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

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 1 g 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	8 hrs	1.5 g
	1000 mg	12 hrs	2 g
Severe - Fully susceptible	500 mg	6 hrs	2 g
Severe and/or Life threatening -	1000 mg	8 hrs	3 g
due to less susceptible organisms	1000 mg	6 hrs	4 g
(primarily some strains of *P. aeruginosa*)			

*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*

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

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/1.73 m^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 I.V. for intravenous infusion is supplied as a sterile powder in vials containing 250 mg imipenem equivalent and 250 mg cilastatin equivalent or 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. TIENAM I.V. 250 contains 18.8 mg of sodium (0.8 mEq) and TIENAM I.V. 500 contains 37.5 mg of sodium (1.6 mEq).
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
250	50	5

Reconstitution of infusion bottles

The infusion bottles of Tienam I.V. should be reconstituted as shown in Table 3.

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℃).
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.
Case reports in the literature have shown that co-administration of carbapenems, including imipenem, to patients receiving valproic acid or divalproex sodium results in a reduction in valproic acid concentrations. 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 valproic acid/divalproex sodium is generally not recommended. Anti-bacterials 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 TIENAM is necessary, supplemental anti-convulsant therapy should be considered (See **DRUG INTERACTIONS**).
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 ≦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.
Case reports in the literature have shown that co-administration of carbapenems, including imipenem, to patients receiving valproic acid or divalproex sodium results in a reduction of 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 **PRECAUTIONS**.)

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.
The following side effects have been reported during clinical studies and in post-marketing experience.

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

To be supplied locally.

Manufactured by Merck & Co., Inc., 2778 S. East Side Highway Elkton VA 22827, U.S.A.

泰寧® 注射劑
TIENAM® INJECTION

TEN-IV-082009
0787B-TWN-2010-001916

本藥限由醫師使用
衛署藥輸字第019279號

TIENAM® (imipenem及cilastatin sodium,MSD)為廣效性乙-內醯氨(beta-lactam)類抗生素。
TIENAM含二種成份：(1) imipenem，係新型beta-lactam抗生素thienamycins之代表 (2) cilastatin sodium，其為阻斷imipenem被腎臟代謝之專一性抑制劑，以增加imipenem原型在泌尿道之濃度。TIENAM中cilastatin及imipenem之重量比為1:1。Imipenem所屬之thienamycin抗生素，以其殺菌活性之強效範圍較任何已研究過之抗生素為廣而著稱。

微生物學

TIENAM為強效之細菌細胞壁合成抑制劑，可有效地殺死(bactericidal)大多數之病原菌-格蘭氏陽性菌，格蘭氏陰性菌，嗜氧菌及厭氧菌。
TIENAM不但和新型cephalosporins及penicillins類一樣對格蘭氏陰性菌具有強效，其亦兼有如早期狹效性beta-lactam類抗生素對格蘭氏陽性菌之強效性。TIENAM之殺菌範圍包括一些易對其他抗生素產生抗藥性之病原菌，如*Pseudomonas aeruginosa*，*Staphylococcus aureus*，*Enterococcus faecalis*及*Bacteroides fragilis*。
TIENAM對細菌所生之beta-lactamase有抵抗力，因此可以有效地對抗對大多數beta-lactam類抗生素先天具有抗藥性之病原菌，如*Pseudomonas aeruginosa*，*Serratia*屬，*Enterobacter*屬。
TIENAM之殺菌範圍比較任何已研究過之抗生素為廣，幾乎包括所有臨床上之各種病原菌，TIENAM在體外之有效抗菌範圍包括：

