Tienam® I.M. 500MG

(Imipenem, cilastatin sodium, M.S.D.)

For Intramuscular Injection

TIENAM® WITH LIDOCAINE 1% is supplied as a sterile powder for injection fluid in vials containing Imipenem monohydrate and Cilastatin Sodium equivalent to 500 mg Imipenem and Cilastatin when reconstituted. It is supplied with an ampule (2ml) containing Lidocaine hydrochloride monohydrate, equivalent to 20 mg Lidocaine hydrochloride (10 mg/ml). The I.M. formulation is not for I.V. use.

PROPERTIES

TIENAM® I.M. (imipenem/cilastatin sodium) is a broad spectrum beta-lactam antibiotic for intramuscular injection only. TIENAM® I.M. 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® I.M. in a 1:1 ratio by weight.

Imipenem, also referred to as N-formimidoyl-thienamycin, is a semi-synthetic derivative of thienamycin, the parent compound produced by the filamentous bacterium *Streptomyces cattleya*.

Cilastatin sodium is a competitive, reversible and specific inhibitor of dehydropeptidase-1, the renal enzyme which metabolizes and inactivates imipenem. It is devoid of intrinsic antibacterial activity and does not affect the antibacterial activity of imipenem.

Microbiology

TIENAM® I.M. 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® I.M. shares with the newer cephalosporins and penicillins a broad spectrum of activity against gram-negative species, but its high potency against gram-negative species was previously associated only with earlier narrow-spectrum beta-lactam antibiotics. The spectrum of activity of TIENAM® I.M. includes *Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus faecalis and Bacteroides fragilis*, a diverse group of problem pathogens.

Imipenem is resistant to degradation by bacterial betalactamases and is often active against microorganisms resistant to other beta-lactam antibiotics.

Organisms against which TIENAM® I.M. is usually active in vitro include:

AEROBIC BACTERIA

gram negative

MIC_{90} 0.01-0.1	MIC_{90} 0.1-1 *µg/ml*	MIC_{90} 1-10 *µg/ml*
Campylobacter spp.	Escherichia coli	Proteus mirabilis
Campylobacter fetus	Serratia marcescens	Proteus vulgaris
spp. jejuni	Serratia liquefaciens	Proteus spp.
	Serratia spp.	Morganella morganii
	Klebsiella oxytoca	Providencia rettgeri
	Klebsiella pneumoniae	Providencia stuartii
	Klebsiella spp.	Providencia spp.
	Citrobacter freundil	Enterobacter aerogenes
	Citrobacter diversus	Enterobacter agglomerans
	Citrobacter spp.	Enterobacter cloacae
	Salmonella typhi	Enterobacter spp.
	Salmonella spp.	Pseudomonas aeruginosa
	Shigella spp.	Pseudomonas fluorescens
	Acinetobacter spp.	Pseudomonas spp.
	Neisseria gonorrhoeae	Haemophilus influenzae
	Neisseria meningitidis	Haemophilus parainfluenzae
	Yersinia spp.	Gardnerella spp.
	Yersinia enterocolitica	
	Yersinia pseudo-tuberculosis	

None of the organisms in the column MIC_{90} (1-10) has MIC value higher than 8 (g/ ml.

gram positive

MIC_{90} 0.01-0.1*µg/ml*	MIC_{90} 0.1-1 *µg/ml*	MIC90 1-10 *µg/ml*
Streptococcus group A	Streptococcus group B	*Staphylococcus aureus*
(S. pyogenes)	(including enterococci)	
Streptococcus group B	*(Streptococcus faecalis)*	
(S. agalactiae)	and non-enterococci)	
Streptococcus group C	*Streptocccus pneumoniae*	
	Streptococcus viridans	
	Staphylococcus epidermidis	
	Listeria monocytogenes	

ANAEROBIC BACTERIA

gram negative

MIC_{90} 0.01-0.1*µg/ml*	MIC_{90} 0.1-1 *µg/ml*	MIC90 1-10 *µg/ml*
	Bacteroides fragilis	
	Bacteroides spp.	
	Veillonella spp.	

gram positive

MIC_{90} 0.01-0.1*µg/ml*	MIC_{90} 0.1-1 *µg/ml*	MIC90 1-10 *µg/ml*
Peptococcus spp.	Actinomyces spp.	Fusobacterium spp.
Peptostreptococcus spp.	Clostridium perfringens	
Propionibacterium spp.	Clostridium spp.	
Propionibacterium acnes		

Xanthomonas maltophilia (formerly Pseudomonas maltophilia) and some strains of Pseudomonas cepacia are generally not susceptible to TIENAM® I.M. Some methicillin-resistent staphylococci and some group D streptococci are not susceptible to TIENAM® I.M. In vitro tests show imipenem to act synergistically with aminoglycoside antibiotics against some isolates of *Pseudomonas* aeruginosa.

