

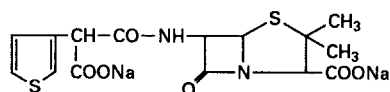
TICAR[®]

brand of

**sterile ticarcillin disodium
for Intramuscular or Intravenous Administration**

DESCRIPTION

Ticar is a semisynthetic injectable penicillin derived from the penicillin nucleus, 6-aminopenicillanic acid. Chemically, it is *N*-(2-Carboxy-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-6-yl)-3-thiophenemalonamic acid disodium salt.



It is supplied as a white to pale yellow powder for reconstitution. The reconstituted solution is clear, colorless or pale yellow, having a pH of 6.0 to 8.0. Ticarcillin is very soluble in water; its solubility is greater than 600 mg/mL.

ACTIONS

Pharmacology

Ticarcillin is not absorbed orally; therefore, it must be given intravenously or intramuscularly. Following intramuscular administration, peak serum concentrations occur within 1/2 to 1 hour. Somewhat higher and more prolonged serum levels can be achieved with the concurrent administration of probenecid.

The minimum inhibitory concentrations (MICs) for many strains of *Pseudomonas* are relatively high by usual standards; serum levels of 60 mcg/mL or greater are required. However, the low degree of toxicity of ticarcillin permits the use of doses large enough to achieve inhibitory levels for these strains in serum or tissues. Other susceptible organisms usually require serum levels in the 10 to 25 mcg/mL range.

TICARCILLIN SERUM LEVELS								
mcg/mL								
Dosage	Route	1/4 hr.	1/2 hr.	1 hr.	2 hr.	3 hr.	4 hr.	6 hr.
Adults:								
500 mg	I.M.	–	7.7	8.6	6.0	4.0	–	2.9
1 gram	I.M.	–	31.0	18.7	15.7	9.7	–	3.4
2 grams	I.M.	–	63.6	39.7	32.3	18.9	–	3.4
3 grams	I.V.	190.0	140.0	107.0	52.2	31.3	13.8	4.2
5 grams	I.V.	327.0	280.0	175.0	106.0	63.0	28.5	9.6
3 grams +	I.V.							
		223.0	166.0	123.0	78.0	54.0	35.4	17.1
1 gram probenecid	Oral							

Neonates:		½ hr.	1 hr.	1½ hr.	2 hr.	4 hr.	8 hr.
50 mg/kg	I.M.	64.0	70.7	63.7	60.1	33.2	11.6

As with other penicillins, ticarcillin is eliminated by glomerular filtration and tubular secretion. It is not highly bound to serum protein (approximately 45%) and is excreted unchanged in high concentrations in the urine. After the administration of a 1 to 2 gram I.M. dose, a urine concentration of 2000 to 4000 mcg/mL may be obtained in patients with normal renal function. The serum half-life of ticarcillin in normal individuals is approximately 70 minutes.

An inverse relationship exists between serum half-life and creatinine clearance, but the dosage of *Ticar* need only be adjusted in cases of severe renal impairment (see DOSAGE AND ADMINISTRATION). The administered ticarcillin may be removed from patients undergoing dialysis; the actual amount removed depends on the duration and type of dialysis.

Ticarcillin can be detected in tissues and interstitial fluid following parenteral administration. Penetration into the cerebrospinal fluid, bile and pleural fluid has been demonstrated.

Microbiology

Ticarcillin is bactericidal and demonstrates substantial *in vitro* activity against both gram-positive and gram-negative organisms. Many strains of the following organisms were found to be susceptible to ticarcillin *in vitro*:

