PRESCRIBING INFORMATION

TIMENTIN®

(ticarcillin disodium and clavulanate potassium)
INJECTION

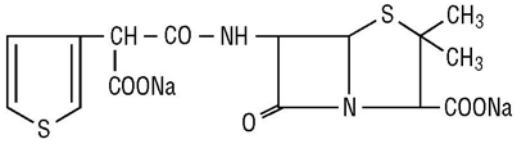
GALAXY® (PL 2040) Plastic Container
(Product Package)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of TIMENTIN (ticarcillin disodium and clavulanate potassium) and other antibacterial drugs, TIMENTIN should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

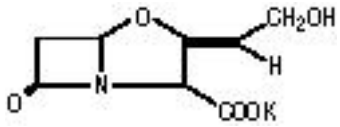
TIMENTIN is an injectable antibacterial combination consisting of the semisynthetic antibiotic, ticarcillin disodium, and the β-lactamase inhibitor, clavulanate potassium (the potassium salt of clavulanic acid), for intravenous administration. Ticarcillin is derived from the basic penicillin nucleus, 6-amino-penicillanic acid.

Chemically, ticarcillin disodium is *N*-(2-Carboxy-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-6-yl)-3-thiophenemalonamic acid disodium salt and may be represented as:



Clavulanic acid is produced by the fermentation of *Streptomyces clavuligerus*. It is a β-lactam structurally related to the penicillins and possesses the ability to inactivate a wide variety of β-lactamases by blocking the active sites of these enzymes. Clavulanic acid is particularly active against the clinically important plasmid-mediated β-lactamases frequently responsible for transferred drug resistance to penicillins and cephalosporins.

Chemically, clavulanate potassium is potassium (*Z*)-(2*R*,5*R*)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate and may be represented structurally as:



TIMENTIN is an iso-osmotic, sterile, nonpyrogenic, frozen solution consisting of 3.0 grams ticarcillin as ticarcillin disodium and 0.1 gram clavulanic acid as clavulanate potassium. Approximately 0.3 gram sodium citrate hydrous, USP, is added as a buffer. Sodium hydroxide is used to adjust pH and convert ticarcillin monosodium to ticarcillin disodium. The pH may have been adjusted with hydrochloric acid. The solution is intended for intravenous use after thawing to room temperature. The pH of thawed solution ranges from 5.5 to 7.5.

For the 3.1 gram of TIMENTIN in the GALAXY® (PL 2040) Plastic Container, the theoretical total sodium content of the 100-mL solution is 18.7 mEq (429 mg), of which 15.6 mEq (359 mg) is

contributed by the ticarcillin disodium component of TIMENTIN. The total theoretical potassium content of the 100-mL solution is 0.50 mEq (19.63 mg).

This plastic container is fabricated from a specially designed multilayer plastic (PL 2040). Solutions are in contact with the polyethylene layer of this container and can leach out certain chemical components of the plastic in very small amounts within the expiration period. The suitability of the plastic has been confirmed in tests in animals according to USP biological tests for plastic containers, as well as by tissue culture toxicity studies.

CLINICAL PHARMACOLOGY

After an intravenous infusion (30 min.) of 3.1 grams of TIMENTIN, peak serum concentrations of both ticarcillin and clavulanic acid are attained immediately after completion of the 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 324 mcg/mL. The corresponding mean peak serum level for clavulanic acid is 8 mcg/mL. (See following table.)

SERUM LEVELS IN ADULTS
AFTER A 30-MINUTE I.V. INFUSION OF TIMENTIN®

TICARCILLIN SERUM LEVELS (mcg/mL)

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

CLAVULANIC ACID SERUM LEVELS (mcg/mL)

Dose	0	15 min.	30 min.	1 hr.	1.5 hr.	3.5 hr.	5.5 hr.
3.1 gram	8.0 (5.3-10.3)	4.6 (3.0-7.6)	2.6 (1.8-3.4)	1.8 (1.6-2.2)	1.2 (0.8-1.6)	0.3 (0.2-0.3)	0

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

The mean serum half-lives of ticarcillin and clavulanic acid in healthy volunteers are 1.1 hours and 1.1 hours, respectively.

