mucosa and lungs, and is about 55 to 73% bound to plasma proteins. It undergoes limited hepatic metabolism and has an elimination half-life of about 7 hours. It is excreted as unchanged drug and metabolites in the faeces and urine. Urinary excretion is by active tubular secretion and is reduced by probenecid. Distribution into milk has been found in *rats*.

Uses and Administration

Gemifloxacin is a fluoroquinolone antibacterial with actions and uses similar to those of ciprofloxacin (p.247).

It is given orally, as the mesilate, for the treatment of community-acquired pneumonia and acute bacterial exacerbations of chronic bronchitis. Doses are expressed in terms of the base; 399 mg of gemifloxacin mesilate is equivalent to about 320 mg of gemifloxacin. The usual dose is 320 mg once daily for 5 days in patients with bronchitis or for 7 days in those with pneumonia.

For details of reduced doses in patients with renal impairment, see below.

◊ Reviews.

1. Lowe MN, Lamb HM. Gemifloxacin. *Drugs* 2000; **59:** 1137–47.
2. Yoo BK, *et al*. Gemifloxacin: a new fluoroquinolone approved for treatment of respiratory infections. *Ann Pharmacother* 2004; **38:** 1226–35.
3. File TM, Tillotson GS. Gemifloxacin: a new, potent fluoroquinolone for the therapy of lower respiratory tract infections. *Expert Rev Anti Infect Ther* 2004; **2:** 831–43.
4. Bhavnani SM, Andes DR. Gemifloxacin for the treatment of respiratory tract infections: in vitro susceptibility, pharmacokinetics and pharmacodynamics, clinical efficacy, and safety. *Pharmacotherapy* 2005; **25:** 717–40.
5. Blondeau JM, Tillotson G. Role of gemifloxacin in the management of community-acquired lower respiratory tract infections. *Int J Antimicrob Agents* 2008; **31:** 299–306.
6. Lode HM, *et al*. Gemifloxacin for community-acquired pneumonia. *Expert Opin Invest Drugs* 2008; **17:** 779–86.
7. Tillotson GS. Role of gemifloxacin in community-acquired pneumonia. *Expert Rev Anti Infect Ther* 2008; **6:** 405–18.

Administration in renal impairment. Doses of gemifloxacin should be halved in patients with a creatinine clearance of 40 mL/minute or less, including those receiving haemodialysis or continuous peritoneal dialysis.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Factive; ***Rus.:*** Factiv (Фактив); ***S.Afr.:*** Factive; ***USA:*** Factive.

Gentamicin Sulfate *(USAN, pINNM)*

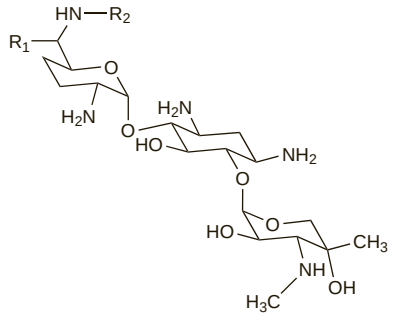
Gentamicin sulfát; Gentamicin Sulphate *(BANM)*; Gentamicine, sulfate de; Gentamicini sulfas; Gentamicino sulfatas; Gentamicin-sulfat; Gentamicin-szulfát; Gentamisiinisulfaatti; Gentamisin Sülfat; Gentamycyny siarczan; NSC-82261; Sch-9724; Sulfato de gentamicina.

Гентамицина Сульфат

CAS — 1403-66-3 (gentamicin); 1405-41-0 (gentamicin sulfate).

ATC — D06AX07; J01GB03; S01AA11; S02AA14; S03AA06.

ATC Vet — QD06AX07; QJ01GB03; QS01AA11; QS02AA14; QS03AA06.



Gentamicin C_1 $R_1 = R_2 = CH_3$
Gentamicin C_2 $R_1 = CH_3$, $R_2 = H$
Gentamicin C_{1a} $R_1 = R_2 = H$

(gentamicin)

NOTE. GNT is a code approved by the BP 2008 for use on single unit doses of eye drops containing gentamicin sulfate where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Gentamicin Sulphate). A mixture of the sulfates of antimicrobial substances produced by *Micromonospora purpurea*, the main components being gentamicins C1, C1a, C2, C2a, and C2b. It contains 20 to 40% of gentamicin C1, 10 to 30% of gentamicin C1a; the sum of gentamicins C2, C2a, and C2b is 40 to 60%. The potency is not less than 590 units/mg, calculated with reference to the anhydrous substance. A white or almost white hygroscopic powder. Freely soluble in water; practically insoluble in alcohol. A 4% solution in water has a pH of 3.5 to 5.5. Store in airtight containers.

USP 31 (Gentamicin Sulfate). The sulfate salt, or a mixture of such salts, of antibiotic substances produced by the growth of *Micromonospora purpurea*. The content of gentamicin C1 is between 25 and 50%, the content of gentamicin C1a is between 10 and 35%, and the sum of the contents of gentamicin C2a and gentamicin C2 is between 25 and 55%. It has a potency equivalent to not less than 590 micrograms of gentamicin per mg, calculated on the dried basis. A white to buff powder. Freely soluble in water; insoluble in alcohol, in acetone, in chloroform, in ether, and in benzene. pH of a 4% solution in water is between 3.5 and 5.5. Store in airtight containers.

Incompatibility. The aminoglycosides are inactivated *in vitro* by various penicillins and cephalosporins via an interaction with the beta-lactam ring, the extent of inactivation depending on temperature, concentration, and duration of contact. The different aminoglycosides vary in their stability, with amikacin apparently the most resistant and tobramycin the most susceptible to inactivation; gentamicin and netilmicin are of intermediate stability. The beta lactams also vary in their ability to produce inactivation, with ampicillin, benzylpenicillin, and antipseudomonal penicillins such as carbenicillin and ticarcillin producing marked inactivation. Inactivation has also been reported with clavulanic acid.

Gentamicin is also incompatible with furosemide, heparin, sodium bicarbonate (the acid pH of gentamicin solutions may liberate carbon dioxide), and some solutions for parenteral nutrition. Interactions with preparations having an alkaline pH (such as sulfadiazine sodium), or drugs unstable at acid pH (for example erythromycin salts), might reasonably be expected.

Given their potential for incompatibility, gentamicin and other aminoglycosides should not generally be mixed with other drugs in syringes or infusion solutions nor given through the same intravenous line. When aminoglycosides are given with a beta lactam, they should generally be given at separate sites.

General references.

1. Henderson JL, *et al*. In vitro inactivation of gentamicin, tobramycin, and netilmicin by carbenicillin, azlocillin, or mezlocillin. *Am J Hosp Pharm* 1981; **38:** 1167–70.
2. Tindula RJ, *et al*. Aminoglycoside inactivation by penicillins and cephalosporins and its impact on drug-level monitoring. *Drug Intell Clin Pharm* 1983; **17:** 906–8.
3. Navarro AS, *et al*. In-vitro interaction between dibekacin and penicillins. *J Antimicrob Chemother* 1986; **17:** 83–9.
4. Courcol RJ, Martin GR. Comparative aminoglycoside inactivation by potassium clavulanate. *J Antimicrob Chemother* 1986; **17:** 682–4.

Stability. There was an average 16% potency loss of gentamicin sulfate from solutions containing 10 and 40 mg/mL when stored at 4° or 25° in plastic disposable syringes for 30 days, and a brown precipitate formed in several. Storage in glass disposable syringes for 30 days produced an average 7% potency loss, which was considered acceptable, but storage for longer resulted in precipitate formation in some cases and was not recommended.[1]

1. Weiner B, *et al*. Stability of gentamicin sulfate injection following unit dose repackaging. *Am J Hosp Pharm* 1976; **33:** 1254–9.

Adverse Effects

The aminoglycosides can produce irreversible, cumulative ototoxicity. This affects both the cochlea (manifest as hearing loss, initially of higher tones, and which, because speech recognition relies greatly on lower frequencies, may not be at first apparent) and the vestibular system (manifest as dizziness or vertigo). The incidence and relative toxicity with different aminoglycosides is a matter of some dispute, but netilmicin is probably less cochleotoxic than gentamicin or tobramycin, and amikacin more so. Netilmicin also exhibits less vestibular toxicity than gentamicin, tobramycin, or amikacin, while streptomycin produces a high incidence of vestibular damage. Vestibular damage is more common than hearing loss in patients receiving gentamicin.

Reversible nephrotoxicity may occur and acute renal failure has been reported, often in association with the use of other nephrotoxic drugs. Renal impairment is usually mild, although acute tubular necrosis and interstitial nephritis have occurred. Decreased glomerular filtration rate is usually seen only after several days, and may even occur after therapy has stopped. Electrolyte disturbances (notably hypomagnesaemia, but also hypocalcaemia and hypokalaemia) have occurred. The nephrotoxicity of gentamicin is reported to be largely due to the gentamicin C_2 component.

