

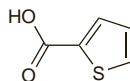
Thenoic Acid

Thenoic Acid; Tenoico, ácido; 2-Thiophenic Acid. Thiophene-2-carboxylic acid.

Тиофенкарбоновая Кислота

$C_6H_4O_2S = 128.1$.

CAS — 527-72-0.



Profile

Thenoic acid has been given orally, rectally, or intranasally as the sodium salt, and orally as the lithium salt, in the treatment of respiratory-tract infections. The monoethanolamine salt has been used sublingually as a mucolytic.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Rhinotrophy; Soufrane.

Multi-ingredient: Fr.: Glossithase; Trophires; Trophires Compose; **Spain:** Trophires†.

Thiamphenicol (BAN, USAN, rINN)

CB-8053; Dextrosulphenicol; Thiamfenicol; Thiamfenikol; Thiamphenicol; Thiamphenicolum; Thiophenicol; Tiamfenicol; Tiamfenikol; Tiamfenikoli; Tiamfenikolis; Tiamfenicol; Win-5063-2; Win-5063 (racephenicol). (α R, β R)-2,2-Dichloro-N-(β -hydroxy- α -hydroxymethyl-4-methylsulphonylphenethyl)acetamide.

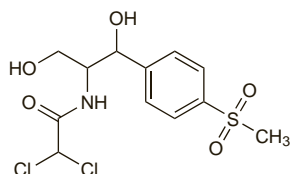
Тиамфеникол

$C_{12}H_{15}Cl_2NO_2S = 356.2$.

CAS — 15318-45-3 (thiamphenicol); 847-25-6 (racephenicol).

ATC — J01BA02.

ATC Vet — QJ01BA02; QJ51BA02.



NOTE. Racephenicol, the racemic form of thiamphenicol, is USAN.

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).

Ph. Eur. 6.2 (Thiamphenicol). A fine, white or yellowish-white, crystalline powder or crystals. Slightly soluble in water and in ethyl acetate; sparingly soluble in dehydrated alcohol and in acetone; freely soluble in acetonitrile and in dimethylformamide; very soluble in dimethylacetamide; soluble in methyl alcohol. Protect from light and moisture.

Thiamphenicol Glycinate Hydrochloride

Thiamphenicol Aminoacetate Hydrochloride; Tiamfenicolo Glicinato Cloridrato; Thiamfenicol, hidrocloruro del glicinato de.

$C_{14}H_{18}Cl_2N_2O_6S.HCl = 449.7$.

CAS — 2393-92-2 (thiamphenicol glycinate); 2611-61-2 (thiamphenicol glycinate hydrochloride).

ATC — J01BA02.

ATC Vet — QJ01BA02.

Pharmacopoeias. In *It.*

Adverse Effects and Precautions

As for Chloramphenicol, p.240.

Thiamphenicol is probably more liable to cause dose-dependent reversible depression of the bone marrow than chloramphenicol but it is not usually associated with aplastic anaemia. Thiamphenicol also appears to be less likely to cause the 'grey syndrome' in neonates.

Doses of thiamphenicol should be reduced in patients with renal impairment. It is probably not necessary to reduce doses in patients with hepatic impairment.

Interactions

As for Chloramphenicol, p.240.

Although thiamphenicol is not metabolised in the liver and might not be expected to be affected by drugs which induce hepatic enzymes, it is reported to inhibit hepatic microsomal enzymes and may affect the metabolism of other drugs.

Antimicrobial Action

Thiamphenicol has a broad spectrum of activity resembling that of chloramphenicol (p.241). Although in general it is less active than chloramphenicol it is reported to be equally effective, and more actively bactericidal, against *Haemophilus* and *Neisseria* spp.

The symbol † denotes a preparation no longer actively marketed

Cross-resistance occurs between thiamphenicol and chloramphenicol. However, some strains resistant to chloramphenicol may be susceptible to thiamphenicol.

Pharmacokinetics

Thiamphenicol is absorbed from the gastrointestinal tract after oral doses and peak serum concentrations of 3 to 6 micrograms/mL have been achieved about 2 hours after a 500-mg dose.