In pediatric patients receiving approximately 50 mg/kg of TIMENTIN (30:1 ratio ticarcillin to clavulanate), mean ticarcillin serum half-lives were 4.4 hours in neonates (n = 18) and 1.0 hour in infants and children (n = 41). The corresponding clavulanate serum half-lives averaged 1.9 hours in neonates (n = 14) and 0.9 hour in infants and children (n = 40). Area under the serum concentration time curves averaged 339 mcg•hr/mL in infants and children (n = 41), whereas the corresponding mean clavulanate area under the serum concentration time curves was approximately 7 mcg•hr/mL in the same population (n = 40).

Approximately 60% to 70% of ticarcillin and approximately 35% to 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. Two hours after an intravenous injection of 3.1 grams of TIMENTIN, concentrations of ticarcillin in urine generally exceed 1,500 mcg/mL. The corresponding concentration of clavulanic acid in urine generally exceeds 40 mcg/mL. By 4 to 6 hours after injection, the urine concentrations of ticarcillin and clavulanic acid usually decline to approximately 190 mcg/mL and 2 mcg/mL, respectively. Neither component of TIMENTIN is highly protein bound; ticarcillin has been found to be approximately 45% bound to human serum protein and clavulanic acid approximately 25% bound.

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.

Ticarcillin can be detected in tissues and interstitial fluid following parenteral administration.

Penetration of ticarcillin into bile and pleural fluid has been demonstrated. The results of experiments involving the administration of clavulanic acid to animals suggest that this compound, like ticarcillin, is well distributed in body tissues.

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.

Microbiology: Ticarcillin is a semisynthetic antibiotic with a broad spectrum of bactericidal activity against many gram-positive and gram-negative aerobic and anaerobic bacteria.

Ticarcillin is, however, susceptible to degradation by β-lactamases, and therefore, the spectrum of activity does not normally include organisms which produce these enzymes.

Clavulanic acid is a β-lactam, structurally related to the penicillins, which possesses the ability to inactivate a wide range of β-lactamase enzymes commonly found in microorganisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid-mediated β-lactamases frequently responsible for transferred drug resistance.

The formulation of ticarcillin with clavulanic acid in TIMENTIN protects ticarcillin from degradation by β-lactamase enzymes and effectively extends the antibiotic spectrum of ticarcillin to include many bacteria normally resistant to ticarcillin and other β-lactam antibiotics. Thus, TIMENTIN possesses the distinctive properties of a broad-spectrum antibiotic and a β-lactamase inhibitor. Ticarcillin/clavulanic acid has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections as described in the INDICATIONS AND USAGE section.

Gram-Positive Aerobes:

Staphylococcus aureus (β-lactamase and non–β-lactamase–producing)[*]

Staphylococcus epidermidis (β-lactamase and non–β-lactamase–producing)[*]

[*]Staphylococci which are resistant to methicillin/oxacillin must be considered resistant to ticarcillin/clavulanic acid.

Gram-Negative Aerobes:

Citrobacter species (β-lactamase and non–β-lactamase–producing)

Enterobacter species including *E. cloacae* (β-lactamase and non–β-lactamase–producing) (Although most strains of *Enterobacter* species are resistant in vitro, clinical efficacy has been demonstrated with TIMENTIN in urinary tract infections and gynecologic infections caused by these organisms).

Escherichia coli (β-lactamase and non–β-lactamase–producing)

Haemophilus influenzae (β-lactamase and non–β-lactamase–producing)[†]

Klebsiella species including *K. pneumoniae* (β-lactamase and non–β-lactamase–producing)

Pseudomonas species including *P. aeruginosa* (β-lactamase and non–β-lactamase–producing)

Serratia marcescens (β-lactamase and non–β-lactamase–producing)

[†]β-lactamase–negative, ampicillin-resistant (BLNAR) strains of *H. influenzae* must be considered resistant to ticarcillin/clavulanic acid.