Although particularly associated with high plasma concentrations, many risk factors have been suggested for ototoxicity and nephrotoxicity in patients receiving aminoglycosides—see Precautions below.

Aminoglycosides possess a neuromuscular-blocking action and respiratory depression and muscular paralysis have been reported, notably after absorption from serous surfaces. Neomycin has the most potent action and several deaths have been associated with its use.

Hypersensitivity reactions have occurred, especially after local use, and cross-sensitivity between aminoglycosides may occur. Very rarely, anaphylactic reactions to gentamicin have occurred. Some hypersensitivity reactions have been attributed to the presence of sulfites in parenteral formulations, and endotoxic shock has also been reported.

Infrequent effects reported for gentamicin include blood dyscrasias, purpura, nausea and vomiting, stomatitis, and signs of liver dysfunction such as increased serum-aminotransferase values and increased serum-bilirubin concentrations. Neurotoxicity has occurred, with both peripheral neuropathies and central symptoms being reported including encephalopathy, confusion, lethargy, hallucinations, convulsions, and mental depression.

Atrophy or fat necrosis has been reported at injection sites. There have been isolated reports of meningeal irritation, arachnoiditis, polyradiculitis, and ventriculitis after intrathecal, intracisternal, or intraventricular use of aminoglycosides. Subconjunctival injection of gentamicin may lead to pain, hyperaemia, and conjunctival oedema, while severe retinal ischaemia has followed intra-ocular injection.

Effects on the ears. Reviews and references to aminoglycoside-induced ototoxicity.

1. Cone LA. A survey of prospective, controlled clinical trials of gentamicin, tobramycin, amikacin, and netilmicin. *Clin Ther* 1982; **5:** 155–62.
2. Kahlmeter G, Dahlager JI. Aminoglycoside toxicity—a review of clinical studies published between 1975 and 1982. *J Antimicrob Chemother* 1984; **13** (suppl A): 9–22.
3. Brummett RE, Fox KE. Aminoglycoside-induced hearing loss in humans. *Antimicrob Agents Chemother* 1989; **33:** 797–800.
4. Mattie H, *et al*. Determinants of efficacy and toxicity of aminoglycosides. *J Antimicrob Chemother* 1989; **24:** 281–93.
5. Schacht J. Aminoglycoside ototoxicity: prevention in sight? *Otolaryngol Head Neck Surg* 1998; **118:** 674–7.
6. Nakashima T, *et al*. Vestibular and cochlear toxicity of aminoglycosides—a review. *Acta Otolaryngol* 2000; **120:** 904–11.
7. Darlington CL, Smith PF. Vestibulotoxicity following aminoglycoside antibiotics and its prevention. *Curr Opin Investig Drugs* 2003; **4:** 841–6.
8. Rizzi MD, Hirose K. Aminoglycoside ototoxicity. *Curr Opin Otolaryngol Head Neck Surg* 2007; **15:** 352–7.

Effects on the kidneys. Reviews and references to aminoglycoside-induced nephrotoxicity.

1. Cone LA. A survey of prospective, controlled clinical trials of gentamicin, tobramycin, amikacin, and netilmicin. *Clin Ther* 1982; **5:** 155–62.
2. Lietman PS, Smith CR. Aminoglycoside nephrotoxicity in humans. *Rev Infect Dis* 1983; **5** (suppl 2): S284–93.
3. Kahlmeter G, Dahlager JI. Aminoglycoside toxicity—a review of clinical studies published between 1975 and 1982. *J Antimicrob Chemother* 1984; **13** (suppl A): 9–22.
4. Kohlhepp SJ, *et al*. Nephrotoxicity of the constituents of the gentamicin complex. *J Infect Dis* 1984; **149:** 605–14.
5. Mattie H, *et al*. Determinants of efficacy and toxicity of aminoglycosides. *J Antimicrob Chemother* 1989; **24:** 281–93.
6. Appel GB. Aminoglycoside nephrotoxicity. *Am J Med* 1990; **88** (suppl 3C): 16S–20S.
7. Bertino JS, *et al*. Incidence of and significant risk factors for aminoglycoside-associated nephrotoxicity in patients dosed by using individualized pharmacokinetic monitoring. *J Infect Dis* 1993; **167:** 173–9.
8. Swan SK. Aminoglycoside nephrotoxicity. *Semin Nephrol* 1997; **17:** 27–33.
9. Baciewicz AM, *et al*. Aminoglycoside-associated nephrotoxicity in the elderly. *Ann Pharmacother* 2003; **37:** 182–6.
10. Rougier F, *et al*. Aminoglycoside nephrotoxicity. *Curr Drug Targets Infect Disord* 2004; **4:** 153–62.
11. Martínez-Salgado C, *et al*. Glomerular nephrotoxicity of aminoglycosides. *Toxicol Appl Pharmacol* 2007; **223:** 86–98.

Endotoxin reactions. Reports of endotoxin reactions associated with intravenous gentamicin have been received by the CDC and the FDA in the USA.[1] Although endotoxin concentrations in the injections used were within USP limits, giving a single daily dose rather than divided doses was thought to have resulted in toxic serum concentrations of endotoxins.[1,2]

1. CDC. Endotoxin-like reactions associated with intravenous gentamicin—California, 1998. *MMWR* 1998; **47:** 877–80.
2. Krieger JA, Duncan L. Gentamicin contaminated with endotoxin. *N Engl J Med* 1999; **340:** 1122.

Treatment of Adverse Effects

Aminoglycosides may be removed by haemodialysis or to a much lesser extent by peritoneal dialysis. Calcium salts given intravenously have been used to counter neuromuscular blockade; the effectiveness of neostigmine has been variable.

◊ For reference to the potential for calcium-channel blockers to reduce aminoglycoside-related nephrotoxicity, see Kidney Disorders, under Uses of Verapamil, p.1424.

Precautions

Gentamicin is contra-indicated in patients with a known history of hypersensitivity to it, and probably in those hypersensitive to other aminoglycosides. It should be avoided in patients with myasthenia gravis, and great care is required in patients with parkinsonism and other conditions characterised by muscular weakness.

The risk of ototoxicity and nephrotoxicity from aminoglycosides is increased at high plasma concentrations and it is therefore generally desirable to determine dosage requirements by individual monitoring. In patients receiving standard multiple-dose regimens of gentamicin, dosage should be adjusted to avoid peak plasma concentrations above 10 micrograms/mL, or trough concentrations (immediately before next dose) exceeding 2 micrograms/mL. Local guidelines on serum concentration should be consulted where once-daily dosage regimens are used. Monitoring is particularly important in patients receiving high doses or prolonged courses, in infants and the elderly, and in patients with renal impairment, who generally require reduced doses. The *BNF* also considers monitoring to be important in patients with cystic fibrosis or significant obesity; again, altered doses may be required. See Pharmacokinetics below for other patient groups in whom pharmacokinetics may be altered. Impaired hepatic function or auditory function, bacteraemia, fever, and perhaps exposure to loud noises have also been reported to increase the risk of ototoxicity, while volume depletion or hypotension, liver disease, or female sex have been reported as additional risk factors for nephrotoxicity. Regular assessment of auditory and renal function is particularly necessary in patients with additional risk factors.

Topical application of gentamicin into the ear is contra-indicated in patients with known or suspected perforation of the ear drum.

Use of aminoglycosides during pregnancy may damage the eighth cranial nerve of the fetus.

Breast feeding. A study[1] involving 10 mothers given gentamicin and their breast-fed infants found measurable gentamicin concentrations in the serum of 5 of the 10 neonates, indicating that appreciable gastrointestinal absorption had occurred. It was, however, considered that these low concentrations would not cause clinical effects and the American Academy of Pediatrics[2] also considers that the use of gentamicin is usually compatible with breast feeding.

1. Celiloglu M, *et al.* Gentamicin excretion and uptake from breast milk by nursing infants. *Obstet Gynecol* 1994; **84:** 263–5.
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 27/05/04)

Interference with assay procedures. The implications of drug interference with assays for aminoglycosides have been reviewed.[1] Other antimicrobials and antineoplastics may alter the results of microbiological assays but this can be overcome by selection of an appropriate assay organism.