Thiamphenicol diffuses into the CSF, across the placenta, into breast milk, and penetrates well into the lungs. About 10% is bound to plasma proteins. The half-life of thiamphenicol is around 2 to 3 hours but unlike chloramphenicol the half-life is increased in patients with renal impairment. It is excreted in the urine, about 70% of a dose being excreted in 24 hours as unchanged drug. It undergoes little or no conjugation with glucuronic acid in the liver. A small amount is excreted in the bile and the faeces.

Uses and Administration

Thiamphenicol has been used similarly to chloramphenicol (p.241) in the treatment of susceptible infections, including sexually transmitted diseases. The usual adult oral dose is 1.5 g daily in divided doses; up to 3 g daily has been given initially in severe infections. A daily dose of 30 to 100 mg/kg may be used in children. Equivalent doses, expressed in terms of thiamphenicol base, may be given by intramuscular or intravenous injection as the more water soluble glycinate hydrochloride; 1.26 g of thiamphenicol glycinate hydrochloride is equivalent to about 1 g of thiamphenicol. Doses should be reduced in patients with renal impairment (see below).

For the treatment of gonorrhoea, oral doses of thiamphenicol have ranged from 2.5 g daily for 1 or 2 days through to 2.5 g on the first day followed by 2 g daily on each of 4 subsequent days. The single daily dose may be most appropriate for male patients with uncomplicated gonorrhoea.

Thiamphenicol glycinate hydrochloride may also be given by inhalation, or by endobronchial or intracavitary instillation.

Thiamphenicol has also been used as thiamphenicol glycinate acetylcysteinate, thiamphenicol sodium glycinate isophthalate, and thiamphenicol palmitate.

Administration in renal impairment. Doses of thiamphenicol should be reduced in patients with renal impairment according to creatinine clearance (CC):

- CC 30 to 60 mL/minute: 500 mg twice daily
- CC 10 to 30 mL/minute: 500 mg once daily

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Fluimucil Antibiotic; Urfamycin; **Braz.:** Glitisol; **Fr.:** Thiophenicol; **Hong Kong:** Urfamycin; **Indon.:** Biothicol; Canicol; Cetathiacol; Comthicol; Conucol; Corsafen; Daiticin; Dexycol; Genicol; Ipibiofen; Kalticol; Lacophen; Lanacol; Nikolam; Nilacol; Nufathiam; Opiphen; Phenobiotic; Promix; Renamoc; Sendicol; Thiambiotic; Thiamet; Thiamflex; Thiamika; Thiamycin; Thialacol; Troviacol; Urfamycin; Urfekol; Venacol; Zumatab; **Ital.:** Fluimucil Antibiotic; Glitisol; **Mex.:** Tiofeniclin; **Rus.:** Fluimucil Antibiotic (Флуимуцил антибиотик); **Spain:** Fluimucil Antibiotic; Urfamycin†; **Switz.:** Urfamycin; **Thai.:** Doqua; Thiamcin; Treomycin; Urfamycin; **Turk.:** Thiophenicol; Tiofen; Urfamycin.

Multi-ingredient: Spain: Flumil Antibiotic; **Thai.:** Fluimucil Antibiotic.

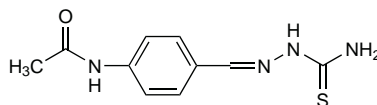
Thioacetazone (BAN, rINN)

Amithiozone; Amitiozon; TBI/698; Tebezonum; Thiacetazone; Thioacétazone; Thioacetazonum; Tiasetazon; Thioacetazona. 4-Acetamidobenzaldehyde thiosemicarbazone.

Тиаоцетазон

$C_{10}H_{12}N_4OS = 236.3$.

CAS — 104-06-3.



Pharmacopoeias. In *Int.*

Adverse Effects

Gastrointestinal disturbances, hypersensitivity reactions including skin rashes, conjunctivitis, and vertigo are the adverse effects most frequently reported with thioacetazone although the incidence appears to vary between countries. Toxic epidermal necrolysis, exfoliative dermatitis (which has sometimes been fatal), and the Stevens-Johnson syndrome have been reported; the incidence of severe skin reactions is especially high in patients with HIV infection (see below). Thioacetazone may cause bone-marrow depression with leucopenia, agranulocytosis, and thrombocytopenia. Acute haemolytic anaemia may occur and a large percentage of patients will have some minor degree of anaemia. Hepatotoxicity with jaundice may also develop and acute hepatic failure has been reported. Cerebral oedema has been reported. Dose-related ototoxicity may occur rarely.