Anaerobic Bacteria:

Bacteroides fragilis group (β-lactamase and non–β-lactamase–producing)

Prevotella (formerly *Bacteroides*) *melaninogenicus* (β-lactamase and non–β-lactamase–producing)

The following in vitro data are available, **but their clinical significance is unknown.**

The following strains exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for ticarcillin/clavulanic acid. However, with the exception of organisms shown to respond to ticarcillin alone, the safety and effectiveness of ticarcillin/clavulanic acid in treating infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Gram-Positive Aerobes:

Staphylococcus saprophyticus (β-lactamase and non–β-lactamase–producing)
Streptococcus agalactiae‡ (Group B)
Streptococcus bovis‡
Streptococcus pneumoniae‡ (penicillin-susceptible strains only)
Streptococcus pyogenes‡
Viridans group streptococci‡

Gram-Negative Aerobes:

Acinetobacter baumannii (β-lactamase and non–β-lactamase–producing)
Acinetobacter calcoaceticus (β-lactamase and non–β-lactamase–producing)
Acinetobacter haemolyticus (β-lactamase and non–β-lactamase–producing)
Acinetobacter lwoffi (β-lactamase and non–β-lactamase–producing)
Moraxella catarrhalis (β-lactamase and non–β-lactamase–producing)
Morganella morganii (β-lactamase and non–β-lactamase–producing)
Neisseria gonorrhoeae (β-lactamase and non–β-lactamase–producing)
Pasteurella multocida (β-lactamase and non–β-lactamase–producing)
Proteus mirabilis (β-lactamase and non–β-lactamase–producing)
Proteus penneri (β-lactamase and non–β-lactamase–producing)
Proteus vulgaris (β-lactamase and non–β-lactamase–producing)
Providencia rettgeri (β-lactamase and non–β-lactamase–producing)
Providencia stuartii (β-lactamase and non–β-lactamase–producing)
Stenotrophomonas maltophilia (β-lactamase and non–β-lactamase–producing)

Anaerobic Bacteria:

Clostridium species including *C. perfringens*, *C. difficile*, *C. sporogenes*, *C. ramosum*, and *C. bifermentans* (β-lactamase and non–β-lactamase–producing)
Eubacterium species
Fusobacterium species including *F. nucleatum* and *F. necrophorum* (β-lactamase and non–β-lactamase–producing)
Peptostreptococcus species‡
Veillonella species‡

‡These are non–β-lactamase–producing strains, and therefore, are susceptible to ticarcillin.

In vitro synergism between TIMENTIN and gentamicin, tobramycin, or amikacin against multiresistant strains of *Pseudomonas aeruginosa* has been demonstrated.

Susceptibility Testing: *Dilution Techniques:* Quantitative methods are used to determine antimicrobial MICs. These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1,3] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of ticarcillin/clavulanate potassium powder.

The recommended dilution pattern utilizes a constant level of 2 mcg/mL clavulanic acid in all tubes with varying amounts of ticarcillin. MICs are expressed in terms of the ticarcillin concentration

in the presence of clavulanic acid at a constant 2 mcg/mL. The MIC values should be interpreted according to the following criteria:

RECOMMENDED RANGES FOR TICARCILLIN/CLAVULANIC ACID SUSCEPTIBILITY TESTING*

For *Pseudomonas aeruginosa:*

MIC (mcg/mL)	Interpretation	
≤64	Susceptible	(S)
≥128	Resistant	(R)

For Enterobacteriaceae:

MIC (mcg/mL)	Interpretation	
≤16	Susceptible	(S)
32-64	Intermediate	(I)
≥128	Resistant	(R)

For Staphylococci†:

MIC (mcg/mL)	Interpretation	
≤8	Susceptible	(S)
≥16	Resistant	(R)

* Expressed as concentration of ticarcillin in the presence of clavulanic acid at a constant 2 mcg/mL.

