TIMENTIN® PRODUCT INFORMATION

(Sterile ticarcillin sodium and potassium clavulanate
for intravenous use)

DESCRIPTION

TIMENTIN is an injectable antibacterial combination consisting of the semi-synthetic antibiotic, ticarcillin sodium and the β-lactamase inhibitor, potassium clavulanate (the potassium salt of clavulanic acid). Ticarcillin is derived from the basic penicillin nucleus, 6-amino-penicillanic acid. Chemically, it is 6-{(carboxy-3-thienylacetyl)amino}-3,3-dimethyl-7-oxo-4-thia-1-azabi-cyclo{3.2.0}heptane-2-carboxylic acid disodium salt.

Clavulanic acid is produced by the fermentation of Streptomyces clavuligerus. It is a β-lactam structurally related to the penicillins but has only weak antibacterial activity. It possesses the ability to inactivate a wide variety of β-lactamases excluding the type 1 Richmond but including the plasmid mediated β-lactamases by blocking the active site of these enzymes. Chemically, potassium clavulanate is potassium Z-(3R,5R)-2-(β-hydroxyethylidene) clavam-3-carboxylate.

TIMENTIN is supplied as a white to pale yellow powder for reconstitution. TIMENTIN is very soluble in water; its solubility being greater than 600mg/mL. The reconstituted solution is clear, colourless or pale yellow, having a pH of 6.0 to 8.0. For the TIMENTIN 3.1g vials, the sodium content is approximately 15.6mmol (360mg). The potassium content is approximately 0.5mmol (20mg).

MICROBIOLOGY

Ticarcillin, like other penicillins, has a bactericidal effect on susceptible bacteria during active multiplication.

Ticarcillin is, however, susceptible to degradation by β-lactamases. The addition of clavulanic acid, a β-lactamase inhibitor, extends the antibacterial spectrum of ticarcillin so as to include organisms which are normally resistant to it by virtue of their ability to produce β-lactamases. Many of the following organisms, whose resistance is often due to β-lactamase production, are therefore susceptible to TIMENTIN.

Gram-negative bacteria

Pseudomonas aeruginosa
(β-lactamase and non-β-lactamase producing)
Escherichia coli
(β-lactamase and non-β-lactamase producing)
Proteus mirabilis
(β-lactamase and non-β-lactamase producing)
Proteus vulgaris

(β-lactamase and non-β-lactamase producing)
*Providencia rettgeri (*formerly *Proteus rettgeri)*
(β-lactamase and non-β-lactamase producing)
*Morganella morganii (*formerly *Proteus morganii)*
(β-lactamase and non-β-lactamase producing)

Enterobacter species
(Although most strains of Enterobacter species are resistant *in vitro*, clinical efficacy has been demonstrated with TIMENTIN in urinary tract infections caused by these organisms).
Haemophilus influenzae
(β-lactamase and non-β-lactamase producing)
*Neisseria meningitidis**
(β-lactamase and non-β-lactamase producing)
Salmonella species
(β-lactamase and non-β-lactamase producing)
Klebsiella pneumoniae
(β-lactamase and non-β-lactamase producing)

Some strains of β-lactamase and non-β-lactamase producing microorganisms such as Mima, Herellea, Citrobacter and Serratia.

Gram-positive bacteria
Staphylococcus aureus
(β-lactamase and non-β-lactamase producing)
Staphylococcus epidermidis
(coagulase negative Staphylococci)
(β-lactamase and non-β-lactamase producing)
*Streptococcus pneumoniae** *(D. pneumoniae)*
*Streptococcus faecalis** (Enterococcus)
*Streptococcus pyogenes** (Group A, β-haemolytic)

Anaerobic bacteria
Bacteroides species including *B. fragilis*
(β-lactamase and non-β-lactamase producing)
Clostridium species
Eubacterium species
Fusobacterium species
Peptococcus species
Peptostreptococcus species*
Veillonella species

*These are non-β-lactamase producing strains and therefore are susceptible to ticarcillin alone (see Indications).

PHARMACOKINETICS

After an intravenous infusion (30 min) of 3.1g TIMENTIN, peak serum concentrations of both ticarcillin and clavulanic acid are attained immediately after completion of infusion. Ticarcillin serum levels are similar to those produced by the administration of equivalent amounts of ticarcillin alone with a mean peak serum level of 324mcg/mL. The corresponding mean peak serum level for clavulanic acid was 8mcg/mL.