Gram(−)嗜氧菌

Achromobacter 屬
Acinetobacter 屬 (前稱 *Mima-Herellea*)
Aeromonas hydrophila
Alcaligenes 屬
Bordetella bronchicanis
Bordetella bronchiseptica
Bordetella pertussis
Brucella melitensis
Burkholderia pseudomallei (前稱 *Pseudomonas pseudomallei*)
Burkholderia stutzeri (前稱 *Pseudomonas stutzeri*)
Campylobacter 屬
Capnocytophaga 屬
Citrobacter 屬
Citrobacter freundii
Citrobacter koseri (前稱 *Citrobacter diversus*)
Eikenella corrodens
Enterobacter 屬
Enterobacter aerogenes
Enterobacter agglomerans
Enterobacter cloacae
Escherichia coli
Gardnerella vaginalis
Haemophilus ducreyi
Haemophilus influenzae (包括產生beta-內醯胺之菌株)
Haemophilus parainfluenzae
Hafnia alvei
Klebsiella 屬
Klebsiella oxytoca
Klebsiella ozaenae
Klebsiella pneumoniae
Moraxella 屬
Morganella morganii (前稱 *Proteus morganii*)
Neisseria gonorrhoeae (包括 *penicillinase-producing strains*)
Neisseria meningitidis
Pasteurella 屬
Pasteurella multocida
Plesiomonas shigelloides
Proteus 屬
Proteus mirabilis
Proteus vulgari
Providencia 屬
Providencia alcalifaciens
Providencia rettgeri (前稱 *Proteus rettgeri*)
Providencia stuartii
Pseudomonas 屬**
Pseudomonas aeruginosa
Pseudomonas fluorescens
Pseudomonas putida
Salmonella 屬
Salmonella typhi
Serratia 屬
Serratia proteamaculans (前稱*Serratia liquefaciens*)
Serratia marcescens
Shigella 屬
Yersinia 屬 (前稱 *Pasteurella*)
Yersinia enterocolitica
Yersinia pseudotuberculosis
** *Stenotrophomonas maltophilia* (前稱*Xanthomonas maltophilia*, 前稱 *Pseudomonas maltophilia*)及某些*Burkholderia cepacia* (前稱*Pseudomonas cepacia*)的菌屬對TIENAM不具感受性。

Gram(+)嗜氧菌

Bacillus 屬
Enterococcus faecalis
Erysipelothrix rhusiopathiae
Listeria monocytogenes
Nocardia 屬
Pediococcus 屬
Staphylococcus aureus (包括青黴素酶產生菌株)
Staphylococcus epidermidis (包括青黴素酶產生菌株)
Staphylococcus saprophyticus
Streptococcus agalactiae
Streptococcus Group C
Streptococcus Group G
Streptococcus pneumoniae
Streptococcus pyogenes
鏈球菌之Viridans菌株群 (包括alpa及gamma溶血性菌株)
*Enterococcus faecium*及methicillin-resistant staphylococci對TIENAM不具感受性。

Gram(−)厭氧菌

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

Gram(+)厭氧菌

Actinomyces 屬
Bifidobacterium 屬
Clostridium 屬
Clostridium perfringens
Eubacterium 屬
Lactobacillus 屬
Microaerophilic streptococcus
Peptococcus 屬
Peptostreptococcus 屬
Propionibacterium 屬 (包括*P. acnes*)

Other

Mycobacterium fortuitum
Mycobacterium smegmatis

體外試驗證實imipenem與aminoglycoside併用時，能加強效果對抗某些分離出的*Pseudomonas aeruginosa*。

適應症

對imipenem具有感受性之革蘭氏陰性菌，革蘭氏陽性菌感染症。
說明：TIENAM因具極寬廣之殺菌活性，故特別適合用於治療多種細菌感染和嗜氧／厭氧菌混合型感染症，也適合用於病原菌尚未鑑定前之初期治療。TIENAM適合用於治療下列具感受性細菌所引起之感染：

＊腹腔內感染
＊下呼吸道感染
＊婦科感染
＊敗血症
＊泌尿生殖道感染
＊骨及關節感染
＊皮膚及軟組織感染
＊心內膜炎

TIENAM可用於治療具感受性之嗜氧／厭氧性菌株所引起之混合感染，此類混合感染大多由來自糞便、陰道、皮膚或口腔之菌株污染所致。在此種混合感染中*Bacteroides fragilis*為最常見之厭氧菌，此菌對aminoglycosides、cephalosporin及 penicillin均具

抗藥性，但對TIENAM仍具感受性。
TIENAM顯示能有效地對抗多種對cephalosporin類(包括：cefazolin、cefoperazone、cephalothin、cefoxitin、cefotaxime、moxalactam、cefamandole、ceftazidime和ceftriaxone)有抗藥性之嗜氧及厭氧性之革蘭氏陰性及陽性菌引起的感染症。同樣地，許多對aminoglycosides (gentamicin、amikacin、tobramycin) 和(或)penicillin類(ampicillin、carbenicillin、penicillin-G、ticarcillin、piperacillin、azlocillin、mezlocillin)有抗藥性之菌株感染，對TIENAM的治療具感受性。
註：TIENAM不適用於治療腦膜炎。