<i>Pseudomonas aeruginosa</i> (and other species)	<i>Salmonella</i> species	Anaerobic bacteria, including:
<i>Escherichia coli</i>	<i>Staphylococcus aureus</i> (non-penicillinase producing)	<i>Bacteroides</i> species including <i>B. fragilis</i>
<i>Proteus mirabilis</i>	<i>Staphylococcus epidermidis</i>	<i>Fusobacterium</i> species
<i>Morganella morganii</i> (formerly <i>Proteus morganii</i>)	Beta-hemolytic streptococci (Group A)	<i>Veillonella</i> species
<i>Providencia rettgeri</i> (formerly <i>Proteus rettgeri</i>)	<i>Streptococcus faecalis</i> (<i>Enterococcus</i>)	<i>Clostridium</i> species
<i>Proteus vulgaris</i>	<i>Streptococcus pneumoniae</i>	<i>Eubacterium</i> species
<i>Enterobacter</i> species		<i>Peptococcus</i> species
<i>Haemophilus influenzae</i>		<i>Peptostreptococcus</i> species
<i>Neisseria</i> species		

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

Some strains of such microorganisms as *Mima-Herellea* (*Acinetobacter*), *Citrobacter* and *Serratia* have shown susceptibility.

Ticarcillin is not stable in the presence of penicillinase.

Some strains of *Pseudomonas* have developed resistance fairly rapidly.

DISK SUSCEPTIBILITY TESTS

Susceptibility Tests: Ticarcillin disks or powders should be used for testing susceptibility to ticarcillin. However, organisms reportedly susceptible to carbenicillin are susceptible to ticarcillin.

Diffusion Techniques: For the disk diffusion method of susceptibility testing a 75 mcg *Ticar* disk should be used. The method for this test is the one outlined in NCCLS publication M2-A3* with the following interpretative criteria:

<u>Culture</u>	<u>Susceptible</u>	<u>Intermediate</u>	<u>Resistant</u>
<i>P. aeruginosa</i> and <i>Enterobacteriaceae</i>	=15 mm	12 to 14 mm	=11 mm

The MIC correlates are: Resistant >128 mcg/mL
Susceptible =64 mcg/mL

Dilution Techniques: Dilution techniques for determining the MIC (minimum inhibitory concentration) are published by NCCLS for the broth and agar dilution procedures. The MIC data should be interpreted in light of the concentrations present in serum, tissue and body fluids. Organisms with MIC =64 are considered susceptible when they are in tissue but organisms with MIC =128 would be susceptible in urine where concentrations of *Ticar* are much greater. At present, only dilution methods can be recommended for testing antibiotic susceptibility of obligate anaerobes.

Susceptibility testing methods require the use of control organisms. The 75 mcg ticarcillin disk should give zone diameters between 22 and 28 mm for *P. aeruginosa* ATCC 27853 and 24 and 30 mm for *E. coli* ATCC 25922. Reference strains are available for dilution testing of ticarcillin. 95% of the MICs should fall within the following MIC ranges and the majority of MICs should be at values close to the center of the pertinent range (reference NCCLS publication M7-A[†]).

S. aureus ATCC 29213, 2.0 to 8.0 mcg/mL; *S. faecalis* ATCC 29212, 16 to 64 mcg/mL; *E. coli* ATCC 25922, 2.0 to 8.0 mcg/mL; *P. aeruginosa* ATCC 27853, 8.0 to 32 mcg/mL.

* Performance Standards for Antimicrobial Disc Susceptibility Tests, National Committee for Clinical Laboratory Standards, Vol. 4, No. 16, pp. 369-402, 1984.

[†] Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically, Vol. 5, No. 22, pp. 579-618, 1985.

INDICATIONS

Ticar is indicated for the treatment of the following infections:

Bacterial septicemia[‡]

Skin and soft-tissue infections[‡]

Acute and chronic respiratory tract infections^{‡§}

[‡] Caused by susceptible strains of *Pseudomonas aeruginosa*, *Proteus* species (both indole-positive and indole-negative) and *Escherichia coli*.

[§] Though clinical improvement has been shown, bacteriological cures cannot be expected in patients with chronic respiratory disease or cystic fibrosis.

Genitourinary tract infections (complicated and uncomplicated) due to susceptible strains of *Pseudomonas aeruginosa*, *Proteus* species (both indole-positive and indole-negative), *Escherichia coli*, *Enterobacter* and *Streptococcus faecalis* (enterococcus).