Susceptibility testing.

Category (mg/l)	*Zone Diameter (mm)*	*Recommended MIC Point*
fully susceptible	≥ 16	≤4
moderately susceptible	14-15	8
resistant	≤ 13	>16

Kirby-Bauer procedure as modified by the National Commitee for Clinical Laboratory Standards (NCCLS).

Zone diameters are based on results obtained using a 10mg imipenem disc.

The recommendation of the Dutch Working Group on susceptibility is:

Category (mg/l)	*Zone Diameter (mm)*	*Recommended MIC Point*
fully susceptible	≥ 24	≤ 2
moderately susceptible	21-23	4-8
Resistant	≤ 20	> 16

MSD

INDICATIONS

Infections due to organisms susceptible to TIENAM® I.M.

- intra-abdominal infections
- lower respiratory tract infections
- septicemia
- genitourinary tract infections
- bone and joint infections
- skin and soft-tissue infections
- endocarditis

TIENAM® I.M. can be used for the treatment of mixed infections caused by susceptible strains of aerobic and anaerobic bacteria. TIENAM® I.M. is not indicated for the treatment of meningitis.

CONTRA-INDICATIONS

Hypersensitivity to any component of this drug.

Patients in whom hypersensitivity reactions such as anaphylactic reactions have occured after administration of penicillins or cephalosporins.

SIDE EFFECTS

In controlled clinical studies, TIENAM® I.M. was found to be tolerated as well as cefalothin, and cefotaxime. Side-effects rarely require cessation of therapy and are generally mild and transient.

Serious side-effects are rare. Although the absolute incidence of adverse experiences is slightly higher at dosages 2 to 4 g per day, the overall safety profile is similar to that seen at lower dosages. The most common adverse reactions have been local reactions following injection.

Local reactions
Erythema, local pain and induration, thrombophlobitis.

Allergic reactions
Rash, pruritis, urticaria, toxic epidermal necrolysis (rarely), fever, anaphylactic reactions.

Gastrointestinal reactions
Nausea, vomiting, diarrhea. In common with virtually all other broad spectrum antibiotics, pseudo-membranous colitis has been reported. Hepatitis has rarely been reported.

Blood
Eosinophilia, leukopenia, neutropenia, including agranulocytosis, thrombocytopenia, thrombocytosis, decreased hemoglobin have been reported. A positive direct Coombe test may develop in some individuals.

Liver function
Mild increases in serum transaminases, bilirubin and/or alkaline phosphatase have been reported.

Renal function
Oliguria/anuria, polyunia, acute renal failure (rarely). In such cases predisposing factors usually were present.

Elevations in serum creatinine and blood urea nitrogen have been reported. Reddish urine discoloration has been observed in the pediatric group. This is harmless and should not be confused with hematuria.

CNS
As with other beta-lactam antibiotics, CNS adverse experiences such as myoclonic activity, psychic disturbance, confusional states, or seizures have been reported with the I.V. formulation.

Special senses
Taste perversion.

ADDITIONAL SIDE-EFFECTS

For the following side-effects, a causal relationship has not been established.

Gastrointestinal: hemorrhagic colitis, gastroenteritis, abdominal pain, glossitis, tongue papillar hypertrophy, heartburn, pharyngeal pain, increased salivation.

Central nervous system: dizziness, somnolence, encephalopathy, paresthesia, vertigo headache.

Special senses: transient hearing loss in patients with impaired hearing, tinnitus.

Respiratory: chest discomfort, dyspnea, bronchospasm, hyperventilation, thoracic spine pain.

Cardiovascular: hypotension, palpitations, tachycardia.

Skin: erythema multiforme, facial edema, flushing, cyanosis, hyperhidrosis, skin texture changes, candidiasis, pruritus vulvae.

Body as a whole: polyarthralgia, asthenia/weakness.

WARNINGS AND PRECAUTIONS

There is some clinical and laboratory evidence or partial cross-allergenicity between TIENAM® I.M. and the other beta-lactam antibiotics, penicillin and cephalosporins. Sever reactions (including anaphylaxis) have been reported with most beta-lactam antibiotics. Before therapy.

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