Microbiological assays for aminoglycosides in samples also containing *imipenem* could be accomplished by using cysteine hydrochloride to inactivate imipenem, since it is stable to most beta-lactamases and resistant strains are extremely rare.[2] Because aminoglycosides may be inactivated by *penicillins* and *cephalosporins*, it has been recommended that aminoglycoside sampling times should be chosen to coincide with a trough plasma concentration for the beta lactam. Samples should be frozen if there is to be a delay before they are assayed[3] or a penicillinase added. However, one group of workers have reported loss of gentamicin activity after storage at –60° before assay.[4] Furthermore, there have been reports that concentrations of aminoglycosides in patients also receiving beta lactams have been overestimated using a homogeneous enzyme immunoassay, probably because of an inability to differentiate between active drug and inactivated products.[5,6]

The radionuclide *gallium-67* interferes with radio-enzymatic assays, and it has been suggested that an agar diffusion method should be used in patients who have received a gallium scan.[7,8]

Heparin has been shown to produce underestimation of aminoglycoside concentrations when using microbiological, enzymatic, or immunoassays.[9-11] It has been recommended that either serum should be used or that blood samples should not be collected in heparinised tubes or from indwelling catheter lines. Some consider that concentrations of heparin reached in the blood of patients receiving heparin are too low to affect gentamicin.[12]

Falsely low concentrations have also been reported in microbiological assays in the presence of *zinc* salts.[13]

Heat treatment of whole *blood* to inactivate human immunodeficiency virus leads to an increase in the concentration of gentamicin subsequently found on assay.[14]

1. Yosselson-Superstine S. Drug interferences with plasma assays in therapeutic drug monitoring. *Clin Pharmacokinet* 1984; **9:** 67–87.
2. McLeod KM, *et al.* Gentamicin assay in the presence of imipenem. *J Antimicrob Chemother* 1986; **17:** 828–9.
3. Tindula RJ, *et al.* Aminoglycoside inactivation by penicillins and cephalosporins and its impact on drug-level monitoring. *Drug Intell Clin Pharm* 1983; **17:** 906–8.
4. Carlson LG, *et al.* Potential liabilities of gentamicin homogeneous enzyme immunoassay. *Antimicrob Agents Chemother* 1982; **21:** 192–4.
5. Ebert SC, Clementi WA. In vitro inactivation of gentamicin by carbenicillin, compared by Emit and microbiological assays. *Drug Intell Clin Pharm* 1983; **17:** 451.
6. Dalmady-Israel C, *et al.* Ticarcillin and assay of tobramycin. *Ann Intern Med* 1984; **100:** 460.
7. Bhattacharya I, *et al.* Effects of radiopharmaceuticals on radioenzymatic assays of aminoglycoside antibiotics: interference by gallium-67 and its elimination. *Antimicrob Agents Chemother* 1978; **14:** 448–53.
8. Shannon K, *et al.* Interference with gentamicin assays by gallium-67. *J Antimicrob Chemother* 1980; **6:** 285–300.
9. Nilsson L. Factors affecting gentamicin assay. *Antimicrob Agents Chemother* 1980; **17:** 918–21. Correction. *ibid.*; **18:** 839.
10. Nilsson L, *et al.* Inhibition of aminoglycoside activity by heparin. *Antimicrob Agents Chemother* 1981: **20:** 155–8.
11. O'Connell MB, *et al.* Heparin interference with tobramycin, netilmicin, and gentamicin concentrations determined by Emit. *Drug Intell Clin Pharm* 1984; **18:** 503–4.
12. Regamey C, *et al.* Inhibitory effect of heparin on gentamicin concentrations in blood. *Antimicrob Agents Chemother* 1972; **1:** 329–32.
13. George RH, Healing DE. The effect of zinc on aminoglycoside assay. *J Antimicrob Chemother* 1978; **4:** 186.
14. Eley A, *et al.* Effect of heat on gentamicin assays. *Lancet* 1987; **ii:** 335–6.

Interactions

Use of other nephrotoxic drugs (including other aminoglycosides, vancomycin, some cephalosporins, ciclosporin, cisplatin, and fludarabine), or of potentially ototoxic drugs such as etacrynic acid and perhaps furosemide, may increase the risk of aminoglycoside toxicity. It has been suggested that use of an antiemetic such as dimenhydrinate may mask the early symptoms of vestibular ototoxicity. Care is also required if other drugs with a neuromuscular-blocking action are used (see Atracurium, p.1903). The neuromuscular-blocking properties of aminoglycosides may be sufficient to provoke severe respiratory depression in patients given general anaesthetics or opioids.

There is a theoretical possibility that the antibacterial effects of aminoglycosides could be reduced by bacteriostatic antibacterials, but such combinations have been used successfully in practice.

Since aminoglycosides have been shown to be incompatible with some beta lactams *in vitro* (see Incompatibility, above), these antibacterials should be given separately if both are required; antagonism *in vivo* has been reported only in a few patients with severe renal impairment, in whom aminoglycoside activity was diminished. Aminoglycosides exhibit synergistic activity with a number of beta lactams *in vivo* (see Antimicrobial Action, below).

Renal excretion of zalcitabine may be reduced by aminoglycosides.

For a report of severe hypocalcaemia in a patient treated with aminoglycosides and bisphosphonates, see p.1091.

Gentamicin may inhibit α-galactosidase activity and should not be used with agalsidase alfa or beta.

Antimicrobial Action

Gentamicin is an aminoglycoside antibiotic and has a bactericidal action against many Gram-negative aerobes and against some strains of staphylococci.

Mechanism of action. Aminoglycosides are taken up into sensitive bacterial cells by an active transport process which is inhibited in anaerobic, acidic, or hyperosmolar environments. Within the cell they bind to the 30S, and to some extent to the 50S, subunits of the bacterial ribosome, inhibiting protein synthesis and generating errors in the transcription of the genetic code. The manner in which cell death is brought about is imperfectly understood, and other mechanisms may contribute, including effects on membrane permeability.

Spectrum of activity. The following pathogenic organisms are usually sensitive to gentamicin (but see also Resistance, below).

Many strains of Gram-negative bacteria including species of *Brucella*, *Calymmatobacterium*, *Campylobacter*, *Citrobacter*, *Escherichia*, *Enterobacter*, *Francisella*, *Klebsiella*, *Proteus*, *Providencia*, *Pseudomonas*, *Serratia*, *Vibrio*, and *Yersinia*. Some activity has been reported against isolates of *Neisseria*, although aminoglycosides are rarely used clinically in neisserial infections.

Among the Gram-positive organisms many strains of *Staphylococcus aureus* are highly sensitive to gentamicin. *Listeria monocytogenes* and some strains of *Staph. epidermidis* may also be sensitive to gentamicin, but enterococci and streptococci are usually insensitive to gentamicin.

Some actinomycetes and mycoplasmas have been reported to be sensitive to gentamicin, but mycobacteria are insensitive at clinically achievable concentrations; anaerobic organisms, yeasts, and fungi are resistant.

Activity with other antimicrobials. Gentamicin exhibits synergy with beta lactams, probably because the effects of the latter on bacterial cell walls enhance aminoglycoside penetration. Enhanced activity has been demonstrated with a penicillin (such as ampicillin or benzylpenicillin) and gentamicin against the enterococci, and gentamicin has been combined with an antipseudomonal penicillin such as ticarcillin for enhanced activity against *Pseudomonas* spp., and with vancomycin for enhanced activity against staphylococci and streptococci.

Resistance to the aminoglycosides may be acquired by three main mechanisms. The first is by mutation of ribosomal target sites leading to reduced affinity for binding; this type of resistance is generally only relevant for streptomycin and, even then, it appears to be rare in Gram-negative bacteria. Secondly, penetration of aminoglycosides into bacterial cells is by an oxygen-dependent active transport process and resistance may occur because of elimination or reduction of this uptake; when it occurs this generally results in cross-resistance to all aminoglycosides. Thirdly, and by far the most important cause of resistance to the aminoglycosides, is inactivation by enzymatic modification. Three main classes of enzyme conferring resistance have been found, operating by phosphorylation, acetylation, or addition of a nucleotide group, usually adenyl. Enzyme production is usually plasmid-determined and resistance can therefore be transferred between bacteria, even of different species. Resistance to other antibacterials may be transferred at the same time. In *Staph. aureus*, transfer of resistance is more likely when these drugs are used topically. Each type of enzyme produces characteristic patterns of resistance, but their overlapping and variable affinities for their substrates result in a wide range of permutations of cross-resistance to the different aminoglycosides. The different enzymes vary in their distribution and prevalence in different locations, and at different times, presumably with variations in antibacterial usage, but relationships to the use of specific aminoglycosides are difficult to establish. These variations in drug sensitiv-

ity require local testing to determine resistance and establish susceptibility of bacteria to the aminoglycoside being used, but such local variations mean that estimates of the incidence of resistance are of limited value. In general, the occurrence of resistant pathogens seems to have been greater in southern than in northern Europe, and perhaps greater in the USA than in Europe. There has been particular concern over the increasing incidence of high-level gentamicin resistance among enterococci (in up to 50% of isolates from some centres), since they already possess inherent or acquired resistance to many drugs, including vancomycin in some cases. A similar problem exists with gentamicin resistance in meticillin-resistant strains of *Staph. aureus*. Such multiply-resistant strains pose a major therapeutic problem in those centres where they occur, since the usual synergistic combinations with other antibacterials are ineffective. However, results from some centres indicate that rational use of a wider range of aminoglycosides (including amikacin which is not affected by most of the aminoglycoside-degrading enzymes) has resulted in a modest decline in overall aminoglycoside resistance.

◊ References.