SERUM LEVELS IN ADULTS AFTER A 30 MINUTE IV INFUSION OF TIMENTIN

TICARCILLIN SERUM LEVELS (mcg/mL)

Dose	**0***	**15min**	**30min**	**1hr**	**1.5hr**	**3.5hr**	**5.5hr**
3.1g	324	223	176	131	90	27	6
	(293-388)	(184-293)	(135-235)	(102-195)	(65-119)	(19-37)	(5-7)

CLAVULANIC ACID SERUM LEVELS (mcg/mL)

Dose	**0***	**15min**	**30min**	**1hr**	**1.5hr**	**3.5hr**	**5.5hr**
3.1g	8	4.6	2.6	1.8	1.2	0.3	0
	(5.3-10.3)	(3.0-7.6)	(1.8-3.4)	(1.6-2.2)	(0.8-1.6)	(0.2-0.3)	

* Time after completion of infusion.

The mean area under the serum concentration curve for ticarcillin was 485mcg/mL.hr. The corresponding area under the serum concentration curve for clavulanic acid was 8.2mcg/mL.hr.

The mean serum half-lives of ticarcillin and clavulanic acid in healthy volunteers are 68 minutes and 64 minutes respectively.

Approximately 60-70% of ticarcillin and approximately 35-45% of clavulanic acid are excreted unchanged in urine during the first 6 hours after administration of a single dose of TIMENTIN to normal volunteers with normal renal function. During the first two hours after an intravenous injection of 3.1g TIMENTIN, concentrations of ticarcillin in urine generally exceed 1500 mcg/mL. The corresponding concentration of clavulanic acid in urine generally exceeds 40mcg/mL following administration of the 3.1g dose. By 4-6 hours after injection, the urine concentrations of ticarcillin and clavulanic acid usually decline to approximately 190mcg/mL and 2mcg/mL.

Neither component of TIMENTIN is highly protein bound; ticarcillin has been found to be approximately 45% bound to human serum protein and clavulanic acid has been variously reported to be bound to human serum in the range of 9 - 30%.

Somewhat higher and more prolonged serum levels of ticarcillin can be achieved with the concurrent administration of probenecid; however, probenecid does not enhance the serum levels of clavulanic acid.

Penetration of ticarcillin into cerebrospinal fluid is poor in the absence of meningeal inflammation.

An inverse relationship exists between the serum half-life of ticarcillin and creatinine clearance. The dosage of TIMENTIN need only be adjusted in cases of severe renal impairment (see Dosage and Administration).

Ticarcillin may be removed from patients undergoing dialysis; the actual amount removed depends on the duration and type of dialysis.

INDICATIONS

TIMENTIN is indicated in the treatment of serious infections caused by susceptible strains of β-lactamase producing organisms in the conditions listed below:

Septicaemia (and bacteraemia) cases caused by β-lactamase producing organisms including strains of *Klebsiella pneumoniae, E.coli, Staphylococcus aureus* and *Pseudomonas aeruginosa*.

Lower Respiratory Infections cases caused by β-lactamase producing susceptible organisms including strains of *Staphylococcus aureus, Haemophilus influenzae* and *Klebsiella pneumoniae.*

Bone and Joint Infections cases caused by β-lactamase producing susceptible organisms including strains of *Staphylococcus aureus.*

Skin and Skin Structure Infections cases caused by β-lactamase producing susceptible organisms including strains of *Staphylococcus aureus, Klebsiella pneumoniae* and *E. coli*.

Urinary Tract Infections cases caused by β-lactamase producing susceptible organisms including strains of *E.coli, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Staphylococcus aureus*.

Gynaecological Infections including cases caused by β-lactamase producing susceptible organisms including strains of *Klebsiella pneumoniae, Staphylococcus aureus* and *Staphylococcus epidermidis*.

While TIMENTIN is indicated only for the conditions listed above, it may be used as a single agent in the treatment of mixed infections caused by ticarcillin susceptible and β-lactamase producing ticarcillin resistant organisms.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to TIMENTIN. Therapy with TIMENTIN may, however, be initiated before results of such tests are known when there is reason to believe the infection may involve any of the β-lactamase producing organisms listed above; however, once these results become available, appropriate therapy should be continued.