Incidence of adverse effects. In a 10-year series of 1212 patients with tuberculosis who were treated with a regimen of streptomycin, isoniazid, and thioacetazone, 171 (14%) had adverse

reactions associated with thioacetazone. The most common adverse effects were giddiness (10%), occurring mainly when used with streptomycin, and skin rashes (3%) including exfoliation and the Stevens-Johnson syndrome.¹

1. Pearson CA. Thiacetazone toxicity in the treatment of tuberculosis patients in Nigeria. *J Trop Med Hyg* 1978; **81**: 238-42.

Effects on the nervous system. Acute peripheral neuropathy which occurred in a 50-year-old man on 2 separate occasions within 15 minutes of a dose of thioacetazone may have been due to an allergic reaction.¹

1. Gupta PK, et al. Acute severe peripheral neuropathy due to thiacetazone. *Indian J Tuberc* 1984; **31**: 126-7.

Effects on the skin. A high incidence of severe and sometimes fatal cutaneous hypersensitivity reactions to thioacetazone has been reported in patients with HIV infection being treated for tuberculosis.^{1,2} WHO advised that thioacetazone should be avoided in such patients.³ Unfortunately, thioacetazone has been one of the mainstays of tuberculosis treatment in the developing world because of its relatively low cost.⁴ Some have supported a change to rifampicin-based regimens in, for example, parts of Africa with a high incidence of HIV infection.⁵ Others have found a lower frequency of fatalities from adverse cutaneous reactions to thioacetazone than reported previously and have suggested that improved management might allow retention of thioacetazone in tuberculosis programmes.⁶ This was rejected by other workers who considered that better and more cost-effective regimens were available than those containing thioacetazone.⁷ A pragmatic approach may be to adopt a strategy depending upon the prevailing incidence of HIV infection in the population.⁸ Thus, where the incidence of HIV infection is high, ethambutol should be substituted for thioacetazone; where the incidence is moderate, routine HIV testing could be used to identify patients at risk; and where the incidence is low, education of patients on the risks of skin reaction would be adequate.

1. Nunn P, et al. Cutaneous hypersensitivity reactions due to thiacetazone in HIV-1 seropositive patients treated for tuberculosis. *Lancet* 1991; **337**: 627-30.

2. Chintu C, et al. Cutaneous hypersensitivity reactions due to thiacetazone in the treatment of tuberculosis in Zambian children infected with HIV-1. *Arch Dis Child* 1993; **68**: 665-8.

3. Ravignone MC, et al. HIV-associated tuberculosis in developing countries: clinical features, diagnosis, and treatment. *Bull WHO* 1992; **70**: 515-26.

4. Nunn P, et al. Thiacetazone—avoid like poison or use with care? *Trans R Soc Trop Med Hyg* 1993; **87**: 578-82.

5. Okwera A, et al. Randomised trial of thiacetazone and rifampicin-containing regimens for pulmonary tuberculosis in HIV-infected Ugandans. *Lancet* 1994; **344**: 1323-8.

6. Ipuge YAI, et al. Adverse cutaneous reactions to thiacetazone for tuberculosis treatment in Tanzania. *Lancet* 1995; **346**: 657-60.

7. Elliott AM, et al. Treatment of tuberculosis in developing countries. *Lancet* 1995; **346**: 1098-9.

8. van Gorkom J, Kibuga DK. Cost-effectiveness and total costs of three alternative strategies for the prevention and management of severe skin reactions attributable to thiacetazone in the treatment of human immunodeficiency virus positive patients with tuberculosis in Kenya. *Tubercle Lung Dis* 1996; **77**: 30-6.