1. Mingeot-Leclercq M-P, *et al.* Aminoglycosides: activity and resistance. *Antimicrob Agents Chemother* 1999; **43:** 727–37.
2. Kotra LP, *et al.* Aminoglycosides: perspectives on mechanisms of action and resistance and strategies to counter resistance. *Antimicrob Agents Chemother* 2000; **44:** 3249–56.
3. Barclay ML, Begg EJ. Aminoglycoside adaptive resistance: importance for effective dosage regimens. *Drugs* 2001; **61:** 713–21.
4. Magnet S, Blanchard JS. Molecular insights into aminoglycoside action and resistance. *Chem Rev* 2005; **105:** 477–98.

Pharmacokinetics

Gentamicin and other aminoglycosides are poorly absorbed from the gastrointestinal tract but are rapidly absorbed after intramuscular injection. Average peak plasma concentrations of about 4 micrograms/mL have been attained in patients with normal renal function 30 to 60 minutes after an intramuscular dose equivalent to gentamicin 1 mg/kg, which is similar to concentrations achieved after intravenous infusion. There may be considerable individual variation. Several doses are required before plasma equilibrium concentrations occur and this may represent the saturation of binding sites in body tissues such as the kidney. Binding of gentamicin to plasma proteins is usually low.

On parenteral use, gentamicin and other aminoglycosides diffuse mainly into extracellular fluids. However, there is little diffusion into the CSF and even when the meninges are inflamed effective concentrations may not be achieved; diffusion into the eye is also poor. Aminoglycosides diffuse readily into the perilymph of the inner ear. They cross the placenta but only small amounts have been reported in breast milk.

Systemic absorption of gentamicin and other aminoglycosides has been reported after topical use on denuded skin and burns and on instillation into, and irrigation of, wounds, body-cavities (except the urinary bladder), and joints.

The plasma elimination half-life for gentamicin has been reported to be 2 to 3 hours though it may be considerably longer in neonates and patients with renal impairment. Gentamicin and other aminoglycosides do not appear to be metabolised and are excreted virtually unchanged in the urine by glomerular filtration. At steady state at least 70% of a dose may be recovered in the urine in 24 hours and urine concentrations in excess of 100 micrograms/mL may be achieved. However, gentamicin and the other aminoglycosides appear to accumulate in body tissues to some extent, mainly in the kidney, although the relative degree to which this occurs may vary with different aminoglycosides. Release from these sites is slow and small amounts of aminoglycosides may be detected in the urine for up to 20 days or more after treatment stops. Small amounts of gentamicin appear in the bile.

The pharmacokinetics of the aminoglycosides are affected by many factors, which may become significant because of the relatively small difference between therapeutic and toxic concentrations, reinforcing the need for monitoring.

- Absorption from intramuscular sites may be reduced in critically ill patients, especially in conditions that reduce perfusion such as shock, resulting in **reduced plasma concentrations**. Plasma concentrations may also be reduced in patients with conditions which expand extracellular fluid volume or increase renal clearance including ascites, cirrhosis, heart failure, malnutrition, spinal cord injury, burns, cystic fibrosis, and possibly leukaemia. Clearance is also reportedly increased in intravenous drug abusers, and in patients who are febrile.
- In contrast, renal impairment or reduced renal clearance for any reason (for example in neonates with immature renal function, or in the elderly in whom glomerular function tends to decline with age) can result in markedly **increased plasma concentrations** and/or prolonged half-lives. However, in neonates initial plasma concentrations may actually be reduced, due to a larger volume of distribution. Plasma concentrations may also be higher than expected for a given dose in obese patients (in whom extracellular volume is low relative to weight), and in patients with anaemia.

Renal clearance, and hence plasma concentrations, of aminoglycosides may vary according to a circadian cycle, and it has been suggested that this should be taken into account when determining and comparing plasma aminoglycoside concentrations.

Uses and Administration

Gentamicin is an aminoglycoside antibiotic used, often with other antibacterials, to treat severe systemic infections due to sensitive Gram-negative and other organisms (see Antimicrobial Action, above). Such infections include biliary-tract infections (acute cholecystitis or cholangitis), brucellosis, cat scratch disease, cystic fibrosis, endocarditis (in the treatment and prophylaxis of endocarditis due to streptococci, enterococci, or staphylococci), endometritis, gastroenteritis, granuloma inguinale, listeriosis, meningitis, otitis externa, otitis media, pelvic inflammatory disease, peritonitis, plague, pneumonia, septicaemia, skin infections such as in burns or ulcers (given systemically for pseudomonal and other Gram-negative infections), tularaemia, and urinary-tract infections (acute pyelonephritis), as well as in the prophylaxis of surgical infection and the treatment of immunocompromised patients and those in intensive care. It may be used as part of a multi-drug regimen for the treatment of inhalation and gastrointestinal anthrax. Gentamicin is also applied topically for localised infections. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Gentamicin is often used with other antibacterials to extend its spectrum of activity or increase its efficacy, e.g. with a penicillin for enterococcal and streptococcal infections, or an antipseudomonal beta lactam for pseudomonal infections, or with metronidazole or clindamycin for mixed aerobic-anaerobic infections.

Administration and dosage. Gentamicin is used as the sulfate but doses are expressed in terms of gentamicin base. For many of the infections above it is given intramuscularly every 8 hours to provide a total daily dose of 3 to 5 mg/kg. In the prophylaxis and treatment of streptococcal and enterococcal endocarditis, a dose of 1 mg/kg every 8 hours with a penicillin or vancomycin has been suggested for treatment in the UK; a suggested dose for prophylaxis in high-risk patients is 120 mg before induction of anaesthesia, with a penicillin or vancomycin or teicoplanin. For urinary-tract infections, if renal function is not impaired, 160 mg once daily may be used.

Gentamicin sulfate may also be given intravenously in similar doses to those used intramuscularly, but there is some disagreement as to the appropriate method, since intravenous infusion has been associated with both subtherapeutic and excessive trough concentrations of gentamicin, while bolus intravenous injection may increase the risk of neuromuscular blockade. In the USA, intravenous infusion over 30 minutes to 2 hours is favoured, but sources in the UK differ, with some licensed product information recommending infusion over no more than 20 minutes, in a limited fluid volume, while other products should not be given by slow infusion, recommending bolus injection over at least 2 to 3 minutes, and yet others allow use in a similar way to the USA.

The course of treatment should generally be limited to 7 to 10 days. As gentamicin is poorly distributed into fatty tissue it has been suggested that dosage calculations should be based on an estimate of lean body-weight.

Doses in infants and children are usually somewhat higher than those in adults but exact dosage recommendations vary. One regimen is gentamicin 3 mg/kg every 12 hours in premature infants and those up to 2 weeks of age, with older neonates and children receiving 2 mg/kg every 8 hours. Alternatively, 2.5 mg/kg every 12 hours in the first week of life, 2.5 mg/kg every 8 hours or 3 mg/kg every 12 hours in infants and neonates, and 1.5 to 2 mg/kg every 8 hours in children has been given.

Dose adjustment and monitoring. Dosage should be adjusted in all patients according to plasma-gentamicin concentrations, and this is discussed in more detail under Administration and Dosage, below.

Once-daily dosage. In many centres, the total daily requirement is increasingly given as a single dose (see Once-daily Dosage, below). In suitable patients this appears to be as safe and effective as conventional regimens, and is more convenient. However, it is not suitable for all patients, especially those with endocarditis, extensive burns, or renal impairment (creatinine clearance less than 20 mL/minute). With once-daily dosage, traditional methods of monitoring peak and trough plasma concentrations may not be applicable and local guidelines on dosage and plasma concentrations should be consulted.

Other routes. Gentamicin has sometimes been given orally for enteric infections and to suppress intestinal flora and has occasionally been given by inhalation in cystic fibrosis. In meningitis it has been given intrathecally or intraventricularly usually in doses of 1 to 5 mg daily with intramuscular therapy. Gentamicin has also been given by subconjunctival injection.

A bone cement impregnated with gentamicin is used in orthopaedic surgery. Acrylic beads containing gentamicin and threaded on to surgical wire are implanted in the management of bone infections.

Gentamicin has also been applied topically for skin infections in concentrations of 0.1%, but such use may lead to the emergence of resistance and is considered inadvisable. Concentrations of 0.3% are used in preparations for topical application to the eyes and ears.

A liposomal formulation of gentamicin is under investigation.

◊ Reviews.

1. Edson RS, Terrell CL. The aminoglycosides. *Mayo Clin Proc* 1999; **74:** 519–28.

Administration and dosage. ***CONCENTRATION MONITORING.*** Measurements of aminoglycoside plasma concentrations are routinely performed to individualise dosage regimens, both in terms of dose given and dosing interval, in order to attain the desired therapeutic range as quickly as possible.[1] This entails measurement of both peak concentrations to monitor efficacy and trough concentrations to avoid accumulation and thereby prevent toxicity. Dosage should be adjusted in all patients according to these concentrations, but this is of particular importance where factors such as age, renal impairment, or high dosage may predispose to toxicity. Although there has been some dispute about the relationship between plasma concentrations and toxicity it is generally

recommended that, for multiple daily dosing with gentamicin, trough plasma concentrations (measured just before the next dose) should be less than 2 micrograms/mL, and peak concentrations should reach at least 4 micrograms/mL but not exceed 10 micrograms/mL. In the UK, peak concentrations are generally measured 1 hour after intramuscular and intravenous doses, but practice has varied between centres and countries and this may lead to difficulties when comparing figures.