Ticarcillin is also indicated in the treatment of the following infections due to susceptible anaerobic bacteria:

1. Bacterial septicemia.
2. Lower respiratory tract infections such as empyema, anaerobic pneumonitis and lung abscess.
3. Intra-abdominal infections such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract).
4. Infections of the female pelvis and genital tract, such as endometritis, pelvic inflammatory disease, pelvic abscess and salpingitis.
5. Skin and soft-tissue infections.

Although ticarcillin is primarily indicated in gram-negative infections, its *in vitro* activity against gram-positive organisms should be considered in treating infections caused by both gram-negative and gram-positive organisms (see Microbiology).

Based on the *in vitro* synergism between ticarcillin and gentamicin sulfate, tobramycin sulfate or amikacin sulfate against certain strains of *Pseudomonas aeruginosa*, combined therapy has been successful, using full therapeutic dosages. (For additional prescribing information, see the gentamicin sulfate, tobramycin sulfate and amikacin sulfate package inserts.)

NOTE: Culturing and susceptibility testing should be performed initially and during treatment to monitor the effectiveness of therapy and the susceptibility of the bacteria.

CONTRAINDICATIONS

A history of allergic reaction to any of the penicillins is a contraindication.

WARNINGS

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients receiving penicillin. These reactions are more likely to occur in persons with a history of sensitivity to multiple allergens.

There are reports of patients with a history of penicillin hypersensitivity reactions who experience severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made about previous hypersensitivity reactions to penicillins, cephalosporins and other allergens. If a reaction occurs, the drug should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to ticarcillin therapy. **Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids and airway management, including intubation, should also be administered as indicated.**

Some patients receiving high doses of ticarcillin may develop hemorrhagic manifestations associated with abnormalities of coagulation tests, such as bleeding time and platelet aggregation. On withdrawal of the drug, the bleeding should cease and coagulation abnormalities revert to normal. Other causes of abnormal bleeding should also be considered. Patients with renal impairment, in whom excretion of ticarcillin is delayed, should be observed for bleeding manifestations. Such patients should be dosed strictly according to recommendations (see DOSAGE AND ADMINISTRATION). If bleeding manifestations appear, ticarcillin treatment should be discontinued and appropriate therapy instituted.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including Ticar, and has ranged in severity from mild to life-threatening. Therefore, it is important to

consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of *clostridia*. Studies indicate that a toxin produced by *Clostridium difficile* is 1 primary cause of “antibiotic-associated colitis.”

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug effective against *C. difficile*.

PRECAUTIONS

Although *Ticar* exhibits the characteristic low toxicity of the penicillins, as with any other potent agent, it is advisable to check periodically for organ system dysfunction (including renal, hepatic and hematopoietic) during prolonged treatment. If overgrowth of resistant organisms occurs, the appropriate therapy should be initiated.

Since the theoretical sodium content is 5.2 mEq (120 mg) per gram of ticarcillin, and the actual vial content can be as high as 6.5 mEq/gram, electrolyte and cardiac status should be monitored carefully.

In a few patients receiving intravenous ticarcillin, hypokalemia has been reported. Serum potassium should be measured periodically, and, if necessary, corrective therapy should be implemented.

As with any penicillin, the possibility of an allergic response, including anaphylaxis, exists, particularly in hypersensitive patients.

Usage During Pregnancy

Reproduction studies have been performed in mice and rats and have revealed no evidence of impaired fertility or harm to the fetus due to ticarcillin. There are no well-controlled studies in pregnant women, but investigational experience does not include any positive evidence of adverse effects on the fetus. Although there is no clearly defined risk, such experience cannot exclude the possibility of infrequent or subtle damage to the fetus. Ticarcillin should be used in pregnant women only when clearly needed.

ADVERSE REACTIONS

The following adverse reactions may occur:

Hypersensitivity Reactions: Skin rashes, pruritus, urticaria, drug fever.

