drug costs. However, thioacetazone is now used as a second-line drug for multidrug-resistant tuberculosis and is not generally recommended for use in HIV-positive patients because of the risk of severe adverse reactions (but see Effects on the Skin, above).

Thioacetazone has been used in the treatment of leprosy (p.176), but WHO now considers that such use is no longer justified.

In the treatment of tuberculosis, thioacetazone has been given orally in doses of 150 mg daily or 2.5 mg/kg daily. Daily use is recommended as the drug is less effective when given intermittently.

Preparations

Proprietary Preparations (details are given in Part 3)
Turk.: Citazon.

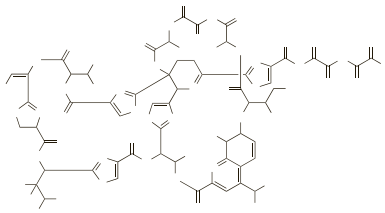
Multi-ingredient: ***India:*** Isokin-T Forte.

Thiostrepton

Thiostreptonum; Tiostreptón; Tiostrepton; Tiostreptoni.

Тиострептон

$C_{72}H_{85}N_{19}O_{18}S_5$ = 1664.9.
CAS — 1393-48-2.



Pharmacopoeias. In *US* for veterinary use only.
USP 31 (Thiostrepton). An antibacterial substance produced by the growth of strains of *Streptomyces azureus*. It has a potency of not less than 900 units/mg, calculated on the dried basis. A white to off-white crystalline solid. Practically insoluble in water, in the lower alcohols, in nonpolar organic solvents, and in dilute aqueous acids or alkalis; soluble in glacial acetic acid, in chloroform, in dimethylformamide, in dimethyl sulfoxide, in dioxan, and in pyridine. Store in airtight containers.

Profile

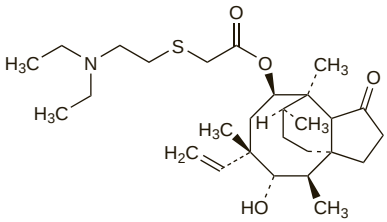
Thiostrepton is an antibacterial produced by strains of *Streptomyces azureus*. It is included in topical antibacterial preparations for veterinary use.

Tiamulin Fumarate *(BANM, USAN, rINNM)*

Fumarato de tiamulina; 81723-hfu; SQ-14055 (tiamulin); SQ-22947 (tiamulin fumarate); Tiamuliinivetyfumaraatti; Tiamuline, Fumarate de; Tiamuline, hydrogénofumarate de; Tiamulin-fumarát; Tiamulini Fumaras; Tiamulini hydrogenofumaras; Tiamulinvätefumarat. 11-Hydroxy-6,7,10,12-tetramethyl-1-oxo-10-vinylperhydro-3a,7-pentanoinden-8-yl (2-diethylaminoethylthio)acetate hydrogen fumarate.

Тиамулина Фумарат

$C_{28}H_{47}NO_4S,C_4H_4O_4$ = 609.8.
CAS — 55297-95-5 (tiamulin); 555297-96-6 (tiamulin fumarate).



(tiamulin)

Pharmacopoeias. In *Eur.* (see p.vii) and *US* for veterinary use only. *Eur.* and *US* also include tiamulin for veterinary use only.
Ph. Eur. 6.2 (Tiamulin Hydrogen Fumarate for Veterinary Use; Tiamulin Hydrogen Fumarate BP(Vet) 2008). A white or light yellow, crystalline powder. Soluble in water and in methyl alcohol; freely soluble in dehydrated alcohol. A 1% solution in water has a pH of 3.1 to 4.1. Protect from light.
USP 31 (Tiamulin Fumarate). A 1.0% solution in water has a pH of 3.1 to 4.1. Store in airtight containers. Protect from light.

Profile

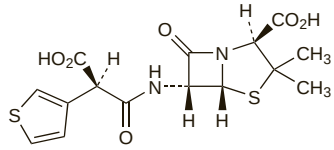
Tiamulin fumarate is an antibacterial used in veterinary medicine.