Methods exist for calculating aminoglycoside dosage requirements, though none has been universally accepted. Simple pharmacokinetic methods involve linear dosage adjustment based on peak or trough concentrations or area under the concentration-time curve, or the use of predictive nomograms.[1] For most patients receiving once-daily dosage (see below), the nomogram is the method of choice, primarily because of its simplicity. However, it has not been validated for children and does not work in patients with either a very high clearance of aminoglycosides or a high volume of distribution, such as those with ascites, burns, or cystic fibrosis, or in other conditions such as pregnancy where the fixed dose assumed in the construction of the nomogram is irrelevant. When a nomogram cannot be applied, a more sophisticated pharmacokinetic method is required, using either Bayesian statistics or non-Bayesian methods such as that of Sawchuk and Zaske.[2,3] Bayesian methods are favoured when the patient population's pharmacokinetic parameters are well known because of their good predictive performance. Otherwise, the Sawchuk and Zaske method is the method of choice because of its robustness and the lack of requirement for prior information about the distribution of parameters within the population.[1]

1. Tod MM, *et al.* Individualising aminoglycoside dosage regimens after therapeutic drug monitoring: simple or complex pharmacokinetic methods? *Clin Pharmacokinet* 2001; **40:** 803–14.
2. Sawchuk RJ, Zaske DE. Pharmacokinetics of dosing regimens which utilize multiple intravenous infusions: gentamicin in burn patients. *J Pharmacokinet Biopharm* 1976; **4:** 183–95.
3. Sawchuk RJ, *et al.* Kinetic model for gentamicin dosing with the use of individual patient parameters. *Clin Pharmacol Ther* 1977; **21:** 362–9.

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1. Isemann BT, *et al.* Optimal gentamicin therapy in preterm neonates includes loading doses and early monitoring. *Ther Drug Monit* 1996; **18:** 549–55.
2. Logsdon BA, Phelps SJ. Routine monitoring of gentamicin serum concentrations in pediatric patients with normal renal function is unnecessary. *Ann Pharmacother* 1997; **31:** 1514–18.
3. Murphy JE, *et al.* Evaluation of gentamicin pharmacokinetics and dosing protocols in 195 neonates. *Am J Health-Syst Pharm* 1998; **55:** 2280–9.
4. Yeung MY, Smyth JP. Targeting gentamicin concentrations in babies: the younger the baby, the larger the loading dose and the longer the dose interval. *Aust J Hosp Pharm* 2000; **30:** 98–101.
5. Stickland MD, *et al.* An extended interval dosing method for gentamicin in neonates. *J Antimicrob Chemother* 2001; **48:** 887–93.
6. Rastogi A, *et al.* Comparison of two gentamicin dosing schedules in very low birth weight infants. *Pediatr Infect Dis J* 2002; **21:** 234–40.
7. Chattopadhyay B. Newborns and gentamicin—how much and how often? *J Antimicrob Chemother* 2002; **49:** 13–16.
8. Murphy JE. Prediction of gentamicin peak and trough concentrations from six extended-interval dosing protocols for neonates. *Am J Health-Syst Pharm* 2005; **62:** 823–7.
9. Hale LS, Durham CR. A simple, weight-based, extended-interval gentamicin dosage protocol for neonates. *Am J Health-Syst Pharm* 2005; **62:** 1613–16.
10. Khan AM, *et al.* Extended-interval gentamicin administration in malnourished children. *J Trop Pediatr* 2006; **52:** 179–84.

IN PATIENTS WITH NON-IDEAL BODY-WEIGHT. References.

1. Traynor AM, *et al.* Aminoglycoside dosing weight correction factors for patients of various body sizes. *Antimicrob Agents Chemother* 1995; **39:** 545–8.

IN RENAL IMPAIRMENT. Although a number of nomograms, schedules, and rules have been devised for the calculation of aminoglycoside dosage in renal impairment, where possible dosage modification should be based on the monitoring of individual pharmacokinetic parameters. Standard dosage calculation methods should not be used for patients undergoing dialysis as they may require supplementary post-dialysis doses. Individualised regimens based on an initial dose (for moderate to severe infections) of 2 to 2.5 mg/kg, modified in the obese or those with excessive fluid retention, and with subsequent doses after haemodialysis ranging from 1 to 1.8 mg/kg, have been reported to be effective.[1] Serum-aminoglycoside concentrations were not routinely requested unless treatment for more than 4 days was thought likely, and the target concentration was adjusted both for the agressiveness of therapy required and the individual haemodialysis regimen. Typically, about 50% of a dose was eliminated in a haemodialysis session.

1. Dager WE, King JH. Aminoglycosides in intermittent hemodialysis: pharmacokinetics with individual dosing. *Ann Pharmacother* 2006; **40:** 9–14.

ONCE-DAILY DOSAGE. The concept of giving aminoglycosides once daily rather than in divided doses is attractive on the grounds of convenience and economy. The rationale cited by proponents of single daily doses for preferring high intermittent plasma concentrations includes the prolonged postantibiotic effect of aminoglycosides (persistent antibacterial activity after plasma concentrations have fallen below the MIC), potentially higher antibacterial concentrations at the site of infection, and theoretical reductions in the incidence of adaptive resistance, with no apparent increase in nephrotoxicity. Clinical studies have generally included small numbers of patients with uncomplicated infections and have excluded patients with altered pharmacokinetic profiles, but several meta-analyses have been published which have concluded that once-daily administration appears to be at least as effective as, and no more toxic than, multiple daily dosing in such patient populations.[1-7] Similar results have been seen in children.[8,9] Many centres now use such regimens in suitable patients.

Several methods for calculating doses and monitoring treatment have been proposed.[10-12] There is insufficient information for pregnant or breast-feeding women, or patients with burns or impaired renal or hepatic function.[12-14] However, preliminary reports suggest that once-daily use may be practical in trauma patients,[15] and children with neutropenia,[16] or cystic fibrosis.[17,18] Once daily dosage may, though, be inappropriate for elderly patients[19] (due to an increased incidence of nephrotoxicity), patients in whom the volume of drug distribution or clearance is difficult to predict or markedly abnormal,[20] and in the treatment of enterococcal endocarditis.[12] In the UK, the *BNF* states that a once-daily high dose regimen should be avoided in patients with endocarditis, extensive burns, or creatinine clearance less than 20 mL/minute. For mention of an increase in endotoxin reactions associated with the use of single daily doses see under Adverse Effects, above.

1. Barza M, *et al.* Single or multiple daily doses of aminoglycosides: a meta-analysis. *BMJ* 1996; **312:** 338–45.
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3. Ferriols-Lisart R, Alos-Almiñana M. Effectiveness and safety of once-daily aminoglycosides: a meta-analysis. *Am J Health-Syst Pharm* 1996; **53:** 1141–50.
4. Munckhof WJ, *et al.* A meta-analysis of studies on the safety and efficacy of aminoglycosides given either once daily or as divided doses. *J Antimicrob Chemother* 1996; **37:** 645–63.
5. Bailey TC, *et al.* A meta-analysis of extended-interval dosing versus multiple daily dosing of aminoglycosides. *Clin Infect Dis* 1997; **24:** 786–95.
6. Ali MZ, Goetz MB. A meta-analysis of the relative efficacy and toxicity of single daily dosing versus multiple daily dosing of aminoglycosides. *Clin Infect Dis* 1997; **24:** 796–809.
7. Hatala R, *et al.* Single daily dosing of aminoglycosides in immunocompromised adults: a systematic review. *Clin Infect Dis* 1997; **24:** 810–15.
8. Nestaas E, *et al.* Aminoglycoside extended interval dosing in neonates is safe and effective: a meta-analysis. *Arch Dis Child Fetal Neonatal Ed* 2005; **90:** F294–F300.
9. Contopoulos-Ioannidis DG, *et al.* Extended-interval aminoglycoside administration for children: a meta-analysis. *Pediatrics* 2004; **114:** e111–8.
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11. Prins JM, *et al.* Validation and nephrotoxicity of a simplified once-daily aminoglycoside dosing schedule and guidelines for monitoring therapy. *Antimicrob Agents Chemother* 1996; **40:** 2494–9.
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14. Anonymous. Aminoglycosides once daily? *Drug Ther Bull* 1997; **35:** 36–7.
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16. Tomlinson RJ, *et al.* Once daily ceftriaxone and gentamicin for the treatment of febrile neutropenia. *Arch Dis Child* 1999; **80:** 125–31.
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18. Vic P, *et al.* Efficacy, tolerance, and pharmacokinetics of once daily tobramycin for pseudomonas exacerbations in cystic fibrosis. *Arch Dis Child* 1998; **78:** 536–9.
19. Koo J, *et al.* Comparison of once-daily versus pharmacokinetic dosing of aminoglycosides in elderly patients. *Am J Med* 1996; **101:** 177–83.
20. Gerberding JL. Aminoglycoside dosing: timing is of the essence. *Am J Med* 1998; **105:** 256–8.