† Staphylococci which are susceptible to ticarcillin/clavulanic acid but resistant to methicillin/oxacillin must be considered as resistant.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard ticarcillin/clavulanate potassium powder should provide the following MIC values:

Microorganism		MIC (mcg/mL)‡
Escherichia coli	ATCC 25922	4-16
Escherichia coli	ATCC 35218	4-16
Pseudomonas aeruginosa	ATCC 27853	8-32
Staphylococcus aureus	ATCC 29213	0.5-2

‡ Expressed as concentration of ticarcillin in the presence of clavulanic acid at a constant 2 mcg/mL.

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2,3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 85 mcg of ticarcillin/clavulanate potassium (75 mcg ticarcillin plus 10 mcg clavulanate potassium) to test the susceptibility of microorganisms to ticarcillin/clavulanic acid.

Reports from the laboratory providing results of the standard single-disk susceptibility test with an 85 mcg of ticarcillin/clavulanate potassium (75 mcg ticarcillin plus 10 mcg clavulanate potassium) disk should be interpreted according to the following criteria:

RECOMMENDED RANGES FOR TICARCILLIN/CLAVULANIC ACID SUSCEPTIBILITY TESTING

For *Pseudomonas aeruginosa:*

Zone Diameter (mm)	Interpretation	
≥15	Susceptible	(S)
≤14	Resistant	(R)

For Enterobacteriaceae:

Zone Diameter (mm)	Interpretation	
≥20	Susceptible	(S)
15-19	Intermediate	(I)
≤14	Resistant	(R)

For Staphylococci[§]:

Zone Diameter (mm)	Interpretation	
≥23	Susceptible	(S)
≤22	Resistant	(R)

[§] Staphylococci which are resistant to methicillin/oxacillin must be considered as resistant to ticarcillin/clavulanic acid.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for ticarcillin/clavulanic acid.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 85 mcg of ticarcillin/clavulanate potassium (75 mcg ticarcillin plus 10 mcg clavulanate potassium) disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism		Zone Diameter (mm)
Escherichia coli	ATCC 25922	24-30
Escherichia coli	ATCC 35218	21-25
Pseudomonas aeruginosa	ATCC 27853	20-28
Staphylococcus aureus	ATCC 25923	29-37

Anaerobic Techniques: For anaerobic bacteria, the susceptibility to ticarcillin/clavulanic acid can be determined by standardized test methods[3,4]. The MIC values obtained should be interpreted according to the following criteria:

RECOMMENDED RANGES FOR TICARCILLIN/CLAVULANIC ACID SUSCEPTIBILITY TESTING[‖]

MIC (mcg/mL)	Interpretation	
≤32	Susceptible	(S)
64	Intermediate	(I)
≥128	Resistant	(R)

[‖] Expressed as concentration of ticarcillin in the presence of clavulanic acid at a constant 2 mcg/mL.

Interpretation is identical to that stated above for results using dilution techniques.

As with other susceptibility techniques, the use of laboratory control microorganisms is required to control the technical aspects of the laboratory standardized procedures. Standardized ticarcillin/clavulanate potassium powder should provide the following MIC values:

Microorganism		Agar dilution MIC Range (mcg/mL)‖	Broth microdilution MIC Range (mcg/mL)‖
Bacteroides thetaiotaomicron	ATCC 29741	0.5-2	0.5-2
Eubacterium lentum	ATCC 43055	16-64	8-32

‖ Expressed as concentration of ticarcillin in the presence of clavulanic acid at a constant 2 mcg/mL.