Based on the *in vitro* synergism between ticarcillin and gentamicin sulphate/tobramycin sulphate/amikacin sulphate against certain strains of *Pseudomonas aeruginosa*, combined therapy has been successful. TIMENTIN may be used as combination therapy concurrently with the aminoglycosides but both drugs should be used in full therapeutic doses. As soon as results of culture and susceptibility tests become available, antimicrobial therapy should be adjusted as indicated. Results of susceptibility tests showing synergy between ticarcillin and one aminoglycoside should not be extrapolated to combination with another aminoglycoside.

Prophylactic Use

TIMENTIN may be administered perioperatively (preoperatively, intraoperatively and postoperatively) to patients undergoing abdominal hysterectomy or elective colorectal surgery when there is a significant risk of surgery related postoperative infections.

If signs of postsurgical infection should appear, these should be treated with appropriate therapy.

CONTRAINDICATIONS

TIMENTIN contains ticarcillin which is a penicillin, and should not be given to patients with a history of hypersensitivity reactions to beta-lactam antibiotics (eg penicillins, cephalosporins).

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY REACTIONS (ANAPHYLAXIS) HAVE BEEN REPORTED IN PATIENTS RECEIVING BETA-LACTAM ANTIBIOTICS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH TIMENTIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER DRUGS. IF AN ALLERGIC REACTION OCCURS, TIMENTIN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH ADRENALINE. OXYGEN, INTRAVENOUS STEROIDS,

AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE PROVIDED AS INDICATED.

Bleeding manifestations have occurred in some patients receiving TIMENTIN or high doses of ticarcillin. These reactions have been associated with abnormalities of coagulation tests such as clotting time, platelet aggregation and prothrombin time and are more likely to occur in patients with renal impairment. If bleeding manifestations appear, TIMENTIN treatment should be discontinued and appropriate therapy instituted.

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including ticarcillin. A toxin produced with Clostridium difficile appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However in moderate to severe cases appropriate therapy with a suitable oral antibiotic agent effective against Clostridium difficile should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis, eg. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

PRECAUTIONS

General: While TIMENTIN possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy.

TIMENTIN has been reported to cause hypokalaemia and the possibility of this occurring should be kept in mind particularly when treating patients with fluid and electrolyte imbalance. Periodic monitoring of serum potassium is advisable in patients receiving prolonged therapy.

The sodium content is approximately 15.6 mmol (360mg) per vial of TIMENTIN 3.1g. This should be considered when treating patients requiring restricted salt intake.

TIMENTIN should be administered with caution to patients with cardiac disease as cardiac failure may be exacerbated.

As with any penicillin, an allergic reaction, including anaphylaxis, may occur during TIMENTIN administration, particularly in a hypersensitive individual.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind, particularly during prolonged treatment. If superinfections occur, appropriate measures should be taken.

Drug Interactions: As with other penicillins, the mixing of TIMENTIN with an aminoglycoside in solutions for parenteral administration can result in substantial inactivation of the aminiglycoside (see Directions for Use).

Probenecid interferes with the renal tubular secretion of ticarcillin, thereby increasing serum concentrations and prolonging serum half-life of the antibiotic.

In common with other antibiotics, ticarcillin may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

Effects on Laboratory Tests: High urine concentrations of ticarcillin may produce false positive protein reactions (pseudoproteinuria) with the following methods; sulfosalicylic acid and boiling test, acetic acid test, biuret reaction, and nitric acid test. The bromphenol blue (Multi-stix®) reagent strip test has been reported to be reliable.

The presence of clavulanic acid in TIMENTIN may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

Pregnancy: Reproduction studies have been performed in rats given doses up to 1050mg/kg/day and have revealed no evidence of impaired fertility or harm to the foetus due to TIMENTIN. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Lactation: Trace quantities of TIMENTIN are excreted in breast milk. The possibility of hypersensitivity reactions must be considered in breast-feeding infants. Therefore TIMENTIN should only be administered to a breast-feeding mother when the potential benefits outweigh the potential risks associated with treatment.