Ménière's disease. Gentamicin and streptomycin have been used for medical ablation in advanced Ménière's disease (p.564). Although gentamicin given systemically is considered to be more ototoxic than streptomycin, evidence from *animal* studies suggests that intratympanic use may be less ototoxic. This, and a higher incidence of adverse effects with streptomycin, has meant that intratympanic gentamicin is now preferred. Intratympanic gentamicin has been reported to control vertigo symptoms in the majority of patients, although some experience a worsening of their hearing loss immediately after treatment.[1-8] However, the ideal regimen for intratympanic gentamicin has yet to be defined.

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3. Quaranta A, *et al.* Intratympanic therapy for Ménière's disease: high-concentration gentamicin with round-window protection. *Ann N Y Acad Sci* 1999; **884:** 410–24.
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6. Marzo SJ, Leonetti JP. Intratympanic gentamicin therapy for persistent vertigo after endolymphatic sac surgery. *Otolaryngol Head Neck Surg* 2002; **126:** 31–3.
7. Cohen-Kerem R, *et al.* Intratympanic gentamicin for Menière's disease: a meta-analysis. *Laryngoscope* 2004; **114:** 2085–91.
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Preparations

BP 2008: Gentamicin and Hydrocortisone Acetate Ear Drops; Gentamicin Cream; Gentamicin Ear Drops; Gentamicin Eye Drops; Gentamicin Injection; Gentamicin Ointment;
USP 31: Gentamicin and Prednisolone Acetate Ophthalmic Ointment; Gentamicin Injection; Gentamicin Sulfate Cream; Gentamicin Sulfate Ointment; Gentamicin Sulfate Ophthalmic Ointment; Gentamicin Sulfate Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Gentaderm; Gentamina; Gentapharma; Gentaren; Gentatenk†; Genticol†; Gentoler; Glevomicina; Plurisemina; Provisual; Rupegen†; Sintepul; Ultradermis†; ***Austral.:*** Genoptic; ***Austria:*** Garamycin†; Gentax; Refobacin; Sulmycin; ***Belg.:*** Geomycine; ***Braz.:*** Emisgenta; Garacin; Garamicina; Garamin; Gentac†; Gentagran; Gentamicil; Gentamil; Gentaron; Gentax†; Vitromicin†; ***Canad.:*** Alcomicin; Diogent†; Garamycin; Garatec†; ***Chile:*** Gentalyn; Oftagen; ***Cz.:*** Garamycin; Megental†; Ophtagram†; ***Denm.:*** Garamycin; Gentacoll; Hexamycin; ***Fin.:*** Gensumycin; Gentacoll; ***Fr.:*** Gentalline; ***Ger.:*** Gencin; Gent-Ophtal; Genta; Gentamytrex; Ophtagram†; Refobacin; Sulmycin; Terramycin N; ***Gr.:*** Dabroson; Garamycin; ***Hong Kong:*** Garamycin; Genoptic; Miramycin; Optigen†; ***Hung.:*** Garamycin; ***India:*** Andregen; Biogaracin; G-80†; Garamycin; Gensyn†; Gentacip; Gentasporin; Genticyn; Genticyn Eye/Ear†; ***Indon.:*** Bioderm; Dermabiotik; Dermagen; Ethigent; Garabiotic; Garamycin; Garapon; Garexin; Gentacyl; Gentamerck; Gentamisin; Ikagen; Isotic Timact; Konigen; Licogenta; Nichogencin; Ottogenta; Sagestam; Salgen; Salticin; Timact; Ximex Konigen; ***Irl.:*** Cidomycin; Genticin; ***Israel:*** Cidomycin†; Gentatrim; Lacromycin; Opti-Genta; ***Ital.:*** Ciclozinil; Dergesol; Eutopic; Gentacream; Gentalyn; Gentamen; Gentibiopta†; Genticol; Gentomil; Nemalin; Ribomicin; Tacigen; ***Malaysia:*** Beagenta; Garamycin; Gentamed†; Gentamytrex†; Miramycin; ***Mex.:*** Barmicil†; Beramicina; Fustermicina; G-I; Garacoll; Garakacin; Garalen; Garamicina; Geclicin; Genemicin; Genkova; Genrex; Genser; Genta; Genta-Micron; Gentacin†; Gentamil; Gentanacin†; Gentapat; Gentarim†; Gentazaf Z; Gentazol; Gentialoquin; Geracin; Ikatin; Lifegram; Lisibac†; Progen; Quilagen; Servigenta; Tamigen; Tondex; Tremax; Yectamicina; ***Neth.:*** Garacol; Garamycin; Gentamytrex; ***Norw.:*** Garamycin; Gensumycin; ***NZ:*** Genoptic; ***Philipp.:*** Garamycin; Gentamytrex; Migentax; Minoglen; Obogen; Opthagen; Orimed; Rocygen; Servigenta; Tangyn; Topigen; ***Pol.:*** Garamycin; Gentamytrex†; ***Port.:*** Cronocol; Garalone; Genta Gobens; Gentalin; Gentocil; Ophtagram; Septopal; ***S.Afr.:*** Cidomycin; Garacoll†; Garamycin; Genoptic†; Sabax Gentamix; Sterisol Fermentmycin; ***Singapore:*** Garamycin†; Genoptic; Gentamytrex; Miramycin; ***Spain:*** Coliriocilina Gentam†; Genta Gobens; Gentamedical†; Gentamival; Genticina†; Gevramycin; Gevramycin Topica; Rexgenta; ***Swed.:*** Garamycin; Gensumycin; ***Switz.:*** Garamycin; Ophtagram; ***Thai.:*** Garamycin†; Genta; Genta-Oph; Gentac†; Gentacin; Gental; Grammicin; Grammixin; Miramycin; Skinfect; Versigen; ***Turk.:*** Genmisin; Genta; Gentagut; Gentamed; Genthaver; Gentreks; Getamisin; Getasin; ***UAE:*** Gental; ***UK:*** Cidomycin; Garamycin†; Genticin; ***USA:*** Garamycin; Genoptic; Gentacidin; Gentak; Gentasol; Ocu-Mycin; ***Venez.:*** Catogen†; Gentalyn; Gentamicil†; Gentamilan; Gentisul; Kincinat†; Refobacin†; Solgenta; Yectamicina†.