Ticarcillin Monosodium *(BANM, rINNM)*

Ticarcilina monosódica; Ticarcilline Monosodique; Ticarcillinum Mononatricum. Monosodium (6*R*)-6-[2-carboxy-2-(3-thienyl)acetamido]penicillanate monohydrate.

Мононатрий Тикарциллин

$C_{15}H_{15}N_2NaO_6S_2,H_2O$ = 424.4.
CAS — 34787-01-4 (ticarcillin); 3973-04-4 (ticarcillin); 74682-62-5 (ticarcillin monosodium).



(ticarcillin)

Pharmacopoeias. In *US*.
USP 31 (Ticarcillin Monosodium). Store in airtight containers.

Ticarcillin Sodium *(BANM, rINNM)*

BRL-2288; Natrii Ticarcillinum; Ticarcilina sódica; Ticarcillin Disodium *(USAN)*; Ticarcilline sodique; Ticarcillinum Dinatricum; Ticarcillinum natricum; Tikarcilin disodná sůl; Tikarcilin sodná sůl; Tikarcilino natrio druska; Tikarcillinnatrium; Tikarcillin-nátrium; Tikarsilliininatrium; Tykarcylina sodowa. Disodium (6*R*)-6-[2-carboxy-2-(3-thienyl)acetamido]penicillanate.

Натрий Тикарциллин

$C_{15}H_{14}N_2Na_2O_6S_2$ = 428.4.
CAS — 4697-14-7; 29457-07-6.
ATC — J01CA13.
ATC Vet — QJ01CA13.

Pharmacopoeias. In *Eur.* (see p.vii) and *US*.
Ph. Eur. 6.2 (Ticarcillin Sodium). A white or slightly yellow, hygroscopic powder. Freely soluble in water; soluble in methyl alcohol. A 5% solution in water has a pH of 5.5 to 7.5. Store in airtight containers at a temperature of 2° to 8°.
USP 31 (Ticarcillin Disodium). A white to pale yellow powder or solid. 1 mg of monograph substance has a potency equivalent to not less than 800 micrograms of ticarcillin, calculated on the anhydrous basis. Freely soluble in water. A 1% solution in water has a pH of 6.0 to 8.0. Store in airtight containers.

Incompatibility. Ticarcillin sodium has been reported to be incompatible with aminoglycosides.

References.

1. Swenson E, *et al.* Compatibility of ticarcillin disodium clavulanate potassium with commonly used intravenous solutions. *Curr Ther Res* 1990; **48**: 385–94.

Stability. References.

1. Zhang Y, Trissel LA. Stability of piperacillin and ticarcillin in AutoDose Infusion System bags. *Ann Pharmacother* 2001; **35:** 1360–3.

Adverse Effects and Precautions

As for Carbenicillin Sodium, p.216.

Cholestatic jaundice and hepatitis have been reported when ticarcillin was used with clavulanic acid; the clavulanic acid component has been implicated.

Ticarcillin should be given with caution to patients with renal impairment.

Breast feeding. Although ticarcillin is distributed into breast milk in small amounts,[1] no adverse effects have been seen in breast-fed infants and the American Academy of Pediatrics considers that it is usually compatible with breast feeding.[2]

1. von Kobyletzki D, *et al.* Ticarcillin serum and tissue concentrations in gynecology and obstetrics. *Infection* 1983; **11:** 144–9.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/05/04)

Effects on the bladder. The Australian Adverse Drug Reactions Advisory Committee had received 15 reports of haemorrhagic cystitis associated with ticarcillin or ticarcillin-clavulanic acid between 1980 and June 2002, mainly in paediatric cystic fibrosis patients.[1] Almost all patients recovered quickly after the withdrawal of ticarcillin.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Haemorrhagic cystitis with ticarcillin in cystic fibrosis patients. *Aust Adverse Drug React Bull* 2002; **21:** 6–7. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0206.pdf (accessed 29/07/08)

Effects on the liver. Cholestatic jaundice and hepatitis have been associated with combined preparations of a penicillin and clavulanic acid (see Amoxicillin, p.202) and 2 cases had been reported to the UK CSM with ticarcillin and clavulanic acid.[1] It appeared that the clavulanic acid was probably responsible.