Paediatric use: The efficacy and safety of TIMENTIN have not been established in infants and children under the age of 14.

Patients with Renal Impairment: In patients with renal impairment, dosage should be adjusted according to the degree of impairment (see Dosage & Administration)

Patients with Hepatic Impairment: There is insufficient evidence on which to base a dosage recommendation in patients with hepatic impairment.

Drug Abuse and Dependence: Neither TIMENTIN abuse nor TIMENTIN dependence has been reported.

ADVERSE REACTIONS

The following adverse reactions may occur:

Hypersensitivity reactions: skin rash, pruritus, urticaria, arthralgia, myalgia, drug fever, chills, bronchospasm, wheezing, and anaphylactic reactions. Erythema multiforme and Stevens-Johnsons syndrome have been reported rarely.

Central nervous system: headache, giddiness, hallucinations, neuromuscular hyperirritability or convulsive seizures. Convulsions may occur rarely, particularly in patients with impaired renal function or in those receiving high doses.

Gastro-intestinal: disturbances of taste and smell, stomatitis, flatulence, nausea, vomiting and diarrhoea, epigastric pain. Pseudomembranous colitis has been reported rarely.

Haemic and Lymphatic systems: thrombocytopenia, leukopenia, neutropenia, eosinophilia, immune haemolytic anaemia and reduction of haemoglobin or haematocrit. Thrombocytosis was noted in about 2% of patients treated with TIMENTIN. Prolongation of prothrombin time and bleeding time, positive Coombs test.

Abnormalities of hepatic and renal function tests: elevation of serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), serum alkaline phosphatase, serum LDH, serum bilirubin. Transient hepatitis and cholestatic jaundice have been reported rarely. Elevation of serum creatinine and/or BUN, hypernatremia. Reduction in serum potassium and uric acid.

Local reactions: pain, burning, erythema, infiltration, swelling and induration at the injection site and thrombophlebitis with intravenous administration.

DOSAGE AND ADMINISTRATION

TIMENTIN should be administered by intravenous infusion (30 min).

The maximum daily adult dose of TIMENTIN 3.1g is 18g, based on the ticarcillin component.

The usual recommended dosage for average (60kg) adults is 3.1g (3.1g vial containing 3g ticarcillin and 100mg clavulanic acid) every 4 or 6 hours except for urinary tract infections where the drug is administered 8 hourly. For patients weighing less than 60kg, the recommended dosage is 200-300mg/kg/day, based on ticarcillin content, given in divided doses every 4 or 6 hours.

Clinical data are insufficient at present to recommend an appropriate dosage regime for TIMENTIN in patients with renal failure. However, on the basis of theoretical considerations (namely absence of any change in the pharmacokinetics of ticarcillin due to clavulanic acid and the apparent greater tissue clearance of clavulanic acid as compared to ticarcillin) it is suggested that for infections complicated by renal insufficiency, the dosage regime as used currently for ticarcillin alone may generally be adopted (see below). Note that this dosage schedule has not been tested in patients with impaired renal function.

DOSAGE REGIME IN RENAL INSUFFICIENCY

An initial loading dose of 3.1g I.V. followed by I.V. doses based on creatinine clearance or type of dialysis as indicated below:

Creatinine clearance mL/min	Dosage
over 60	3.1g every 4 hours
30-60	2g every 4 hours
10-30	2g every 8 hours
less than 10	2g every 12 hours
less than 10 with hepatic dysfunction	2g every 24 hours
patients on peritoneal dialysis	3.1g every 12 hours
patients on haemodialysis	2g every 12 hours supplemented with 3.1g after each dialysis.

The half-life of Ticarcillin in patients with renal failure is approximately 13 hours.

To calculate creatinine clearance* from a serum creatinine value use the following formula:

$$C_{cr} = \frac{(140 - Age)\ (wt\ in\ kg)}{72 \times s_{cr}(mg/100ml)}$$

This is the calculated creatinine clearance for adult males, for females it is 15% less.

* Cockroft, D.W. et al. Prediction of Creatinine Clearance from Serum Creatinine. Nephron, 1976; 16:31-41.

Dosage for any individual patient must take into consideration the site and severity of infection, the susceptibility of the organisms causing infections, and the status of the patient's host defence mechanisms.