預防用途：
病人進行已遭污染或可能導致污染之手術時，TIENAM可用於預防手術後感染；或當手術後感染會產生嚴重之後果時，可事先投予TIENAM預防。

劑量及給藥法

TIENAM之建議劑量係以所需之imipenem量表示，其中含有等量之cilastatin。
TIENAM之每日總劑量，需視其感染之種類及嚴重程度而定；其給藥間隔則視其病原菌感受性、腎功能及體重而定。

靜脈滴注：
治療：成人之劑量(病人具正常腎功能)
表一所示之劑量係以具正常腎功能(creatinine清除率大於70 mL/min/1.73 m^2)且體重大(等)於70 kg之患者為標準。對於病人之creatinine清除率小(等)於70 mL/min/1.73 m^2，以及(或)體重小於70 kg時，必須減低劑量(見表二)。尤其當病人之體重很輕且(或)有中度(或重度)腎功能不足時，更需減低劑量。
大多數之感染對每天1-2 gm分成3-4次之給藥法有良好反應。對中度感染，可用每天2次，每次1 gm之劑量來治療。對感受性較差之病菌所引起之感染，靜脈投與TIENAM之每日總劑量可增至4 gm/day，或50 mg/kg/day，以選取較低劑量為原則。當靜脈滴注TIENAM之劑量小(等)於500 mg時，其滴注時間需大於20-30分鐘；當劑量大於500 mg時，其滴注時間需大於40-60分鐘。當滴注時，病人若有噁心感時，宜降低其滴注速率。

表一
具正常腎功能且體重大(等)於70 kg*之成人靜脈給藥劑量表

感染嚴重程度	劑量 (mg of imipenem)	給藥間隔 (hr)	每日總劑量 (gm)
輕微	250	6	1
中度	500	8	1.5
	1000	12	2
嚴重(且具感受性)	500	6	2
嚴重且(或)具生命危險－由感受性較差的病菌造成(主為*P. aeruginosa*類菌株)	1000	8	3
	1000	6	4

* 當病人之體重小於70 kg時，必須依比例降低劑量。

因TIENAM具高抗菌活性，故其每日總劑量最大不宜超過50 mg/kg/day或4 gm/day，以選取較低劑量為原則。但具正常腎功能之嚢性纖維化症患者曾以高達90 mg/kg/day (分數次給藥，但不超過4 gm/day)之劑量治療。
TIENAM曾成功地以單一治療方式處理免疫力系統受損之癌症患者之確定(或疑似)之感染，如敗血症。
治療：成人之劑量(病人之腎功能不足)
決定腎功能不足成人患者之劑量如下：
1. 依感染性質由表一選擇每日總劑量。
2. 依病人creatinine清除率分類及由表一選擇之每日總劑量，由表二選擇適當之減量療程。(其滴注時間請參考具正常腎功能患者靜脈給藥劑量表)。

表二
腎功能不足之成人患者且體重大(等)於70 kg*之靜脈TIENAM減量劑量表

每日總劑量 (由表一)	Creatinine清除率(mL/min/1.73 m^2) 41-70	21-40	6-20
1.0 g/day	250 mg q8h	250 mg q12h	250 mg q12h
1.5 g/day	250 mg q6h	250 mg q8h	250 mg q12h
2.0 g/day	500 mg q8h	250 mg q6h	250 mg q12h
3.0 g/day	500 mg q6h	500 mg q8h	500 mg q12h
4.0 g/day	750 mg q8h	500 mg q6h	500 mg q12h