Hypertrichosis. Hypertrichosis occurred in 2 children receiving thioacetazone.¹

1. Nair LV, Sugathan P. Thiacetazone induced hypertrichosis. *Indian J Dermatol Venereol* 1982; **48**: 161-3.

Precautions

The efficacy and toxicity of a regimen of treatment which includes thioacetazone should be determined in a community before it is used widely since there appear to be geographical differences.

Thioacetazone should not be given to patients with hepatic impairment. It has also been suggested that, because thioacetazone has a low therapeutic index and is excreted mainly in the urine, it should not be given to patients with renal impairment. Treatment should be stopped if rash or other signs of hypersensitivity occur. It should probably be avoided in HIV-positive patients because they are at increased risk of severe adverse effects (see Effects on the Skin, above).

Interactions

Thioacetazone may enhance the ototoxicity of streptomycin.

Antimicrobial Action

Thioacetazone is bacteriostatic. It is effective against most strains of *Mycobacterium tuberculosis*, although sensitivity varies in different parts of the world.

Thioacetazone is also bacteriostatic against *M. leprae*. Resistance to thioacetazone develops when used alone. Cross-resistance can develop between thioacetazone and ethionamide or prothionamide.

Pharmacokinetics

Thioacetazone is absorbed from the gastrointestinal tract and peak plasma concentrations of 1 to 2 micrograms/mL have been obtained about 4 to 5 hours after a 150-mg dose. About 20% of a dose is excreted unchanged in the urine. A half-life of about 12 hours has been reported.

Uses and Administration

Thioacetazone has been used with other antimycobacterials as a first-line drug in the treatment of tuberculosis (p.196). Thioacetazone-containing regimens are less effective than the short-course regimens recommended by WHO but are used in long-term regimens with isoniazid in some developing countries to reduce

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.

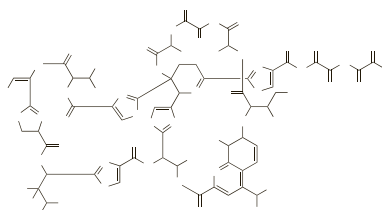
Thiostrepton

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.

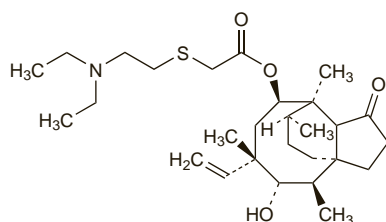
Tiamulin Fumarate (BANM, USAN, rINN)

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

Тиамулина Фумарат

$C_{28}H_{47}NO_4 \cdot C_4H_4O_4 = 609.8$.

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.

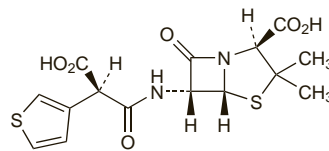
Ticarcillin Monosodium (BANM, rINN)

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

Мононатрий Тикарциллин

$C_{15}H_{15}N_3NaO_6S_2 \cdot H_2O = 424.4$.

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, rINN)

BRL-2288; Natrii Ticarcillinum; Ticarcilina sódica; Ticarcillin Disodium (USAN); Ticarcilline sodique; Ticarcillinum Dinatricum; Ticarcillinum natricum; Tikarcilin disodná sůl; Tikarcilin sodná sůl; Tikarcilino natrio druska; Tikarcillinatium; Tikarcillin-nátrium; Tikarsil-iininatium; Tykarcylina sodowa. Disodium (6R)-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

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

Stability. References.

- 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

- von Kobyletzki D, *et al.* Ticarcillin serum and tissue concentrations in gynecology and obstetrics. *Infection* 1983; **11**: 144-9.
- 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.

- 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/adrb/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.

- 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

- 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.
- Masterton RG, *et al.* Timentin resistance. *Lancet* 1987; **ii**: 975-6.
- Fass RJ, Prior RB. Comparative in vitro activities of piperacillin-tazobactam and ticarcillin-clavulanate. *Antimicrob Agents Chemother* 1989; **33**: 1268-74.
- Kempers J, MacLaren DM. Piperacillin/tazobactam and ticarcillin/clavulanic acid against resistant Enterobacteriaceae. *J Antimicrob Chemother* 1990; **26**: 598-9.
- 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.