDULE

For prophylaxis against post-surgical infections in adults, 1000 mg TIENAM I.V. should be given intravenously on induction of anesthesia and 1000 mg three hours later. For high-risk (e.g. colorectal) surgery, two additional 500 mg doses can be given at eight and sixteen hours after induction.

There are insufficient data on which to base a dosage recommendation for prophylaxis in patients with a creatinine clearance of ≤ 70 mL/min/1.73m^2.

TREATMENT: PEDIATRIC DOSAGE SCHEDULE (3 months or older)

For children and infants the following dosage schedule is recommended:

(a) CHILDREN ≥ 40 kg body weight should receive adult doses.

(b) CHILDREN AND INFANTS < 40 kg body weight should receive 15 mg/kg at six hour intervals. The total daily dose should not exceed 2 gm.

Clinical data are insufficient to recommend dosing for children less than 3 months of age, or pediatric patients with impaired renal function (serum creatinine > 2 mg/dL).

TIENAM is not recommended for the therapy of meningitis. If meningitis is suspected, an appropriate antibiotic should be used.

TIENAM may be used in children with sepsis as long as they are not suspected of having meningitis.

RECONSTITUTION, INTRAVENOUS SOLUTION

TIENAM IV for intravenous infusion is supplied as a sterile powder in vials containing 500 mg imipenem equivalent and 500 mg cilastatin equivalent.

TIENAM I.V. is buffered with sodium bicarbonate 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.

Sterile powder TIENAM I.V. should be reconstituted as shown in Table 3. It should be shaken until a clear solution is obtained. Variations of color, from colorless to yellow, do not affect the potency of the product.

TABLE 3. RECONSTITUTION OF TIENAM I.V.

DOSE OF TIENAM I.V. (mg of imipenem)	VOLUME OF DILUENT TO BE ADDED (mL)	APPROXIMATE AVERAGE CONCENTRATION OF TIENAM I.V. (mg/mL of imipenem)
500	100	5

Reconstitution of 20 ml vial

Contents of the vials must be suspended and transferred to 100 mL of an appropriate infusion solution. A suggested procedure is to add approximately 10 mL from the appropriate infusion solution (see the STABILITY, TIENAM I.V.) to the vial. Shake well and transfer the resulting suspension to the infusion solution container.
CAUTION: THE SUSPENSION IS NOT FOR DIRECT INFUSION.
Repeat with an additional 10 mL of infusion solution to ensure complete transfer of vial

contents to the infusion solution. The resulting mixture should be agitated until clear.

STABILITY, TIENAM I.V.

Store the dry powder at room temperature (E.P. = 15-25°C).

Table 4 shows the stability period for TIENAM I.V. when reconstituted with selected infusion solutions, and stored at room temperature or under refrigeration.

CAUTION: TIENAM I.V. is chemically incompatible with lactate and should not be reconstituted in diluents containing lactate. TIENAM I.V. can be administered, however, into an I.V. system through which a lactate solution is being infused.

TIENAM I.V. should not be mixed with or physically added to other antibiotics.

TABLE 4. STABILITY OF RECONSTITUTED OF TIENAM I.V.

Diluent	**Stability Period**	
	Room Temperature (25°C)	**Refrigeration (4°C)**
Isotonic Sodium Chloride	4 hrs	24 hrs
5% Dextrose in Water	4 hrs	24 hrs
10% Dextrose in Water	4 hrs	24 hrs
5% Dextrose & 0.9% NaCl	4 hrs	24 hrs
5% Dextrose & 0.45% NaCl	4 hrs	24 hrs
5% Dextrose & 0.225% NaCl	4 hrs	24 hrs
5% Dextrose & 0.15% KCl	4 hrs	24 hrs
Mannitol 5% and 10%	4 hrs	24 hrs

CONTRAINDICATIONS

Hypersensitivity to any component of this product.

PRECAUTIONS

GENERAL

There is some clinical and laboratory evidence of partial cross-allergenicity between TIENAM and the other beta-lactam antibiotics, penicillins and cephalosporins. Severe reactions (including anaphylaxis) have been reported with most beta-lactam antibiotics. Before therapy with TIENAM, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics. If an allergic reaction to TIENAM occurs, the drug should be discontinued and appropriate measures undertaken.

Pseudomembranous colitis has been reported with virtually all antibiotics and can range from mild to life-threatening in severity. Antibiotics should, therefore, be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis. It is important to consider a diagnosis of pseudomembranous colitis in patients who develop diarrhea in association with antibiotic use. While studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of antibiotic-associated colitis, other causes should also be considered.