INDICATIONS AND USAGE

TIMENTIN is indicated in the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

Septicemia (including bacteremia) caused by β-lactamase–producing strains of *Klebsiella* spp.*, *E. coli**, *S. aureus**, or *P. aeruginosa** (or other *Pseudomonas* species*)

Lower Respiratory Infections caused by β-lactamase–producing strains of *S. aureus*, *H. influenzae**, or *Klebsiella* spp.*

Bone and Joint Infections caused by β-lactamase–producing strains of *S. aureus*

Skin and Skin Structure Infections caused by β-lactamase–producing strains of *S. aureus*, *Klebsiella* spp.*, or *E. coli**

Urinary Tract Infections (complicated and uncomplicated) caused by β-lactamase–producing strains of *E. coli*, *Klebsiella* spp., *P. aeruginosa** (or other *Pseudomonas* spp.*), *Citrobacter* spp.*, *Enterobacter cloacae**, *S. marcescens**, or *S. aureus**

Gynecologic Infections endometritis caused by β-lactamase–producing strains of *P. melaninogenicus**, Enterobacter spp. (including *E. cloacae**), *E. coli*, *Klebsiella pneumoniae**, *S. aureus*, or *S. epidermidis*

Intra-abdominal Infections peritonitis caused by β-lactamase–producing strains of *E. coli*, *K. pneumoniae*, or *B. fragilis** group

*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

NOTE: For information on use in pediatric patients (≥3 months of age) see PRECAUTIONS—Pediatric Use and CLINICAL STUDIES sections. There are insufficient data to support the use of TIMENTIN in pediatric patients under 3 months of age or for the treatment of septicemia and/or infections in the pediatric population where the suspected or proven pathogen is *H. influenzae* type b.

While TIMENTIN is indicated only for the conditions listed above, infections caused by ticarcillin-susceptible organisms are also amenable to treatment with TIMENTIN due to its ticarcillin content. Therefore, mixed infections caused by ticarcillin-susceptible organisms and β-lactamase–producing organisms susceptible to ticarcillin/clavulanic acid should not require the addition of another antibiotic.

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 ticarcillin/clavulanic acid. Because of its broad spectrum of bactericidal activity against gram-positive and gram-negative bacteria, TIMENTIN is particularly useful for the treatment of mixed infections and for presumptive therapy prior to the identification of the causative organisms. TIMENTIN has been shown to be effective as single drug therapy in the treatment of some serious infections where normally combination antibiotic therapy might be employed. Therapy with TIMENTIN may 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.

Based on the in vitro synergism between ticarcillin/clavulanic acid and aminoglycosides against certain strains of *P. aeruginosa*, combined therapy has been successful, especially in patients with impaired host defenses. Both drugs should be used in full therapeutic doses.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of TIMENTIN and other antibacterial drugs, TIMENTIN should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

TIMENTIN is contraindicated in patients with a history of hypersensitivity reactions to any of the penicillins.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. 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 ALLERGENS. IF AN ALLERGIC REACTION OCCURS, TIMENTIN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE PROVIDED AS INDICATED.**

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including TIMENTIN, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile.*

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

When very high doses of TIMENTIN are administered, especially in the presence of impaired renal function, patients may experience convulsions. (See ADVERSE REACTIONS and OVERDOSAGE.)

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 hematopoietic function, is advisable during prolonged therapy.

Bleeding manifestations have occurred in some patients receiving β-lactam antibiotics. 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, treatment with TIMENTIN should be discontinued and appropriate therapy instituted.

TIMENTIN has only rarely been reported to cause hypokalemia; however, the possibility of this occurring should be kept in mind particularly when treating patients with fluid and electrolyte imbalance. Periodic monitoring of serum potassium may be advisable in patients receiving prolonged therapy.

The theoretical total sodium content of the 100 mL premixed solution is 429 mg (359 mg contributed by the ticarcillin disodium component of TIMENTIN). This should be considered when treating patients requiring restricted salt intake.

As with any penicillin, an allergic reaction, including anaphylaxis, may occur during administration of TIMENTIN, 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.