Multi-ingredient: ***Arg.:*** Adenil; Aeromicrosona C†; Anginotrat; Bacticort; Bacticort Complex; Bactisona; Becortin; Betacort Plus; Blamy; Calmurid; Cevaderm; Cicatrizol; Ciprocort; Cuta Crema; Denvercrem; Dercotex; Dermizol G; Dermizol Trio; Dermoperative; Dermosona; Dermovit†; Dexamytrex; Diprogenta; Factor Dermico; Floderma; Filoderma Plus; Gentacler; Gentasol; Gentocelina†; Griseocrem; Hifamonil Crema; Lazar-Cort Complex; Linfol Dermico; Lisoderma; Macril; Micozol Compuesto†; Microsona C; Miklogen; Monizol Cort Crema; Novo Bacticort Complex†; Novo Bacticort†; Otalex G; Otonorthia; Pancutan; Provisual Compuesto; Prurisedan Biotic†; Quadriderm; Quiacort G; Quiacort G Plus; Septopal†; Sirotamicin BG; Start NP†; Tribiocort; Tricur; Tridermal; Triefect†; Triliver; Triplex; Vitacortil; ***Austral.:*** Celestone VG†; Palacos E with Garamycin; Palacos R with Garamycin; Septopal; ***Austria:*** Decoderm Compositum; Decoderm trivalent; Dexagenta; Diprogenta; Septopal; Voltamicin; ***Belg.:*** Decoderm Compositum; Dexagenta-POS; Duracoll; Garasone†; Infectoflam; Palacos LV avec Gentamicine†; Palacos R avec Gentamicine†; Septopal; ***Braz.:*** Cauterex; Cremederme; Dexamytrex†; Diprogenta; Emecort†; Garasone; Gentacort; Gino-Cauterex; Microbiogen†; Pan-Emecort†; Permut; Policderms; Quadriderm; Quadrikin; Quadrilon; Quadriplus; Qualiderm; Septopal; Tetraderm; ***Canad.:*** Diprogen†; Garasone; Pentasone; Valisone-G; ***Chile:*** Diprospan G; Gentasone; Labosona G; Mixgen; Oftagen Compuesto; Palacos E con Gentamicina; Palacos R con Gentamicina; Perlas De PMMA con Gentamicina; Pred G†; Vilterm†; ***Cz.:*** Belogent; Clenigen†; Dexa-Gentamicin; Garasone; Infectoflam†; Septopal†; Voltamicin†; ***Denm.:*** Septopal; ***Fin.:*** Celestoderm cum Garamycin; Palacos R cum Gentamicin†; Septopal; ***Fr.:*** Collatamp G†; Indobiotic; Palacos LV avec Gentamicine; Palacos R avec Gentamicine; ***Ger.:*** Betagentam; Cibaflam; CMW mit Gentamicin; Copal; Decoderm Comp; Dexa-Gentamicin; Dexamytrex; Diprogenta; Inflanegent; Palamed G; Refobacin-Palacos R; Septocoll; Septopal; SmartSet GHV; Sulmycin mit Celestan-V; Terracortril N; ***Gr.:*** Celestoderm-V/GA; Dexamytrex; Efemoline; Garamat; Gentadex; Luzin; Palacos R with Gentamycin†; Propiogenta; Septopal†; ***Hong Kong:*** Becogem; Celestoderm-V with Garamycin; Clobeta-G; Conazole; Dermafacte; Diprogenta; Garasone; Lycobeta-G; Quadriderm; Septopal; Triderm; Tridital-G; ***Hung.:*** Garasone; Gentason; Septopal; Vipsogal†; Voltamicin†; ***India:*** Betamil-GM; Betnederm GM; Betnovate-GM; Candiderma†; Cloben-G; Cloderm GM; Clomycin; Cutinorm†; Diclogenta; Ecodax†; Eumosone-G; Fourderm; Fourderm AF; Gentacip D; Genticyn B Eye/Ear†; Genticyn HC†; Lobate-G; Lobate-GM; Quiss; Septopal; Sigmaderm; Tenovate G; Translipo-Triple; ***Indon.:*** Benoson G; Betagentam; Betasin; Biocort; Celestoderm-V with Garamycin; Cinogenta; Digenta; Diprogenta; Diprosta; Garasone; Genolon; Gentacortin; Gentasolon; Isotic Betaracin; Mastroson; Salgen Plus; Sinobiotik; Skilone; Skinal; Sonigen; ***Irl.:*** Gentisone HC; ***Israel:*** Aflumycin; Betacorten-G; Cicloderm-C; Diprogenta; Triderm; ***Ital.:*** Batasalgin; Betacream; Citrizan Antibiotico; Dermabiolene; Egerian; Fidagenbeta; Formomicin; Genalfa; Genatrop; Gentacort; Gentalyn Beta; Kamelyn; Sterozinil; Vasosterone Oto; Voltamicin†; ***Malaysia:*** B-Mycin; Beprogent; Betagen; Betamethasone G; Celestoderm-V with Garamycin†; Dexa-Gentamicin†; Dexamytrex†; Diprogenta; Garasone; Gentadexa; Infectoflam†; Joysun; Septopal†; ***Mex.:*** Barmicil Compuesto; Beclogen; Betrigen; Clotricina; Diprosone G; Garamicina-V; Garasone; Miclobet; Prubagen; Quadriderm NF; Triderm; ***Neth.:*** Dexagenta-POS; Dexamytrex; Septopal; ***Norw.:*** Septopal; ***NZ:*** CMW Gentamicin; Palacos with Garamycin; Vacu-Mix Plus with CMW gentamicin; ***Philipp.:*** Dexamytrex; Diprogenta; Garasone; Infectoflam; Ophtasone; Quadriderm; Quadrotopic; Septopal; Triderm; ***Pol.:*** Bedicort G; Dexamytrex; Diprogenta; Triderm; ***Port.:*** Dexamytrex; Diprogenta; Epione; Gentadexa; Indobiotic; Quadriderme; ***Rus.:*** Akriderm Genta (Акридерм Гента); Akriderm GK (Акридерм ГК); Belogent (Белогент); Betagenot (Бетагенот); Celestoderm-V with Garamycin

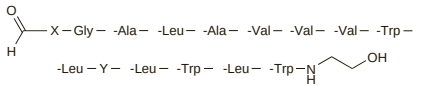
(Целестодерм-В с Гарамицином); Dexa-Gentamicin (Декса-Гентамицин); Triderm (Тридерм); ***S.Afr.:*** Celestoderm-V with Garamycin†; Diprogenta; Garasone†; Palacos R with Garamycin; Quadriderm; Septopal; ***Singapore:*** B-Tasone-G; Beprogent; Celestoderm-V with Garamycin†; Combiderm; Conazole; Dexamytrex; Diprogenta; Garasone; Gentriderm; Gentrisone; Infectoflam; Modaderm; Neoderm; Quadriderm†; Refobacin Bone Cement R; Refobacin-Palacos R†; Septopal†; Tri-Micon; Triderm; Voltamicin†; ***Spain:*** Celestoderm Gentamicina; Cuatroderm; Diprogenta; Epitelizante; Flugen; Flutenal Gentamicina; Gentadexa; Interderm; Novoter Gentamicina; ***Swed.:*** Celeston valerat med gentamicin; Septopal†; ***Switz.:*** Diprogenta; Indobiotic†; Infectoflam; Ophtasone; Quadriderm; Septopal; Triderm; Voltamicin; ***Thai.:*** Beprogent; Beprogenta; Dexamytrex; Diprogenta†; Genquin; Gental-F; Infectoflam; Pred Oph; Refobacin-Palacos R; Septopal; ***Turk.:*** Indobiotic; ***UK:*** Collatamp EG; Gentisone HC; Palacos LV with Gentamicin; Palacos R with Gentamicin; Septopal; Vipsogal; ***USA:*** Pred G; ***Venez.:*** Betaderm con Gentamicina; Celestoderm con Gentalyn; Diprogenta; Garabet; Garasone; Gentidexa; Gentisor†; Propiogenta†; Quadriderm; Triderm; Tridetarmon.

Gramicidin *(BAN, rINN)*

Gramicidin D; Gramicidin (Dubos); Gramicidina; Gramicidinas; Gramicidine; Gramicidinum; Gramisidiini; Gramisidin.

Грамицидин

CAS — 1405-97-6.
ATC — R02AB30.
ATC Vet — QR02AB30.



Gramicidin	X	Y	Mol. Formula
A1	-Val	-Trp	C H N O
A2	-Ile	-Trp	C H N O
B1	-Val	-Phe	C H N O
C1	-Val	-Tyr	C H N O
C2	-Ile	-Tyr	C H N O

NOTE. The name gramicidin was formerly applied to tyrothricin.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Gramicidin). It consists of a family of antimicrobial linear polypeptides usually obtained by extraction from tyrothricin, the complex isolated from the fermentation broth of *Bacillus brevis*. The main component is gramicidin A1, together with gramicidins A2, B1, C1, and C2 in particular. The potency is not less than 900 units/mg calculated with reference to the dried substance. A white or almost white, slightly hygroscopic, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 31 (Gramicidin). An antibacterial substance produced by the growth of *Bacillus brevis* (Bacillaceae); it may be obtained from tyrothricin. It has a potency of not less than 900 micrograms of gramicidin per mg, calculated on the dried basis. A white or practically white, odourless, crystalline, powder. Insoluble in water; soluble in alcohol. Store in airtight containers.

Profile

Gramicidin has properties similar to those of tyrothricin (p.358) and is too toxic to be given systemically. It is used topically for the local treatment of susceptible infections usually with other antibacterials such as neomycin and polymyxin B, and often with a corticosteroid as well.