* 當病人之體重小於70 kg時，必須依比例進一步降低劑量。

當病人之creatinine清除率為6-20 mL/min/1.73 m^2而使用500 mg之劑量時，可能增加癲癇發作(seizure)之危險性。
當病人之creatinine清除率為小(等)於5 mL/min/1.73 m^2時，不應使用靜脈注射之TIENAM，除非在48小時內安排血液透析。
血液透析：
當病人之creatinine清除率為小(等)於5 mL/min/1.73 m^2且正接受血液透析時，可選用creatinine清除率為6-20 mL/min/1.73 m^2那組之建議劑量(請參考腎功能不足成人患者劑量表)。
血液透析時imipenem及cilastatin兩者均由血液中清除。在血液透析完成後及12小時後病人應接受靜脈投予TIENAM。血液透析患者(尤其有患有中樞神經系統疾患者)需密切監測，僅在其治療效益大於其癲癇發作之危險性時，才可靜脈投予TIENAM。(請參考注意事項)
病人進行腹膜透析時，目前資料尚無法建議其靜脈投予TIENAM時所需之劑量。
老年患者之腎功能狀態不能單靠血尿氮或creatinine之數據來評估，但測定其creatinine清除率可為此類病人劑量調節之參考。
預防用途：成人劑量及給藥法
成人預防手術後感染時，可在麻醉誘導時靜脈投予1000 mg TIENAM，三小時後再投予1000 mg。高感染性(如結腸直腸)手術時，可在誘導後8及16小時增投500 mg。
當病人之creatinine清除率為小(等)於70 mL/min/1.73 m^2時，目前資料尚無法建議其預防用途時所需之劑量。
治療用途：小兒科劑量及給藥法(三個月或更大)
嬰幼兒之劑量及給藥法建議如下：
(a)小孩之體重大(等)於40 kg時可採用成人劑量。
(b)小孩及幼兒之體重小於40 kg時可每六小時給予15 mg/Kg，但每日總劑量不宜超(b)過2 gm。
臨床資料尚無法對三個月以下之幼兒或腎功能不良幼兒患者(血清creatinine大於2 mg/dL)建議其所需之劑量。
TIENAM不被建議用於治療腦膜炎，當有腦膜炎之可能時，需選用適合之抗生素。當無腦膜炎時，TIENAM可用於治療幼兒之敗血症。
靜脈滴注溶液之調配：
供靜脈滴注之TIENAM I.V. 係滅菌粉末裝於藥瓶中。每瓶含有相當於250 mg之imipenem及相當於250 mg之 cilastatin，或是含有相當於500 mg之imipenem及相當於500 mg之cilastatin。
TIENAM I.V.以碳酸氫鈉當緩衝溶液，調節其pH值介於6.5-8.5之間。當溶液依指示調配及使用時，其pH值之變化很小。TIENAM I.V. 250含18.8 mg之鈉(0.8 mEq)，而TIENAM I.V. 500則含37.5 mg之鈉(1.6 mEq)。
TIENAM I.V.滅菌粉末需依表三所示調配，並振搖至溶液澄清為止。溶液呈現無色至黃色，其顏色之差異並不影響藥效。

表三
TIENAM I.V.之調配

TIENAM I.V.劑量 (mg of imipenem)	稀釋液添加量 (mL)	TIENAM I.V.平均濃度 (mg/mL of imipenam)
500	100	5
250	50	5

輸注瓶(Infusion bottles)之調配
請參見表三 TIENAM I.V.之調配
20 mL小瓶(vials)之調配
小瓶中的內容物必須調配成懸浮液後，再移入輸注容器中，最終輸注溶液為100 mL。建議調配方法是加入大約10 mL輸注溶液至小瓶中(請參考TIENAM I.V.之安定性)，充分搖動後，將此懸浮液移入輸注容器。
注意：此懸浮液不可直接輸注用。
重覆加10 mL輸注溶液至小瓶中，確保能完全將小瓶中的內容物移入輸注容器中。混合輸注溶液必須搖動至澄清。
TIENAM I.V.之安定性：
滅菌粉末：宜於室溫下貯存(E.P.=15-25℃)。
表四為當TIENAM I.V.與特定浸輸液調配後，溶液於室溫下或冷藏下之安定期。
注意：TIENAM I.V.與乳酸鹽(lactate)屬化學配伍禁忌,所以不應以含乳酸鹽之稀釋液來調配。然而TIENAM I.V.可加入正在進行靜脈輸注的含乳酸鹽溶液一同輸注。
TIENAM I.V.不可與其它種抗生素混合或併用。