Prescribing TIMENTIN in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Information for Patients: Patients should be counseled that antibacterial drugs, including TIMENTIN, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When TIMENTIN is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may: (1) decrease the effectiveness of the immediate treatment, and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by TIMENTIN or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as 2 or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Drug/Laboratory Test Interactions: As with other penicillins, the mixing of TIMENTIN with an aminoglycoside in solutions for parenteral administration can result in substantial inactivation of the aminoglycoside.

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, ticarcilin disodium/clavulanate potassium may affect the gut flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral estrogen/progesterone contraceptives.

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 nonspecific 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 potential. However, results from assays for gene mutation in vitro using bacteria (Ames tests) and yeast, and for chromosomal effects in vitro in human lymphocytes, and in vivo in mouse bone marrow (micronucleus test) indicate that TIMENTIN is without any mutagenic potential.

Pregnancy (Category B): Reproduction studies have been performed in rats given doses up to 1,050 mg/kg/day and have revealed no evidence of impaired fertility or harm to the fetus 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.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TIMENTIN is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of TIMENTIN have been established in the age group of 3 months to 16 years. Use of TIMENTIN in these age groups is supported by evidence from adequate and well-controlled studies of TIMENTIN in adults with additional efficacy, safety, and pharmacokinetic data from both comparative and non-comparative studies in pediatric patients. There are insufficient data to support the use of TIMENTIN in pediatric patients under 3 months of age or for the treatment of septicemia and/or infections in the pediatric population where the suspected or proven pathogen is *H. influenzae* type b. The potential for toxic effects in children from chemicals that may leach from the single dose premixed intravenous preparation in plastic containers has not been determined.

In those patients in whom meningeal seeding from a distant infection site or in whom meningitis is suspected or documented, or in patients who require prophylaxis against central nervous system infection, an alternate agent with demonstrated clinical efficacy in this setting should be used.

ADVERSE REACTIONS

As with other penicillins, the following adverse reactions may occur:

Hypersensitivity Reactions: Skin rash, pruritus, urticaria, arthralgia, myalgia, drug fever, chills, chest discomfort, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, and anaphylactic reactions.

Central Nervous System: Headache, giddiness, neuromuscular hyperirritability, or convulsive seizures.

Gastrointestinal Disturbances: Disturbances of taste and smell, stomatitis, flatulence, nausea, vomiting and diarrhea, epigastric pain, and pseudomembranous colitis have been reported. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment. (See WARNINGS.)

Hemic and Lymphatic Systems: Thrombocytopenia, leukopenia, neutropenia, eosinophilia, reduction of hemoglobin or hematocrit, and prolongation of prothrombin time and bleeding time.

Abnormalities of Hepatic and Renal Function Tests: Elevation of serum aspartate aminotransferase (SGOT), serum alanine aminotransferase (SGPT), serum alkaline phosphatase, serum LDH, serum bilirubin. There have been reports of transient hepatitis and cholestatic jaundice—as with some other penicillins and some cephalosporins. Elevation of serum creatinine and/or BUN, hypernatremia, reduction in serum potassium and uric acid.

Local Reactions: Pain, burning, swelling and induration at the infusion site and thrombophlebitis with intravenous administration.

Available safety data for pediatric patients treated with TIMENTIN demonstrate a similar adverse event profile to that observed in adult patients.

DRUG ABUSE AND DEPENDENCE

Neither abuse of nor dependence on TIMENTIN has been reported.

OVERDOSAGE

As with other penicillins, neurotoxic reactions may arise when very high doses of TIMENTIN are administered, especially in patients with impaired renal function. (See WARNINGS and ADVERSE REACTIONS –Central Nervous System.)

In case of overdosage, discontinue TIMENTIN, treat symptomatically, and institute supportive measures as required. Ticarcillin may be removed from circulation by hemodialysis. The molecular weight, degree of protein binding, and pharmacokinetic profile of clavulanic acid together with information from a single patient with renal insufficiency all suggest that this compound may also be removed by hemodialysis.