USE IN PREGNANCY

There are no adequate and well-controlled studies in pregnant women. TIENAM should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Imipenem has been detected in human milk. If the use of TIENAM is deemed essential, the patient should stop nursing.

PEDIATRIC USE

Clinical data are insufficient to recommend the use of TIENAM for children under 3 months of age, or pediatric patients with impaired renal function (serum creatinine >2 mg/dL). (See also pediatric dosage schedule.)

CENTRAL NERVOUS SYSTEM

As with other beta-lactam antibiotics, CNS side effects such as myoclonic activity, confusional states, or seizures have been reported, especially when recommended dosages based on renal function and body weight were exceeded. These experiences have been reported most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function in whom accumulation of the administered entities could occur. Hence, close adherence to recommended dosage schedules is urged, especially in these patients (see DOSAGE AND ADMINISTRATION). Anticonvulsant therapy should be continued in patients with a known seizure disorder.

If focal tremors, myoclonus or seizures occur, patients should be evaluated neurologically and placed on anticonvulsant therapy if not already instituted. If CNS symptoms continue, the dosage of TIENAM should be decreased or discontinued.

Patients with creatinine clearances of $\leq$ 5 mL/min/1.73m^2 should not receive TIENAM unless hemodialysis is instituted within 48 hours. For patients on hemodialysis, TIENAM is recommended only when the benefit outweighs the potential risk of seizures.

DRUG INTERACTIONS

Generalized seizures have been reported in patients who received ganciclovir and TIENAM I.V. These drugs should not be used concomitantly unless the potential benefits outweigh the risks.

Also see STABILITY section.

Decreased serum levels of valproic acid with co-administration of carbapenem antibiotics have been reported during post-marketing and in some cases breakthrough seizures have occurred. Careful monitoring of serum levels of valproic acid should be considered if imipenem is to be co-administered with valproic acid.

SIDE EFFECTS

TIENAM is generally well tolerated. In controlled clinical studies, TIENAM was found to be tolerated as well as cefazolin, cephalothin, and cefotaxime. Side effects rarely require cessation of therapy and are generally mild and transient; serious side effects are rare. The most common adverse reactions have been local reactions.

LOCAL REACTIONS

Erythema, local pain and induration, thrombophlebitis.

ALLERGIC REACTIONS/SKIN

Rash, pruritus, urticaria, erythema multiforme, Stevens-Johnson syndrome, angioedema, toxic epidermal necrolysis (rarely), exfoliative dermatitis (rarely), candidiasis, fever including drug fever, anaphylactic reactions.

GASTROINTESTINAL REACTIONS

Nausea, vomiting, diarrhea, staining of teeth and/or tongue. In common with virtually all other broad spectrum antibiotics, pseudomembranous colitis has been reported.

BLOOD

Eosinophilia, leukopenia, neutropenia, including agranulocytosis, thrombocytopenia, thrombocytosis, and decreased hemoglobin, pancytopenia and prolonged prothrombin time have been reported. A positive direct Coombs' test may develop in some individuals.

LIVER FUNCTION

Increases in serum transaminases, bilirubin and/or serum alkaline phosphatase; hepatic failure (rarely), hepatitis (rarely) and fulminant hepatitis (very rarely)**.**

RENAL FUNCTION

Oliguria/anuria, polyuria, acute renal failure (rarely). The role of TIENAM 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.

Elevations in serum creatinine and blood urea nitrogen have been observed. Urine discoloration. This is harmless and should not be confused with hematuria.

NERVOUS SYSTEM /PSYCHIATRIC

As with other beta-lactam antibiotics, CNS side effects such as myoclonic activity, psychic disturbances, including hallucinations, confusional states, or seizures have been reported. Paresthesia, encephalopathy.

SPECIAL SENSES

Hearing loss, taste perversion.

GRANULOCYTOPENIC PATIENTS

Drug-related nausea and/or vomiting appear to occur more frequently in granulocytopenic patients than in non-granulocytopenic patients treated with TIENAM I.V.

OVERDOSAGE

No specific information is available on the treatment of overdosage with TIENAM. Imipenem-cilastatin sodium is hemodialyzable. However, usefulness of this procedure in the overdosage setting is unknown.

AVAILABILITY

TIENAM 500mg I.V is available in one vial pack.

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