表四
已調配之TIENAM I.V.溶液安定性

稀釋液	安定期 室溫(25℃)	冷藏(4℃)
氯化鈉等張溶液	4小時	24小時
5%葡萄糖液	4小時	24小時
10%葡萄糖液	4小時	24小時
5%葡萄糖液及0.9%氯化鈉	4小時	24小時
5%葡萄糖液及0.45%氯化鈉	4小時	24小時
5%葡萄糖液及0.225%氯化鈉	4小時	24小時
5%葡萄糖液及0.15%氯化鉀	4小時	24小時
5%, 10%甘露醇	4小時	24小時

禁忌
TIENAM禁用於對該品任何成分過敏的病人。

注意事項
一般通則
臨床文獻顯示本品與其他Beta-內醯胺類抗生素、cephalosporins及penicillin類有部分交叉過敏性現象。大多數Beta-內醯胺類抗生素曾有嚴重反應(包括過敏性休克)報告。啟用TIENAM治療前，應詢問病患有無對Beta-內醯胺類抗生素過敏之病史。如對TIENAM發生過敏反應，應停藥並採取適當處置。
由文獻病例報告顯示，病人服用valproic acid或divalproex sodium，合併使用carbapenems類，包括imipenem，會使valproic acid血中濃度減少。相互作用的結果，valproic acid的血中濃度可能下降低於治療範圍，因此增加了突發性癲癇的風險。增加valproic acid或divalproex sodium的劑量可能不足以克服這種相互作用。一般不建議imipenem和valproic acid或divalproex sodium合併使用。服用valproic acid或divalproex sodium，癲癇有良好控制的病人，應考慮使用除了carbapenems類以外的抗菌劑，來治療感染。如果必須使用TIENAM，應考慮追加抗痙攣治療(見**藥物相互作用**)。
幾乎所有的抗生素都曾有引起偽膜性結腸炎的報告。其程度由輕微至威脅生命不等，凡是抗生素類藥品都應小心的使用於那些曾經罹患過胃腸疾病(尤其是結腸炎)的病人身上，如果病人在使用抗生素後有下痢的情況出現時，應該去檢查是否罹患了偽膜性結腸炎。雖然研究報告顯示，由*Clostridium difficile*所產生的毒素是引起偽膜性結腸炎的主要原因，但是其他原因也應列入考慮。
孕婦
TIENAM使用於懷孕婦女方面的安全性報告尚未確立，除非已針對胎兒危險性進行效益評估後，才建議使用。
哺乳婦女
母乳中可測得imipenem之存在，如果病人非採用TIENAM治療不可時，必須停止哺乳。
兒童
臨床資料仍不充份，尚無法對三個月以下之幼兒或腎功能不良幼兒患者(血清creatinine大於2 mg/mL)建議其所需之劑量。
中樞神經系統
本品與其他Beta-內醯胺類抗生素一樣，曾被報告有中樞神經系統副作用，例如肌肉陣攣，混淆感或癲癇發作(Seizure)，特別是服用超過依腎功能及體重計算之建議劑量者。而這些副作用大多發生於中樞神經系統障礙，(如腦部損害或曾 有癲癇發作者)及腎功能損壞者，此類病人會發生藥物聚積，因 此這類患者的使用劑量必須小心觀察後訂定(參考「劑量及給藥法」)，有癲癇病症的人應繼續使用抗痙攣藥治療。
如發生局部性顫抖、肌陣攣、癲癇，應評估病人的神經狀況並進行抗痙攣治療，如果中樞神經系統症狀仍持續，則必須減少TIENAM的劑量或停止使用。
當病人之creatinine清除率為小(等)於5 mL/min/1.73 m^2時，不應使用TIENAM，除非在48小時內安排血液透析。血液透析患者(尤其有患有中樞神經系統疾患者)需密切監測，僅在其治療效益大於其癲癇發作之危險性時，才可投予TIENAM。