1. Committee on Safety of Medicines/Medicines Control Agency. Cholestatic jaundice with co-amoxiclav. *Current Problems* 1993; **19:** 2. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024454&RevisionSelectionMethod=LatestReleased (accessed 22/07/08)

Sodium content. Each g of ticarcillin sodium contains about 4.7 mmol of sodium.

Interactions

As for Benzylpenicillin, p.214.

Antimicrobial Action

Ticarcillin is bactericidal and has a mode of action and range of activity similar to that of carbenicillin (p.216), but is reported to be 2 to 4 times more active against *Pseudomonas aeruginosa*.

Combinations of ticarcillin and aminoglycosides have been shown to be synergistic *in vitro* against *Ps. aeruginosa* and Enterobacteriaceae.

The activity of ticarcillin against organisms usually resistant because of the production of certain beta-lactamases is enhanced by clavulanic acid, a beta-lactamase inhibitor. Such organisms have included staphylococci, many Enterobacteriaceae, *Haemophilus influenzae*, and *Bacteroides* spp.; the activity of ticarcillin against *Ps. aeruginosa* is not enhanced by clavulanic acid. Resistance to ticarcillin with clavulanic acid has been reported.

There is cross-resistance between carbenicillin and ticarcillin.

◊ References.

1. Pulverer G, *et al.* In-vitro activity of ticarcillin with and without clavulanic acid against clinical isolates of Gram-positive and Gram-negative bacteria. *J Antimicrob Chemother* 1986; **17** (suppl C): 1–5.
2. Masterton RG, *et al.* Timentin resistance. *Lancet* 1987; **ii:** 975–6.
3. Fass RJ, Prior RB. Comparative in vitro activities of piperacillin-tazobactam and ticarcillin-clavulanate. *Antimicrob Agents Chemother* 1989; **33:** 1268–74.
4. Kempers J, MacLaren DM. Piperacillin/tazobactam and ticarcillin/clavulanic acid against resistant Enterobacteriaceae. *J Antimicrob Chemother* 1990; **26:** 598–9.
5. Klepser ME, *et al.* Comparison of the bactericidal activities of piperacillin-tazobactam, ticarcillin-clavulanate, and ampicillin-sulbactam against clinical isolates of Bacteroides fragilis, Enterococcus faecalis, Escherichia coli, and Pseudomonas aeruginosa. *Antimicrob Agents Chemother* 1997; **41:** 435–9.

Pharmacokinetics

Ticarcillin is not absorbed from the gastrointestinal tract. After intramuscular injection of 1 g peak plasma concentrations in the range of 22 to 35 micrograms/mL are achieved after 0.5 to 1 hour. About 50% of ticarcillin in the circulation is bound to plasma proteins. A plasma half-life of 70 minutes has been reported. A shorter half-life in patients with cystic fibrosis (about 50 minutes in one study) has been attributed to increased renal and non-renal elimination. The half-life is prolonged in neonates and also in patients with renal impairment, especially if hepatic function is also impaired. A half-life of about 15 hours has been reported in severe renal impairment.

Distribution of ticarcillin in the body is similar to that of carbenicillin. Relatively high concentrations have been reported in bile, but ticarcillin is excreted principally by glomerular filtration and tubular secretion. Concentrations of 2 to 4 mg/mL are achieved in the urine after the intramuscular injection of 1 or 2 g. Ticarcillin is metabolised to a limited extent. Up to 90% of a dose is excreted unchanged in the urine, mostly within 6 hours after a dose. Plasma concentrations are enhanced by probenecid.

Ticarcillin is removed by haemodialysis and, to some extent, by peritoneal dialysis.

Ticarcillin crosses the placenta and small amounts are distributed into breast milk.

Ticarcillin with clavulanic acid. The pharmacokinetics of ticarcillin and clavulanic acid are broadly similar and neither appears to affect the other to any great extent.

