*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.

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# 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.

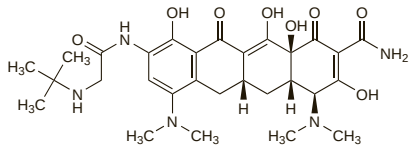
Тигециклин

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

**Administration in hepatic impairment.** Dosage of tigecycline should be adjusted in patients with severe hepatic impairment (Child-Pugh category C); the initial intravenous loading dose should be 100 mg with reduced maintenance doses of 25 mg every 12 hours.

## Preparations

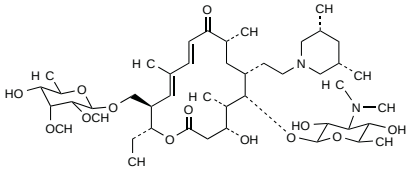
**Proprietary Preparations** (details are given in Part 3)
***Arg.:*** Tygacil; ***Austral.:*** Tygacil; ***Braz.:*** Tygacil; ***Chile:*** Tygacil; ***Cz.:*** Tygacil; ***Gr.:*** Tygacil; ***Hung.:*** Tygacil; ***Indon.:*** Tygacil; ***Malaysia:*** Tygacil; ***Mex.:*** Tygacil; ***Pol.:*** Tygacil; ***Port.:*** Tygacil; ***UK:*** Tygacil; ***USA:*** Tygacil; ***Venez.:*** Tygacil.

### Tilmicosin *(BAN, USAN, rINN)*

EL-870; LY-177370; Tilmicosina; Tilmicosine; Tilmicosinum. 4$^A$-*O*-De(2,6-dideoxy-3-*C*-methyl-α-L-*ribo*-hexopyranosyl)-20-deoxo-20-(*cis*-3,5-dimethyl-piperidino)tylosin.

Тильмикозин

$C_{46}H_{80}N_2O_{13}$ = 869.1.
*CAS — 108050-54-0.*
*ATC Vet — QJ01FA91.*



cis-form

**Pharmacopoeias.** In *US* for veterinary use only.
**USP 31** (Tilmicosin). White to off-white amorphous solid. Slightly soluble in water and in *n*-hexane. Store at a temperature not exceeding 40°. Protect from light.

### Tilmicosin Phosphate *(BANM, USAN, rINNM)*

Fosfato de tilmicosina; Tilmicosine, Phosphate de; Tilmicosini Phosphas.

Тильмикозина Фосфат

$C_{46}H_{80}N_2O_{13},H_3O_4P$ = 967.1.
*CAS — 137330-13-3.*

#### Profile

Tilmicosin is a macrolide antibacterial used as the base or the phosphate in veterinary medicine.

**Adverse effects.** Accidental self-injection of tilmicosin by a farm worker, resulting in asthenia and temporary pulmonary, gastrointestinal, and neuromuscular toxicity has been reported.[1] A review[2] of human exposures to tilmicosin injection reported between March 1992 and March 2005 suggested that the overall risk of serious adverse effects was about 2 cases per million doses. Serious cardiovascular adverse effects, including bradycardia, hypertension, hypotension, tachycardia, and tachypnoea, occurred in 156 of 3168 reported cases and, of these, fatalities occurred in 13.

1. Crown LA, Smith RB. Accidental veterinary antibiotic injection into a farm worker. *Tenn Med* 1999; **92:** 339–40.
2. Veenhuizen MF, *et al.* Analysis of reports of human exposure to Micotil 300 (tilmicosin injection). *J Am Vet Med Assoc* 2006; **229:** 1737–42.

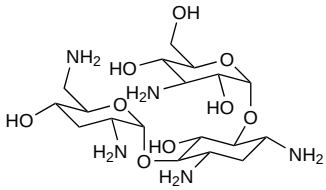
**Handling.** Contact with tilmicosin should be avoided. It is irritating to the eyes and may cause allergic reactions.

## Tobramycin *(BAN, USAN, rINN)*

47663; Nebramycin Factor 6; Tobramicin; Tobramicina; Tobramicinas; Tobramisin; Tobramycine; Tobramycinum; Tobramycyna; Tobramysiini. 6-*O*-(3-Amino-3-deoxy-α-D-glucopyranosyl)-2-deoxy-4-*O*-(2,6-diamino-2,3,6-trideoxy-α-D-*ribo*-hexopyranosyl)streptamine.