藥物相互作用
TIENAM I.V.曾有報告與ganciclovir併用時，發生癲癇大發作。因此僅在其治療效益大於其危險性時，才可投予TIENAM。
也參見安定性。
由文獻病例報告顯示，病人服用valproic acid或divalproex sodium，合併使用carbapenems類，包括imipenem，會使valproic acid血中濃度減少。相互作用的結果，valproic acid的血中濃度可能下降低於治療範圍，因此增加了突發性癲癇的風險。雖然此相互作用的作用機轉尚不清楚，由in-vitro和動物試驗的結果顯示，carbapenems類可能抑制valproic acid的葡萄糖醛酸代謝物(VPA-g)水解為valproic acid，因此降低了valproic acid的血中濃度(見**注意事項**)。

副作用
一般來說，TIENAM的耐受性極佳，一項臨床對照試驗顯示TIENAM的耐受性與cefazolin、cephalothin及cefotaxime一樣好，其所引起的副作用大多溫和且短暫，必須停藥的情形很少發生，至於嚴重的副作用亦甚少發生，最常見的不良反應均為局部反應。
臨床研究期間及上市後使用經驗已有以下的副作用告。
局部反應
紅斑，局部發痛及硬塊，血栓靜脈炎。
過敏反應/皮膚
發疹、搔癢、蕁麻疹、多形性紅斑、Stevens-Johnson氏症候群、血管神經性水腫、毒性表皮壞死(甚少)、剝落性皮膚炎(甚少)、念珠菌病、發熱包括藥物性發熱、過敏反應。
胃腸道方面
噁心、嘔吐、腹瀉、牙齒及(或)舌部著色。亦曾發生一般廣效型抗生素均可能引起的偽膜性腸炎。
血液方面
嗜伊紅血球過多症、白血球減少症、中性白血球減少症，(包括顆粒性白血球減少症、血小板減少症、血小板過多症及血色素減少，全血球減少和凝血時間延長)。有些病患對Coomb's Test呈現陽性反應。
肝功能
血清轉氨酵素、膽紅素及(或)血清鹼性磷酸酯酵素上升；肝衰竭(甚少)、肝炎(甚少)及猛爆性肝炎(極少)。
腎功能
少尿無尿、多尿、急性腎衰竭(甚少)。TIENAM對腎功能之影響，因病人常已先有腎前氮血症或腎功能受損情形，故很難加以確認。
血中肌酸酐及尿素氮增加，尿液變色，通常這種情況是無害的，但不應與血尿症混為一談。
神經系統/精神病學方面
與其他Beta-內醯胺類抗生素一樣，曾被報告引起CNS方面的副作用，如肌肉陣攣，精神障礙包括幻覺、精神混亂，以及癲癇發作。感覺異常，腦病。
特殊感覺方面
聽力喪失、味覺受影響。
粒性血球減少症(Granulocytopenic)病人
粒性血球減少症病人使用TIENAM I.V.比無此症之人較易發生由藥物引發之噁心、嘔吐。

藥物過量
臨床資料尚無討論TIENAM藥物過量之治療法，雖然血液透析時imipenem及cilastatin兩者均由血液中清除，但血液透析在處理藥物過量時之有效性尚未確立。

上市產品
供靜脈滴注之TIENAM I.V. 有兩種劑量可用：
a. 相當於250 mg之imipenem及相當於250 mg cilastatin。
b. 相當於500 mg之imipenem及相當於500 mg cilastatin。
兩種強度均為滅菌粉末裝於20 mL 或120 mL之藥瓶供應。

製造廠：Merck & Co., Inc.
廠　址：2778 South East Side Highway Elkton, VA 22827, U.S.A.

包裝廠：Merck Sharp & Dohme (Australia) Pty. Ltd.
廠　址：54-68 Ferndell St., South Granville, N.S.W. 2142 Australia
藥　商：美商默沙東藥廠股份有限公司臺灣分公司
地　址：台北市敦化南路二段216號14樓

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I.V. Infusion
TIENAM®
(imipenem and cilastatin sodium, MSD)

TIENAM® (imipenem and cilastatin sodium, MSD) is a broad spectrum beta-lactam antibiotic.
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 multocida*
- *Plesiomonas shigelloides*
- *Proteus* spp.
- *Proteus mirabilis*
- *Proteus vulgaris*
- *Providencia* spp.
- *Providencia alcalifaciens*
- *Providencia rettgeri* (formerly *Proteus rettgeri*)
- *Providencia stuartii* (formerly *Citrobacter diversus*)
- *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.

GRAM-POSITIVE AEROBES
- *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,