◊ References.
1. Staniforth DH, *et al*. Pharmacokinetics of parenteral ticarcillin formulated with clavulanic acid: Timentin. *Int J Clin Pharmacol Ther Toxicol* 1986; **24:** 123–9.
2. Brogard JM, *et al*. Biliary elimination of ticarcillin plus clavulanic acid (Claventin): experimental and clinical study. *Int J Clin Pharmacol Ther Toxicol* 1989; **27:** 135–44.
3. de Groot R, *et al*. Pharmacokinetics of ticarcillin in patients with cystic fibrosis: a controlled prospective study. *Clin Pharmacol Ther* 1990; **47:** 73–8.
4. Wang J-P, *et al*. Disposition of drugs in cystic fibrosis IV: mechanisms for enhanced renal clearance of ticarcillin. *Clin Pharmacol Ther* 1993; **54:** 293–302.
5. Burstein AH, *et al*. Ticarcillin-clavulanic acid pharmacokinetics in preterm neonates with presumed sepsis. *Antimicrob Agents Chemother* 1994; **38:** 2024–8.

Uses and Administration

Ticarcillin is a carboxypenicillin used in the treatment of severe Gram-negative infections, especially those due to *Pseudomonas aeruginosa*. Pseudomonal infections where ticarcillin is used include those in cystic fibrosis (respiratory-tract infections), immunocompromised patients (neutropenia), peritonitis, and septicaemia. Other infections that may be due to *Ps. aeruginosa* include bone and joint infections, meningitis, otitis media (chronic), skin infections (burns, ecthyma gangrenosum, ulceration), and urinary-tract infections. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Administration and dosage. Ticarcillin is given by injection as the sodium salt. Doses are expressed in terms of the equivalent amount of ticarcillin; 1.1 g of ticarcillin sodium is equivalent to about 1 g of ticarcillin. Doses may need to be reduced in renal impairment (see below).

Ticarcillin is given to adults and children in a dose of 200 to 300 mg/kg daily by intravenous infusion in divided doses every 4 or 6 hours.

In adults the use of probenecid 500 mg four times daily by mouth may produce higher and more prolonged plasma concentrations of ticarcillin, but caution is advised in patients with renal impairment.

In the treatment of complicated urinary-tract infections, adults and children may be given a dose of ticarcillin 150 to 200 mg/kg daily by intravenous infusion in divided doses every 4 or 6 hours. In uncomplicated urinary-tract infections, the usual adult dose is ticarcillin 1 g every 6 hours intramuscularly or by slow intravenous injection. Children with uncomplicated urinary-tract infections may be given 50 to 100 mg/kg daily in divided doses every 6 or 8 hours. Not more than 2 g of ticarcillin should be injected intramuscularly into one site.

In patients with cystic fibrosis, ticarcillin has been given by nebuliser in the management of respiratory-tract infections.

Ticarcillin is often used with an aminoglycoside but the injections must be given separately because of possible incompatibility.

Ticarcillin with clavulanic acid. Ticarcillin may be used with clavulanic acid (p.250), a beta-lactamase inhibitor, to widen its antibacterial spectrum to organisms usually resistant because of the production of beta-lactamases. This combination is given by intravenous infusion in a ratio of 15 or 30 parts of ticarcillin (as the sodium salt) to 1 part of clavulanic acid (as the potassium salt). Doses are according to the content of ticarcillin, and usual adult doses range from 9 to 18 g daily in 3 to 6 divided doses.

Administration in renal impairment. Doses of ticarcillin may need to be reduced in patients with renal impairment. After an initial intravenous loading dose of 3 g, the intravenous maintenance dosage should be adjusted according to the patient's creatinine clearance (CC):

- CC 30 to 60 mL/minute: 2 g every 4 hours
- CC 10 to 30 mL/minute: 2 g every 8 hours
- CC less than 10 mL/minute: 2 g every 12 hours (or 1 g intramuscularly every 6 hours)
- CC less than 10 mL/minute in presence of *hepatic impairment*: 2 g intravenously every 24 hours or 1 g intramuscularly every 12 hours
- peritoneal dialysis patients: 3 g every 12 hours
- haemodialysis patients: 2 g every 12 hours plus an additional dose of 3 g after each dialysis session

Preparations

USP 31: Ticarcillin and Clavulanic Acid for Injection; Ticarcillin and Clavulanic Acid Injection; Ticarcillin for Injection.