Gastrointestinal Disturbances: Nausea and vomiting, pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment. (See WARNINGS.)

Hemic and Lymphatic Systems: As with other penicillins, anemia, thrombocytopenia, leukopenia, neutropenia and eosinophilia.

Abnormalities of Blood, Hepatic and Renal Laboratory Studies: As with other semisynthetic penicillins, SGOT and SGPT elevations have been reported. To date, clinical manifestations of hepatic or renal disorders have not been observed which could be ascribed solely to ticarcillin.

CNS: Patients, especially those with impaired renal function, may experience convulsions or neuromuscular excitability when very high doses of the drug are administered.

Other: Local reactions such as pain (rarely accompanied by induration) at the site of the injection have been reported. Vein irritation and phlebitis can occur, particularly when undiluted solution is directly injected into the vein.

DOSAGE AND ADMINISTRATION

Clinical experience indicates that in serious urinary tract and systemic infections, intravenous therapy in the higher doses should be used. Intramuscular injections should not exceed 2 grams per injection.

Adults:

Bacterial septicemia	200 to 300 mg/kg/day by I.V. infusion in divided doses every 4 or 6 hours.
Respiratory tract infections	(The usual dose is 3 grams given every 4 hours [18 grams/day] or 4 grams given every 6 hours [16 grams/day] depending on weight and the severity of the infection.)
Skin and soft-tissue infections	
Intra-abdominal infections	

Infections of the female pelvis and genital tract

Urinary tract infections	
Complicated:	150 to 200 mg/kg/day by I.V. infusion in divided doses every 4 or 6 hours. (Usual recommended dosage for average [70 kg] adults: 3 grams q.i.d.)
Uncomplicated:	1 gram I.M. or direct I.V. every 6 hours.

Infections complicated by renal insufficiency*: Initial loading dose of 3 grams I.V. followed by I.V. doses, based on creatinine clearance and type of dialysis, as indicated below:

Creatinine clearance mL/min.:	
over 60	3 grams every 4 hours
30 to 60	2 grams every 4 hours
10 to 30	2 grams every 8 hours
less than 10	2 grams every 12 hours (or 1 gram I.M. every 6 hours)
less than 10 with hepatic dysfunction	2 grams every 24 hours (or 1 gram I.M. every 12 hours)
patients on peritoneal dialysis	3 grams every 12 hours
patients on hemodialysis	2 grams every 12 hours supplemented with 3 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.

Children under 40 kg (88 lbs):

The daily dose for children should not exceed the adult dosage.

Bacterial septicemia	200 to 300 mg/kg/day by I.V. infusion in divided doses every 4 or 6 hours.
Respiratory tract infections	4 or 6 hours.
Skin and soft-tissue infections	
Intra-abdominal infections	

Infections of the female pelvis and genital tract

Urinary tract infections

Complicated: 150 to 200 mg/kg/day by I.V. infusion in divided doses every 4 or 6 hours.

Uncomplicated: 50 to 100 mg/kg/day I.M. or direct I.V. in divided doses every 6 or 8 hours.

Infections complicated by renal insufficiency: Clinical data are insufficient to recommend an optimum dose.

Children weighing more than 40 kg (88 lbs) should receive adult dosages.

Neonates: In the neonate, for severe infections (sepsis) due to susceptible strains of *Pseudomonas*, *Proteus* and *E. coli*, the following ticarcillin dosages may be given I.M. or by 10 to 20 minute I.V. infusion:

Infants under 2000 grams body weight:		Infants over 2000 grams body weight:	
Aged 0 to 7 days	75 mg/kg/12 hours (150 mg/kg/day)	Aged 0 to 7 days	75 mg/kg/8 hours (225 mg/kg/day)
Aged over 7 days	75 mg/kg/8 hours (225 mg/kg/day)	Aged over 7 days	100 mg/kg/8 hours (300 mg/kg/day)

This dosage schedule is intended to produce peak serum concentrations of 125 to 150 mcg/mL 1 hour after a dose of ticarcillin and trough concentrations of 25 to 50 mcg/mL immediately before the next dose.