The duration of therapy depends upon the severity of infection. Generally, TIMENTIN should be continued for at least 2 days after the signs and symptoms of infection have disappeared. The usual duration is 10 to 14 days; however, in difficult and complicated infections, more prolonged therapy may be required.

Frequent bacteriologic and clinical appraisal is necessary during therapy of chronic urinary tract infection and may be required for several months after therapy has been completed.

In certain infections, involving abscess formation, appropriate surgical drainage should be performed in conjunction with antimicrobial therapy.

Prophylaxis
For prophylactic use, the following dose is recommended.

For patients undergoing cesarean section, the first dose of 3.1g is administered intravenously as soon as the umbilical cord is clamped. This is to be followed by 2 additional doses of 3.1g every 4 hours after the first dose for a total of 3 doses.

For patients undergoing abdominal hysterectomy, a dose of 3.1g administered half to one hour prior to the initial incision followed by 2 additional doses of 3.1g every 4 hours for a total of 3 doses.

For patients undergoing elective colorectal surgery, a dose of 3.1g administered intravenously half to one hour prior to the initial incision followed by 2 additional doses of 3.1g every 8 hours for a total of 3 doses. An alternative regimen in which a dose of 3.1g administered intravenously 15 minutes prior to induction of anaesthesia and followed 2 hours later by a second dose of 3.1g, has also proved effective.

Directions for intravenous infusion: The 3.1g vial should be reconstituted by shaking with approximately 13mL of Sterile Water for Injection, or Sodium Chloride Injection; when dissolved, the concentration of ticarcillin will be approximately 200mg/mL and the concentration of clavulanic acid 6.7mg/mL. Each 5.0mL of the 3.1g dose reconstituted with approximately 13mL of diluent will contain approximately 1g of ticarcillin and 33mg of clavulanic acid.

The dissolved drug should be further diluted to desired volume using a suitable solution listed in the Compatibility and Stability section. The solution of reconstituted drug may then be administered over a period of 30 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place. If this method or the "piggyback" method of administration is used, it is advisable to discontinue temporarily the administration of any other solutions during the infusion of TIMENTIN.

When TIMENTIN is given in combination with another antimicrobial, such as an aminoglycoside, each drug should be given separately in accordance with the recommended dosage and routes of administration for each drug.

After reconstitution and prior to administration, TIMENTIN, as with other parenteral drugs, should be inspected visually for particulate matter and discoloration and discarded if unsuitable.

Compatibility and Stability: The stock solution at 200mg/mL is stable for up to 6 hours at room temperature (25°C) or up to 72 hours under refrigeration (4°C). TIMENTIN stability studies in the following intravenous solutions indicate that TIMENTIN will provide sufficient activity at either room temperature or stored under refrigeration within the stated time periods and at concentrations between 10mg/mL and 100mg/mL with any of the diluents on the following list.

Intravenous Solution	Room Temp. 25°C	Refrigeration 4°C	Frozen -18°C
Sodium Chloride Injection	24 hours	72 hours	7 days
Dextrose Injection 5%	6 hours	24 hours	-
Lactated Ringer's Injection	12 hours	-	7 days
0.224% Potassium Chloride/ 4% Dextrose/0.18% Sodium Chloride Injection	12 hours	24 hours	-

Note: TIMENTIN is incompatible with Sodium Bicarbonate.
It is not recommended that Dextrose containing solutions be frozen.
Frozen solutions should be thawed at room temperature (25°C) and used immediately.

Unused solutions must be discarded after the time period stated above.

OVERDOSAGE

As with other penicillins, TIMENTIN in overdosage has the potential to cause neuromuscular hyperirritability or convulsive seizures. Ticarcillin may be removed from circulation by haemodialysis. The molecular weight, degree of protein binding and pharmcokinetic profile of clavulanic acid together with information from a single patient with renal insufficiency all suggest that this compound may also be removed by haemodialysis.

PRESENTATION

3.1g vial containing sterile ticarcillin sodium equivalent to 3g ticarcillin and sterile potassium clavulanate equivalent to 0.1g clavulanic acid.

TIMENTIN vials should be stored at or below 25°C.

NAME AND ADDRESS OF SPONSOR:

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