Preparations

USP 31: Neomycin and Polymyxin B Sulfates and Gramicidin Cream; Neomycin and Polymyxin B Sulfates and Gramicidin Ophthalmic Solution; Neomycin and Polymyxin B Sulfates, Gramicidin, and Hydrocortisone Acetate Cream; Neomycin Sulfate and Gramicidin Ointment; Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Cream; Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Ointment.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Antibiocort†; Aseptobron N; Biotaer Nasal; Bucoangin N; Caext; Carnot Colutorio; Desenfriol Caramelos†; Gargaletas; Gramibiotic†; Graneodin; Graneodin N; Kenacomb; Nasomicina; Neo Coltirot; Neo Pelvicillin; Pantometil; Proetztotal; ***Austral.:*** Kenacomb; Neosporin; Otocomb Otic; Otodex; Sofradex; Soframycin; ***Austria:*** Mycostatin V; Topsym polyvalent; Volon A antibiotikahaltig; ***Belg.:*** Mycolog; Polyspectran Gramicidine; ***Braz.:*** Fonergin; Londerm-N; Mud; Neolon-D; Omcilon A M; Onciplus; ***Canad.:*** Antibiotic Cream†; Kenacomb†; Neosporin; Opticort; Optimyxin; Optimyxin Plus; Polycidin†; Polysporin; Polysporin Complete Antibiotic; Polysporin For Kids; Polysporin Plus Pain Relief; Polysporin Triple Antibiotic; Polytopic; ratio-Triacomb; Sofracort; Soframycin; Triacomb†; Viaderm-KC; ***Chile:*** Gnifoftal†; Oftabiotico; ***Cz.:*** Sofradex†; ***Denm.:*** Kenalog Comp med Mycostatin; Sofradex; ***Fin.:*** Bafucin; Polysporin; Sofradex; ***Ger.:*** Polyspectran; ***Gr.:*** Kenacomb; Neo-Priphen; ***Hong Kong:*** Kenacomb; Neosporin; Polyoph; Sofradex; Triacomb; ***Hung.:*** Polyspor; ***India:*** Kenacomb; Kenalog-S; Neosporin; Sofracort; ***Indon.:*** Blecidex; Isotic Enpigi; Neosyd; Sofradex; ***Irl.:*** Graneodin; Kenacomb; Neosporin†; Sofradex; Soframycin†; ***Israel:*** Dermacombin; Kenacomb†; ***Ital.:*** Eta Biocortilen VC; Vasosterone Antibiotico; ***Malaysia:*** Kenacomb; Pocin G; Sofradex; ***Mex.:*** Biotarson N; Biotarson O; Kenacomb; Neosporin; Nicobio†; Polixin; Poly-Micron; Septilisin; Sulned; ***Neth.:*** Mycolog; Polyspectran G†; Sofradex; ***Norw.:*** Sofradex; ***NZ:*** Kenacomb; Sofradex; Soframycin; Viaderm-KC; ***Philipp.:*** Kenacomb; Lidex NGN; Neosporin; Novasorin; ***Pol.:*** Dicortineff; Triacomb; ***Port.:*** Dropcina; Kenacomb; ***S.Afr.:*** Kenacomb; Neosporin†; Sofradex; ***Singapore:*** Kenacomb†; Sofradex; ***Spain:*** Flodermol; Fludronef; Intradermo Cort Ant Fung†; Midacina; Oftalmowell; Spectrocin†; Tivitis; Trigon Topico; ***Swed.:*** Bafucin; ***Switz.:*** Angidine; Mycolog N; Mycolog†; Neosporin; Sofradex; Topsym polyvalent; Tyrothricine + Gramicidine; ***Thai.:*** Dermacombin; Kenacomb; Neosporin†; Opsacin†; Polyoph; Sofradex; Topifram; Xanalin; ***Turk.:*** Neosporin; ***UAE:*** Panderm; ***UK:*** Graneodin†; Neosporin; Sofradex; Tri-Adcortyl; ***USA:*** Neosporin; Ocu-Spor-G; Ocutricin; Polymycin; ***Venez.:*** Kenacomb.

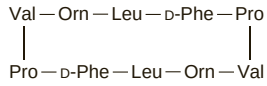
Gramicidin S *(rINN)*

Gramicidin C; Gramicidina S; Gramicidine S; Gramicidinum S; Soviet Gramicidin.

Грамицидин С

$C_{60}H_{92}N_{12}O_{10}$ = 1141.4.

CAS — 113-73-5.



Profile

Gramicidin S is an antibacterial polypeptide, produced by *Bacillus brevis*, and has similar properties to tyrothricin (p.358). It is unsuitable for systemic use and is used topically for the local treatment of susceptible infections and as lozenges for infections of the mouth and throat. The hydrochloride is used similarly.

Preparations

Proprietary Preparations (details are given in Part 3)

Rus.: Grammidin.

Multi-ingredient: ***Indon.:*** FG Ointment; FG Troches.

Halquinol *(BAN)*

Chlorhydroxyquinoline; Chlorquinol; Halquinols *(USAN)*; SQ-16401. A mixture of the chlorinated products of quinolin-8-ol containing 57 to 74% of 5,7-dichloroquinolin-8-ol (chloroxine, p.242), 23 to 40% of 5-chloroquinolin-8-ol (cloxiquine, p.530), and not more than 4% of 7-chloroquinolin-8-ol.

CAS — 8067-69-4.

Profile

Halquinol is a halogenated hydroxyquinoline with properties similar to those of clioquinol (p.254). It is used topically in infected skin conditions.

Preparations

Proprietary Preparations (details are given in Part 3)

UK: Valpeda.

Multi-ingredient: ***Denm.:*** Kenacutan; ***Norw.:*** Kenacutan; ***Swed.:*** Kenacutan.

Ibafloxacin *(BAN, USAN, rINN)*

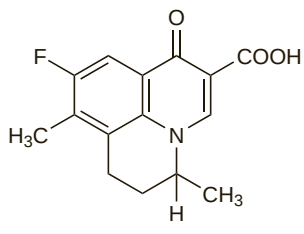
Ibafloksasiini; Ibafloxacine; Ibafloxacino; Ibafloxacinum; R-835; S-25930. 9-Fluoro-6,7-dihydro-5,8-dimethyl-1-oxo-1*H*,5*H*-benzo[*ij*]quinolizine-2-carboxylic acid.

Ибафлоксацин

$C_{15}H_{14}FNO_3$ = 275.3.

CAS — 91618-36-9.

ATC Vet — QJ01MA96.



Profile

Ibafloxacin is a fluoroquinolone antibacterial that is used in veterinary medicine for the treatment of susceptible infections in cats and dogs.

Imipenem *(BAN, USAN, rINN)*

N-Formimidoyl Thienamycin; Imipemide; Imipeneemi; Imipénem; Imipenem monohydrát; Imipenemas; Imipenemum; Imipenemum Monohydricum; MK-787; MK-0787. (5*R*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-3-(2-iminomethylaminoethylthio)-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate.

Имипенем

$C_{12}H_{17}N_3O_4S,H_2O$ = 317.4.

CAS — 64221-86-9 (anhydrous imipenem); 74431-23-5 (imipenem monohydrate).

Description. Imipenem is the *N*-formimidoyl derivative of thienamycin, an antibiotic produced by *Streptomyces cattleya*.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Imipenem). A white, almost white, or pale yellow powder. Sparingly soluble in water; slightly soluble in methyl alcohol. A 0.5% solution in water has a pH of 4.5 to 7.0. Store in airtight containers at a temperature of 2° to 8°.

USP 31 (Imipenem). A white to tan-coloured crystalline powder. Sparingly soluble in water; slightly soluble in methyl alcohol. Store at a temperature not exceeding 8°.

Incompatibility and stability. Imipenem is unstable at alkaline or acidic pH and the commercially available injection of imipenem with cilastatin sodium for intravenous use is buffered to provide, when reconstituted, a solution with pH 6.5 to 7.5. Licensed product information advises against mixing with other antibacterials.

References.

1. Bigley FP, *et al.* Compatibility of imipenem-cilastatin sodium with commonly used intravenous solutions. *Am J Hosp Pharm* 1986; **43**: 2803–9.
2. Smith GB, *et al.* Stability and kinetics of degradation of imipenem in aqueous solution. *J Pharm Sci* 1990; **79**: 732–40.

Adverse Effects

Imipenem is always given with the enzyme inhibitor cilastatin and thus clinical experience relates to the combination.

Adverse effects with imipenem-cilastatin are similar in general to those with other beta lactams (see Benzylpenicillin, p.213, and Cefalotin, p.219). Hypersensitivity reactions such as skin rashes, urticaria, eosinophilia, fever, and, rarely, anaphylaxis may occur. Gastrointestinal effects include nausea, vomiting, diarrhoea, tooth or tongue discoloration, and altered taste. Superinfection with non-susceptible organisms such as *Enterococcus faecium*, strains of *Pseudomonas aeruginosa* with acquired resistance, and *Candida* may also occur. Pseudomembranous colitis may develop. Erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported rarely. Increases in liver enzymes and abnormalities in haematological parameters, including a positive Coombs' test, have been noted.

Local reactions such as pain or thrombophlebitis may occur after injection.

Seizures or convulsions have been reported with imipenem-cilastatin, particularly in patients with a history of CNS lesions and/or poor renal function, but sometimes in those without predisposing factors for seizures given recommended doses. Mental disturbances and confusion have also been reported.

Cilastatin has protected against the nephrotoxicity seen with high doses of imipenem given experimentally to *animals*. A harmless reddish coloration of urine has been observed in children.

Effects on the nervous system. References.

1. Eng RH, *et al.* Seizure propensity with imipenem. *Arch Intern Med* 1989; **149**: 1881–3.
2. Brown RB, *et al.* Seizure propensity with imipenem. *Arch Intern Med* 1990; **150**: 1551.
3. Job ML, Dretler RH. Seizure activity with imipenem therapy: incidence and risk factors. *DICP Ann Pharmacother* 1990; **24**: 467–9.
4. Leo RJ, Ballow CH. Seizure activity associated with imipenem use: clinical case reports and review of the literature. *DICP Ann Pharmacother* 1991; **25**: 351–4.
5. Duque A, *et al.* Vertigo caused by intravenous imipenem/cilastatin. *DICP Ann Pharmacother* 1991; **25**: 1009.
6. Lucena M, *et al.* Imipenem/cilastatin-associated hiccups. *Ann Pharmacother* 1992; **26:** 1459.
7. Norrby SR. Neurotoxicity of carbapenem antibacterials. *Drug Safety* 1996; **15:** 87–90.

Hypersensitivity. A retrospective analysis[1] involving a total of 211 patients appeared to show that those with a history of reported or documented penicillin allergy had an 11% incidence of hypersensitivity reactions when treated with a carbapenem antibacterial compared with 2.7% for those without such a history of