Тобрамицин

$C_{18}H_{37}N_5O_9$ = 467.5.
*CAS — 32986-56-4.*
*ATC — J01GB01; S01AA12.*
*ATC Vet — QJ01GB01; QS01AA12.*



**Pharmacopoeias.** In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.
**Ph. Eur. 6.2** (Tobramycin). A substance produced by *Streptomyces tenebrarius* or obtained by any other means. A white or almost white powder. Freely soluble in water; very slightly soluble in alcohol. A 10% solution in water has a pH of 9.0 to 11.0.
**USP 31** (Tobramycin). A white to off-white, hygroscopic powder. Freely soluble in water; very slightly soluble in alcohol; practically insoluble in chloroform and in ether. Contains not more than 8.0% w/w of water. A 10% solution in water has a pH of 9.0 to 11.0. Store in airtight containers.

### Tobramycin Sulfate *(rINNM)*

Sulfato de tobramicina; Tobramycin Sulphate *(BANM)*; Tobramycine, Sulfate de; Tobramycini Sulfas; Tobramycyny siarczan.

Тобрамицина Сульфат

$(C_{18}H_{37}N_5O_9)_2,5H_2SO_4$ = 1425.4.
*CAS — 49842-07-1 ($C_{18}H_{37}N_5O_9$,x$H_2SO_4$); 79645-27-5 ($(C_{18}H_{37}N_5O_9)_2,5H_2SO_4$).*
*ATC — J01GB01; S01AA12.*
*ATC Vet — QJ01GB01; QS01AA12.*

**Pharmacopoeias.** In *Pol.* and *US*.
**USP 31** (Tobramycin Sulfate). It has a potency of not less than 634 micrograms and not more than 739 micrograms of tobramycin per mg. A 4% solution in water has a pH of 6.0 to 8.0. Store in airtight containers.

**Incompatibility.** For discussion of the incompatibility of aminoglycosides, including tobramycin, with beta lactams, see under Gentamicin Sulfate, p.282. Tobramycin is also reported to be incompatible with various other drugs and, as injections have an acid pH, incompatibility with alkaline preparations or with drugs unstable at acid pH may reasonably be expected.

## Adverse Effects, Treatment, and Precautions

As for Gentamicin Sulfate, p.282. Some studies suggest that tobramycin is slightly less nephrotoxic than gentamicin, but others have not found any significant difference in their effects on the kidneys.

Peak plasma-tobramycin concentrations greater than 12 micrograms/mL (the *BNF* suggests 10 micrograms/mL) and trough concentrations greater than 2 micrograms/mL should be avoided.

When tobramycin is given by inhalation with other inhaled drugs, they should be given first before the dose of tobramycin. After the first inhaled dose of tobramycin, patients should be monitored for bronchospasm and if it occurs, the test should be repeated using a bronchodilator. Peak flow should be measured before nebulisation and again after it. Caution should be exercised in the presence of severe haemoptysis. Renal function should be monitored before treatment and every six months during use.

**Effects on the ear.** Reversible vestibular toxicity (ataxia, dizziness, and oscillopsia) occurred in a patient on haemodialysis after about 3 weeks' treatment with inhaled tobramycin for bronchiectasis due to colonisation with *Pseudomonas aeruginosa*.[1]

1. Edson RS, *et al.* Vestibular toxicity due to inhaled tobramycin in a patient with renal insufficiency. *Mayo Clin Proc* 2004; **79:** 1185–91.

**Effects on the kidney.** Irreversible acute renal failure requiring haemodialysis occurred in a high-risk patient with chronic renal failure after being treated for 4 weeks with inhaled tobramycin for *Pseudomonas aeruginosa* pneumonia.[1]

1. Cannella CA, Wilkinson ST. Acute renal failure associated with inhaled tobramycin. *Am J Health-Syst Pharm* 2006; **63:** 1858–61.

**Effects on the liver.** A case of possible tobramycin-induced hepatotoxicity was reported in a 20-year-old patient receiving antibacterial treatment for *Pseudomonas aeruginosa* bacteraemia and osteomyelitis. Liver enzyme values started to increase when empirical treatment was changed to intravenous tobramycin and ceftazidime, and markedly increased when the regimen was changed, increasing the dose of tobramycin and replacing ceftazidime with piperacillin/tazobactam and then later aztreonam. Enzyme values began to decrease after all treatment was stopped on day 12.[1]

1. Nisly SA, *et al.* Tobramycin-induced hepatotoxicity. *Ann Pharmacother* 2007; **41:** 2061–5.

## Interactions

As for Gentamicin Sulfate, p.283.