NOTE: Gentamicin, tobramycin or amikacin may be used concurrently with ticarcillin for initial therapy until results of culture and susceptibility studies are known.

Seriously ill patients should receive the higher doses. *Ticar* has proved to be useful in infections in which protective mechanisms are impaired, such as in acute leukemia and during therapy with immunosuppressive or oncolytic drugs.

DIRECTIONS FOR USE

3 gram Standard Vials

Intramuscular Use (concentration of approximately 385 mg/mL): For initial reconstitution use Sterile Water for Injection, USP, Sodium Chloride Injection, USP, or 1% Lidocaine Hydrochloride solution[‡] (without epinephrine).

Each gram of ticarcillin should be reconstituted with 2 mL of Sterile Water for Injection, USP, Sodium Chloride Injection, USP, or 1% Lidocaine Hydrochloride solution[‡] (without epinephrine) and **used promptly**. Each 2.6 mL of the resulting solution will then contain 1 gram of ticarcillin.

[‡] For full product information, refer to manufacturer's package insert for Lidocaine Hydrochloride.

Do not use more than 1 gram of reconstituted *Ticar* in a single intramuscular injection. As with all intramuscular preparations, *Ticar* (ticarcillin disodium) should be injected well within the body of a relatively large muscle using usual techniques and precautions.

Intravenous Administration (concentration of approximately 200 mg/mL): For initial reconstitution use Sodium Chloride Injection, USP, Dextrose Injection 5% or Lactated Ringer's Injection.

Reconstitute each gram of ticarcillin with 4 mL of the appropriate diluent. After the addition of 4 mL of diluent per gram of ticarcillin, each 1.0 mL of the resulting solution will have an approximate concentration of 200 mg. Once dissolved, further dilute if desired.

Direct Intravenous Injection: In order to avoid vein irritation, administer solution as slowly as possible.

Intravenous Infusion: Administer by continuous or intermittent intravenous drip. Intermittent infusion should be administered over a 30 minute to 2-hour period in equally divided doses.

In order to avoid vein irritation, the solution should be administered as slowly as possible. A dilution of approximately 50 mg/mL or more will further reduce the incidence of vein irritation.

Stability studies in the intravenous solutions listed below indicate that ticarcillin disodium will provide sufficient activity between 21° and 24°C (70° and 75°F) within the stated time periods at concentrations between 10 mg/mL and 50 mg/mL — see Stability Period section below.

After reconstitution and prior to administration *Ticar* as with other parenteral drugs should be inspected visually for particulate matter and discoloration.

STABILITY PERIOD		
Intravenous Solution (concentration of 10 mg/mL to 100 mg/mL)	Room Temperature 21° to 24°C (70° to 75°F)	Refrigeration 4°C (40°F)
Sodium Chloride Injection, USP	72 hours	14 days
Dextrose Injection 5%	72 hours	14 days
Lactated Ringer's Injection	48 hours	14 days

Refrigerated solutions stored longer than 72 hours should not be used for multidose purposes.

After reconstitution and dilution to a concentration of 10 mg/mL to 100 mg/mL, this solution can be frozen -18°C (0°F) and stored for up to 30 days. The thawed solution must be used within 24 hours.

Unused solutions should be discarded after the time periods mentioned above.

It is recommended that *Ticar* and gentamicin sulfate, tobramycin sulfate or amikacin sulfate not be mixed together in the same I.V. solution due to the gradual inactivation of gentamicin sulfate, tobramycin sulfate or amikacin sulfate under these circumstances. The therapeutic effect of *Ticar* and these aminoglycoside drugs remains unimpaired when administered separately.

HOW SUPPLIED

Ticar (sterile ticarcillin disodium). Each vial contains ticarcillin disodium equivalent to 3 grams of ticarcillin.

NDC 0029-6552-26 3 gram Vial

Store dry powder at room temperature or below.

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