Proprietary Preparations (details are given in Part 3)
Fr.: Ticarpen; ***Neth.:*** Ticarpen; ***Spain:*** Ticarpen; ***USA:*** Ticar.

Multi-ingredient: ***Austral.:*** Timentin; ***Belg.:*** Timentin; ***Braz.:*** Timentin; ***Canad.:*** Timentin; ***Cz.:*** Timentin; ***Fr.:*** Claventin; ***Gr.:*** Timentin; ***Hong Kong:*** Timentin; ***India:*** Timentin; ***Irl.:*** Timentin†; ***Israel:*** Timentin; ***Ital.:*** Clavucar†; Timentin; ***Mex.:*** Timentin; ***Neth.:*** Timentin; ***NZ:*** Timentin; ***Philipp.:*** Timentin; ***Pol.:*** Timentin; ***Rus.:*** Timentin (Тиментин); ***Switz.:*** Timenten†; ***UK:*** Timentin; ***USA:*** Timentin.

Tigecycline *(USAN, rINN)*

GAR-936; TBG-MINO; Tigeciclina; Tigécycline; Tigecyclinum; WAY-GAR-936. (4*S*,4a*S*,5a*R*,12a*S*)-9-[2-(*tert*-Butylamino)acetamido]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide.

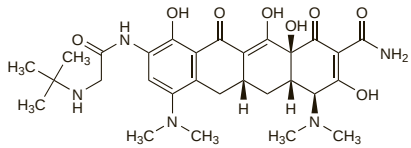
Тигециклин

$C_{29}H_{39}N_5O_8$ = 585.6.

CAS — 220620-09-7.

ATC — J01AA12.

ATC Vet — QJ01AA12.



Stability and compatibility. Formulations of tigecycline without excipients should be used immediately after reconstitution; however, a pH-adjusted formulation with lactose monohydrate is available in the USA, and may be stored at room temperature for up to 24 hours after reconstitution (up to 6 hours in the vial and the remaining time in the infusion bag), or up to 45 hours at 2 to 8° after reconstitution and transfer to an infusion bag.

The latter formulation is compatible when given via a Y-site with amikacin, gentamicin, haloperidol, morphine, noradrenaline, piperacillin with tazobactam, propofol, and tobramycin; it is incompatible with diazepam. Both formulations are stated to be compatible with dobutamine, dopamine hydrochloride, lidocaine hydrochloride, potassium chloride, ranitidine hydrochloride, and theophylline, but are incompatible with amphotericin B. The excipient-free formulation should also not be given with chlorpromazine, methylprednisolone, or voriconazole.

Adverse Effects

Tigecycline is a glycylcycline antibacterial with structural similarity to the tetracyclines and adverse effects similar to those of tetracyclines may potentially occur (see p.347). The most common adverse effects associated with tigecycline have been nausea, vomiting, and diarrhoea. Other common adverse effects include abscess, abdominal pain, anorexia, dyspepsia, dizziness, headache, phlebitis, pruritus, and rash. Infection-related serious adverse events, including sepsis or septic shock have been reported; however, a causal relationship could not be established. Raised liver enzymes, bilirubinaemia, increased serum amylase, and increased blood urea nitrogen have also been reported. Local reactions have been reported at the infusion site and thrombocythaemia, anaemia, and leucocytosis may occur. Acute pancreatitis has been reported, usually after at least one week of treatment; symptoms generally resolve on stopping tigecycline. Potentially life-threatening anaphylaxis or anaphylactoid reactions have also been reported.

Precautions

Due to the potential for similar adverse effects, precautions applicable to the tetracyclines (see p.348) should be taken with tigecycline. In particular, tigecycline should not be given in pregnancy as it has caused fetal harm in *animal* studies. Distribution into milk has also been found in *animal* studies. It should also not be given during tooth development (up to 8 years of age) as it may cause permanent tooth discoloration. Caution should be exercised when using tigecycline as monotherapy in patients with complicated intra-abdominal infections secondary to intestinal perforation. Patients taking anticoagulants should be closely monitored as tigecycline may prolong both the prothrombin time and the activated partial thromboplastin time. Dosage of tigecycline should be adjusted in patients with severe hepatic impairment (see below).