## Antimicrobial Action

As for Gentamicin Sulfate, p.283. Tobramycin is reported to be somewhat more active *in vitro* than gentamicin against *Pseudomonas aeruginosa* and less active against *Serratia*, staphylococci, and enterococci; however these differences do not necessarily translate into differences in clinical effectiveness.

Cross-resistance between tobramycin and gentamicin is generally seen, but about 10% of strains resistant to gentamicin are susceptible to tobramycin.

◊ References to activity against *Pseudomonas aeruginosa*.

1. Barclay ML, *et al.* Adaptive resistance to tobramycin in Pseudomonas aeruginosa lung infection in cystic fibrosis. *J Antimicrob Chemother* 1996; **37:** 1155–64.
2. den Hollander JG, *et al.* Synergism between tobramycin and ceftazidime against a resistant Pseudomonas aeruginosa strain, tested in an in vitro pharmacokinetic model. *Antimicrob Agents Chemother* 1997; **41:** 95–100.
3. Wu YL, *et al.* Ability of azlocillin and tobramycin in combination to delay or prevent resistance development in Pseudomonas aeruginosa. *J Antimicrob Chemother* 1999; **44:** 389–92.
4. Shawar RM, *et al.* Activities of tobramycin and six other antibiotics against Pseudomonas aeruginosa isolates from patients with cystic fibrosis. *Antimicrob Agents Chemother* 1999; **43:** 2877–80.

## Pharmacokinetics

As for Gentamicin Sulfate, p.284.

After intramuscular use of tobramycin, peak plasma concentrations are achieved within 30 to 90 minutes and concentrations of about 4 micrograms/mL have been reported following doses of 1 mg/kg. Usual doses by slow intravenous injection may result in plasma concentrations which briefly exceed 12 micrograms/mL. A plasma half-life of 2 to 3 hours has been reported. Sufficient tobramycin may be absorbed after inhalation to produce systemic adverse effects (see above).

**Inhalation.** References.

1. Touw DJ, *et al.* Pharmacokinetics of aerosolized tobramycin in adult patients with cystic fibrosis. *Antimicrob Agents Chemother* 1997; **41:** 184–7.
2. Beringer PM, *et al.* Pharmacokinetics of tobramycin in adults with cystic fibrosis: implications for once-daily administration. *Antimicrob Agents Chemother* 2000; **44:** 809–13.

## Uses and Administration

Tobramycin is an aminoglycoside antibiotic with actions and uses similar to those of gentamicin (p.284). It is used, usually as the sulfate, particularly in the treatment of pseudomonal infections.

As with gentamicin, tobramycin may be used with penicillins or cephalosporins; the injections should be given separately.

Doses of tobramycin sulfate are expressed in terms of tobramycin base; 1.5 g of tobramycin sulfate is equivalent to about 1 g of tobramycin. Doses are similar to those of gentamicin, with the usual adult dose ranging from 3 to 5 mg/kg daily in 3 or 4 divided doses. In patients with cystic fibrosis, doses of 8 to 10 mg/kg daily in divided doses may be necessary to achieve therapeutic plasma concentrations.

The usual dose for children is 6 to 7.5 mg/kg daily in 3 or 4 divided doses. Premature and full-term neonates may be given 2 mg/kg every 12 hours.

For mild to moderate urinary-tract infections in adults, a dose of 2 to 3 mg/kg once daily may be effective. As with some other aminoglycosides, once-daily dosage has been used successfully in selected patients for the treatment of other infections without increasing toxicity but local guidelines should be consulted for dosage and serum concentrations (see also Once-daily Dosage, under Gentamicin, p.285).

Tobramycin sulfate is given by intramuscular injection, or by intravenous infusion over 20 to 60 minutes in 50 to 100 mL of sodium chloride 0.9% or glucose 5% injection; proportionately less fluid should be given to children. It has also been given slowly by direct intravenous injection.

Treatment should generally be limited to 7 to 10 days, and peak plasma concentrations greater than 12 micrograms/mL (the *BNF* suggests 10 micrograms/mL) or trough concentrations greater than 2 micrograms/mL should be avoided. In all patients, dosage should be adjusted according to plasma-tobramycin concentrations and particularly where factors such as age, renal impairment, or prolonged thera-