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.

**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 with earlier narrow-spectrum beta-lactam antibiotics. The spectrum of activity of TIENAM includes virtually all clinically significant pathogens. Organisms against which TIENAM has been shown to be bactericidal or bacteriostatic include:

**GRAM-POSITIVE AEROBES**
- Enterococcus faecalis
- Enterococcus faecalis
- Enterococcus faecalis
- Enterococcus faecalis
- Enterococcus faecalis

**GRAM-NEGATIVE AEROBES**
- Bacteroides distasonis
- Bacteroides fragilis
- Bacteroides thetaiotaomicron
- Bacteroides uniformis
- Bacteroides vulgatus
- Bifidobacteria
- Fusiobacterium
- Fusobacterium necrophorum
- Fusobacterium nucleatum
- Porphymonas asaccharolytica (formerly Bacteroides asaccharolyticus)
- Prevotella dora (formerly Bacteroides disiens)
- Prevotella disiens (formerly Bacteroides disiens)
- Prevotella intermedia (formerly Bacteroides intermedius)
- Prevotella melaninogenica (formerly Bacteroides melaninogenicus)
- Veillonella parvula

**GRAM-POSITIVE anaEROBES**
- Actinomyces spp.
- Bifidobacterium spp.
- Clostridium difficile
- Clostridium tetani
- Eubacterium spp.
- Lactobacillus spp.
- Mobilicoccus spp.
- Microaerophilic streptococcus
- Peptococcus spp.
- Peptostreptococcus spp.
- Propionibacterium spp. (including P. acnes)

**anaEROBES**
- Bacteroides fragilis
- Clostridium difficile
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- Eubacterium spp.
- Lactobacillus spp.
- Mobilicoccus spp.
- Microaerophilic streptococcus
- Peptococcus spp.
- Peptostreptococcus spp.
- Propionibacterium spp. (including P. acnes)

**INDICATIONS**

**TREATMENT**

The activity of TIENAM against an unusually broad spectrum of aerobic and anaerobic bacteria makes it particularly useful in the treatment of polymeric and mixed aerobic/anaerobic infections. For patients with impaired renal function, the dosage recommendations for TIENAM are based on the creatinine clearance of the patient, not the creatinine level of the test of the patient's urine. The dosage recommendations for TIENAM are based on the creatinine clearance of the patient, not the creatinine level of the test of the patient's urine. The dosage recommendations for TIENAM are based on the creatinine clearance of the patient, not the creatinine level of the test of the patient's urine. The dosage recommendations for TIENAM are based on the creatinine clearance of the patient, not the creatinine level of the test of the patient's urine.

**DOSEAGE AND ADMINISTRATION**

The total daily dosage of TIENAM should be based on the level or severity of infection and given in equally divided doses based on the creatinine clearance of the patient, not the creatinine level of the test of the patient's urine. The dosage recommendations for TIENAM are based on the creatinine clearance of the patient, not the creatinine level of the test of the patient's urine. The dosage recommendations for TIENAM are based on the creatinine clearance of the patient, not the creatinine level of the test of the patient's urine. The dosage recommendations for TIENAM are based on the creatinine clearance of the patient, not the creatinine level of the test of the patient's urine.
Determination of creatinine clearance is suggested to provide guidance for dosing in such patients (see SUPPLEMENTAL PRESCRIBING INFORMATION, CREATININE CLEARANCE).

PRECAUTIONS: 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 m².

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, INTRAVENTRICAL SOLUTION

TIENAM I.V. for intravenous infusion is supplied as a sterile powder in vials containing 250 mg imipenem equivalent and 255 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

<table>
<thead>
<tr>
<th>RECONSTITUTION OF TIENAM I.V.</th>
<th>DOSE OF TIENAM I.V. (mg of imipenem)</th>
<th>VOLUME OF DILUENT TO BE ADDED (mL)</th>
<th>APPROXIMATE AVERAGE CONCENTRATION OF TIENAM I.V. (mg/mL of imipenem)</th>
</tr>
</thead>
<tbody>
<tr>
<td>500</td>
<td>100</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>250</td>
<td>50</td>
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</table>

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°C).

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

CAUTION: TIENAM I.V. is chemically incompatible with lactate and should not be reconstituted in dextrose-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.

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 guidance for dosing 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 severe. 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 that indicate 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/1.73m² 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.

SIDE EFFECTS

TIENAM is generally well tolerated. In controlled clinical studies, TIENAM was found to be as well tolerated 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 fulminating hepatitis (very rarely).

RENAL FUNCTION

Oliguric/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 discolored. 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.