Antimicrobial Action

Tigecycline is generally bacteriostatic and acts by binding to the 30S subunit of the ribosome and preventing the binding of aminoacyl transfer RNA, similarly to tetracyclines (see p.348). It has activity against a broad range of Gram-positive and Gram-negative bacteria, including tetracycline-resistant organisms, and some anaerobic organisms. Tigecycline has demonstrated activity both *in vitro* and in clinical infection with both meticillin-susceptible and meticillin-resistant *Staphylococcus aureus*, vancomycin-susceptible *Enterococcus faecalis*, and some streptococci. Gram-negative organisms that have proven susceptible include *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, and some *Klebsiella* spp. Tigecycline also has activity against some anaerobic bacteria including *Bacteroides fragilis* and some other *Bacteroides* spp., *Clostridium perfringens*, and *Peptostreptococcus micros.*

Pharmacokinetics

After intravenous doses tigecycline is widely distributed into the tissues. Binding to plasma proteins has been reported to be 71 to 89% *in vitro*. Tigecycline is not thought to be extensively metabolised, although some trace metabolites have been identified including a glucuronide, an *N*-acetyl metabolite, and a tigecycline epimer. Tigecycline is primarily eliminated (about 60%) via biliary excretion of unchanged drug and some metabolites with a reported half-life of about 42 hours after multiple doses. About 22% is excreted unchanged in the urine.

◊ Reviews.
1. Meagher AK, *et al*. The pharmacokinetic and pharmacodynamic profile of tigecycline. *Clin Infect Dis* 2005; **41** (suppl 5): S333–S340.
2. Rello J. Pharmacokinetics, pharmacodynamics, safety and tolerability of tigecycline. *J Chemother* 2005; **17** (suppl 1): 12–22.
3. Agwuh KN, MacGowan A. Pharmacokinetics and pharmacodynamics of the tetracyclines including glycylcyclines. *J Antimicrob Chemother* 2006; **58:** 256–65.

Uses and Administration

Tigecycline is a glycylcycline antibacterial used in adults for the intravenous treatment of complicated skin and skin structure infections or complicated intra-abdominal infections caused by susceptible organisms. It may also be given empirically. Tigecycline is given by intravenous infusion over 30 to 60 minutes in an initial loading dose of 100 mg followed by 50 mg every 12 hours. For details of reduced dosage to be given in severe hepatic impairment, see below.

◊ Reviews.
1. Zhanel GG, *et al*. The glycylcyclines: a comparative review with the tetracyclines. *Drugs* 2004; **64:** 63–88.
2. Rubinstein E, Vaughan D. Tigecycline: a novel glycylcycline. *Drugs* 2005; **65:** 1317–36.
3. Frampton JE, Curran MP. Tigecycline. *Drugs* 2005; **65:** 2623–35.
4. Kasbekar N. Tigecycline: a new glycylcycline antimicrobial agent. *Am J Health-Syst Pharm* 2006; **63:** 1235–43.
5. Stein GE, Craig WA. Tigecycline: a critical analysis. *Clin Infect Dis* 2006; **43:** 518–24.
6. Slover CM, *et al.* Tigecycline: a novel broad-spectrum antimicrobial. *Ann Pharmacother* 2007; **41:** 965–72.
7. Grolman DC. Therapeutic applications of tigecycline in the management of complicated skin and skin structure infections. *Int J Infect Dis* 2007; **11** (suppl 1): S7–S15.
8. Karageorgopoulos DE, *et al*. Tigecycline for the treatment of multidrug-resistant (including carbapenem-resistant) Acinetobacter infections: a review of the scientific evidence. *J Antimicrob Chemother* 2008; **62:** 45–55.
9. Curcio D. Tigecycline for treating bloodstream infections: a critical analysis of the available evidence. *Diagn Microbiol Infect Dis* 2008; **61:** 358–9.
10. Mullangi PK, Pankey GA. Tigecycline in critical care. *Crit Care Clin* 2008; **24:** 365–75.