DOSAGE AND ADMINISTRATION

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

Adults: The usual recommended dosage for systemic and urinary tract infections for average (60 kg) adults is 3.1 grams of TIMENTIN (3.1-gram vial containing 3 grams ticarcillin and 100 mg clavulanic acid) given every 4 to 6 hours. For gynecologic infections, TIMENTIN should be administered as follows: Moderate infections 200 mg/kg/day in divided doses every 6 hours and for severe infections 300 mg/kg/day in divided doses every 4 hours. For patients weighing less than 60 kg, the recommended dosage is 200 to 300 mg/kg/day, based on ticarcillin content, given in divided doses every 4 to 6 hours.

Pediatric Patients (≥3 months): *For patients <60 kg:* In patients <60 kg, TIMENTIN is dosed at 50 mg/kg/dose based on the ticarcillin component. TIMENTIN should be administered as follows: Mild to moderate infections 200 mg/kg/day in divided doses every 6 hours; for severe infections, 300 mg/kg/day in divided doses every 4 hours.

For patients ≥60 kg: For mild to moderate infections, 3.1 grams of TIMENTIN (3 grams of ticarcillin and 100 mg of clavulanic acid) administered every 6 hours; for severe infections, 3.1 grams every 4 hours.

Renal Impairment: For infections complicated by renal insufficiency[†], an initial loading dose of 3.1 grams should be followed by doses based on creatinine clearance and type of dialysis as indicated below:

Creatinine clearance mL/min.	Dosage
over 60	3.1 grams every 4 hrs.
30 to 60	2 grams every 4 hrs.
10 to 30	2 grams every 8 hrs.
less than 10	2 grams every 12 hrs.
less than 10 with hepatic dysfunction	2 grams every 24 hrs.
patients on peritoneal dialysis	3.1 grams every 12 hrs.
patients on hemodialysis	2 grams every 12 hrs. supplemented with 3.1 grams after each dialysis

To calculate creatinine clearance[‡] from a serum creatinine value use the following formula:

$$C_{cr} = \frac{(140 - \text{Age})\ (\text{wt. in kg})}{72 \times S_{cr}\ (\text{mg}/100\ \text{mL})}$$

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

[‡] Cockcroft, D.W., et al: Prediction of Creatinine Clearance from Serum Creatinine. Nephron 16:31-41, 1976.

[†] The half-life of ticarcillin in patients with renal failure is approximately 13 hours.

Dosage for any individual patient must take into consideration the site and severity of infection, the susceptibility of the organisms causing infection, and the status of the patient's host defense 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 appraisals are necessary during therapy of chronic urinary tract infection and may be required for several months after therapy has been completed. Persistent infections may require treatment for several weeks and doses smaller than those indicated above should not be used.

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

DIRECTIONS FOR USE OF TIMENTIN
Injection
in Plastic Containers
GALAXY®§ (PL 2040) Plastic Container

TIMENTIN supplied as an iso-osmotic, sterile, nonpyrogenic, frozen solution in GALAXY® (PL 2040) Plastic Containers is for intravenous administration only.

Storage: Avoid unnecessary handling of bags. Store in a freezer capable of maintaining a temperature -20°C (-4°F).

Thawing of Plastic Containers: Thaw frozen bag at room temperature 22°C (72°F) or in a refrigerator 4°C (39°F). [DO NOT FORCE THAW BY IMMERSION IN WATER BATHS OR BY MICROWAVE IRRADIATION.] Check for minute leaks by squeezing bag firmly. If leaks are detected discard solution as sterility may be impaired. Do not add supplementary medication.

The bag should be visually inspected. Thawed solutions should not be used unless clear; solutions will be light to dark yellow in color. Components of the solution may precipitate in the frozen state and will dissolve upon reaching room temperature with little or no agitation. If, after visual inspection, the solution remains cloudy or if an insoluble precipitate is noted or if any seals or outlet ports are not intact, the bag should be discarded.

Use sterile equipment.

The thawed solution is stable for 24 hours at room temperature 22°C (72°F) or for 7 days under refrigeration 4°C (39°F).

DO NOT REFREEZE

Caution: Do not use plastic containers in series connections. Such use could result in an embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

Preparation for Administration:

1. Suspend container from eyelet support.
2. Remove protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying set.

HOW SUPPLIED

TIMENTIN Injection intravenous solution is supplied as a frozen solution in 100-mL single-dose GALAXY® (PL 2040) Plastic Containers.

Each 100-mL single-dose container of TIMENTIN contains ticarcillin disodium equivalent to 3.0 grams ticarcillin and clavulanate potassium equivalent to 0.1 gram clavulanic acid (NDC 0029-6571-31).

Store at or below -20°C (-4°F) [see DIRECTIONS FOR USE OF TIMENTIN Injection in Plastic Containers].

TIMENTIN Injection in GALAXY® (PL 2040) Plastic Containers is manufactured for GlaxoSmithKline by Baxter Healthcare Corporation, Deerfield, Illinois 60015.

TIMENTIN is also supplied as:

NDC 0029-6571-40 3.1-gram ADD-VANTAGE®‖ Antibiotic Vial

Each 31-gram Pharmacy Bulk Package contains sterile ticarcillin disodium equivalent to 30 grams ticarcillin and sterile clavulanate potassium equivalent to 1 gram clavulanic acid.

NDC 0029-6579-21 .....31-gram Pharmacy Bulk Package

Each 3.1-gram vial contains sterile ticarcillin disodium equivalent to 3 grams ticarcillin and sterile clavulanate potassium equivalent to 0.1 gram clavulanic acid.

NDC 0029-6571-26 .....3.1-gram Vial

CLINICAL STUDIES

TIMENTIN has been studied in a total of 296 pediatric patients (excluding neonates and infants less than 3 months) in 6 controlled clinical trials. The majority of patients studied had intra-abdominal infections, and the primary comparator was clindamycin and gentamicin with or without ampicillin. At the end-of-therapy visit, comparable efficacy was reported in the trial arms using TIMENTIN and an appropriate comparator.

TIMENTIN was also evaluated in an additional 408 pediatric patients (excluding neonates and infants less than 3 months) in 3 uncontrolled US clinical trials. Patients were treated across a broad range of presenting diagnoses including: Infections in bone and joint, skin and skin structure, lower respiratory tract, urinary tract, as well as intra-abdominal and gynecologic infections. Patients received TIMENTIN either 300 mg/kg/day (based on the ticarcillin component) divided every 4 hours for severe infection or 200 mg/kg/day (based on the ticarcillin component) divided every 6 hours for mild to moderate infections. The efficacy rates were comparable to those obtained in the controlled trials.

The adverse event profile in these 704 pediatric patients treated with TIMENTIN was comparable to that seen in adult patients.

REFERENCES

1. National Committee for Clinical Microbiology Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically* - Sixth Edition. Approved Standard. NCCLS Document M7-A6, Vol. 23, No. 2 (ISBN 1-56238-486-4). NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, January, 2003.
2. National Committee for Clinical Microbiology Standards. *Performance Standards for Antimicrobial Disk Susceptibility Tests* - Eighth Edition. Approved Standard. NCCLS Document M2-A8, Vol. 23, No. 1 (ISBN 1-56238-485-6). NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, January, 2003.
3. National Committee for Clinical Microbiology Standards. *Performance Standards for Antimicrobial Susceptibility Testing* - Thirteenth Informational Supplement. NCCLS Document M100-S13 (M7), Vol. 23, No. 2. NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, January, 2003.
4. National Committee for Clinical Laboratory Standards. *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria* - Fifth Edition. Approved Standard. NCCLS Document M11-A5, Vol. 21, No. 2 (ISBN 1–56238-429-5). NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, January, 2001.

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January 2007 TI:L18G