Pharmacopoeias. In *Eur.* (see p.vii) and *US*, both for veterinary use.

Ph. Eur. 6.2 (Tylosin for Veterinary Use; Tylosin BP 2008; Tylosin BP(Vet) 2008). A mixture of macrolide antibiotics produced by a strain of *Streptomyces fradiae* or by any other means. The main component of the mixture is tylosin A, but tylosin B (desmycosin), tylosin C (macrocin), and tylosin D (relomycin) may also be present. An almost white or slightly yellow powder. Slightly soluble in water; freely soluble in dehydrated alcohol and in dichloromethane. It dissolves in dilute solutions of mineral acids. A 2.5% suspension in water has a pH of 8.5 to 10.5. Protect from light.

USP 31 (Tylosin). A macrolide antibiotic substance or mixture of such substances produced by the growth of *Streptomyces fradiae* or by any other means. A white to buff-coloured powder. Slightly soluble in water; soluble in alcohol, in amyl acetate, in chloroform, and in dilute mineral acids; freely soluble in methyl alcohol. It loses not more than 5% of its weight on drying. Protect from light, moisture, and temperatures exceeding 40°.

Tylosin Tartrate *(BANM, rINNM)*

Tartrato de tilosina; Tilozin-tartarát; Tylosiinitartraatti; Tylosin tartarát; Tylosine, tartrate de; Tylosini tartras; Tylosintartrat; Tylozyny winian.

Тилозина Тартрат

$(C_{46}H_{77}NO_{17})_2,C_4H_6O_6$ = 1982.3.

CAS — 1405-54-5.

Pharmacopoeias. In *Eur.* (see p.vii) and *US* for veterinary use.

Ph. Eur. 6.2 (Tylosin Tartrate for Veterinary Use; Tylosin Tartrate BP 2008; Tylosin Tartrate BP(Vet) 2008). An almost white or slightly yellow hygroscopic powder. Freely soluble in water and in dichloromethane; slightly soluble in dehydrated alcohol. It dissolves in dilute solutions of mineral acids. A 2.5% solution in water has a pH of 5.0 to 7.2. Store in airtight containers. Protect from light.

USP 31 (Tylosin Tartrate). A tartrate of a mixture of macrolide antibiotic substances, or the mixture of such substances, produced by the growth of *Streptomyces fradiae*, or by any other means. Its potency is not less than 800 micrograms of tylosin per mg, calculated on the dried basis.

An almost white or slightly yellow, hygroscopic powder. Freely soluble in water and in dichloromethane; slightly soluble in alcohol. It dissolves in dilute solutions of mineral acids. pH of a 2.5% solution in water is between 5.0 and 7.2. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Profile

Tylosin is a macrolide antibacterial with actions similar to those of erythromycin (p.269). Tylosin and its phosphate and tartrate salts are used in veterinary medicine in the prophylaxis and treatment of infections caused by susceptible organisms.

Tylosin and tylosin phosphate have been added to animal feeding stuffs as growth promotors for pigs.

Tylvalosin Tartrate *(USAN, rINNM)*

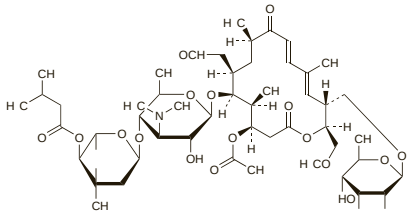
Acetyl Isovaleryl Tylosin Tartrate; Acetylisovaleryltylosin Tartrate; Tartrato de tilvalosina; Tylvalosine, Tartrate de; Tylvalosini Tartras. (4*R*,5*S*,6*S*,7*R*,9*R*,11*E*,13*E*,15*R*,16*R*)-15-{[(6-Deoxy-2,3-di-*O*-methyl-β-*D*-allopyranosyl)oxy]methyl}-6-({3,6-dideoxy-4-*O*-[2,6-dideoxy-3-*C*-methyl-4-*O*-(3-methylbutanoyl)-α-L-*ribo*-hexopyranosyl]-3-(dimethylamino)-β-D-glucopyranosyl}oxy)-16-ethyl-5,9,13-trimethyl-2,10-dioxo-7-(2-oxoethyl)oxacyclohexadeca-11,13-dien-4-yl acetate (2*R*,3*R*)-2,3-dihydroxybutanedioate.

Тильвальозина Тартрат

$C_{53}H_{87}NO_{19},xC_4H_6O_6$.

CAS — 63409-12-1 (tylvalosin); 63428-13-7 (tylvalosin tartrate).

ATC Vet — QJ01FA92.



(tylvalosin)

Profile

Tylvalosin is a derivative of tylosin (p.357) and is used similarly as the tartrate in veterinary medicine.

Tyrothricin *(BAN, rINN)*

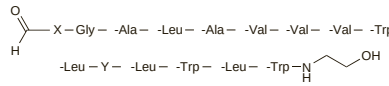
Tirotricina; Tirotricinas; Tirotrisin; Tyrothricine; Tyrothricinum; Tyrotricin; Tyrotrisiini.

Тиротрицин

CAS — 1404-88-2.

ATC — D06AX08; R02AB02; S01AA05.

ATC Vet — QD06AX08; QR02AB02; QS01AA05.



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

Tyrocidin	Mol. Formula	X	Y	Z
A	C H N O	-Phe	-Phe	-Tyr
B	C H N O	-Trp	-Phe	-Tyr
C	C H N O	-Trp	-Trp	-Tyr
D	C H N O	-Trp	-Trp	-Trp
E	C H N O	-Phe	-Phe	-Phe

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

Ph. Eur. 6.2 (Tyrothricin). A mixture of antimicrobial linear and cyclic polypeptides, isolated from the fermentation broth of *Bacillus brevis*. It consists mainly of gramicidins and tyrocidins; other related compounds may be present in smaller amounts. The potency is 180 to 280 international units/mg, calculated with reference to the dried substance. A white or almost white powder. Practically insoluble in water; soluble in alcohol and in methyl alcohol. Store in airtight containers. Protect from light.

USP 31 (Tyrothricin). An antibacterial substance produced by the growth of *Bacillus brevis*. It is a mixture consisting chiefly of gramicidin and tyrocidine, the latter being usually present as the hydrochloride. Store in airtight containers.

Adverse Effects and Precautions

Tyrothricin is too toxic to be used systemically; effects that have been reported include hepatic and renal toxicity as well as Stevens-Johnson syndrome. It damages the sensory epithelium of the nose and instances of prolonged loss of smell have occurred after its use as a nasal spray or instillation. Tyrothricin should not be instilled into the nasal cavities or into closed body cavities.

Uses and Administration

Tyrothricin is unsuitable for systemic use. It is active *in vitro* against many Gram-positive bacteria and has been used either alone or with other antibacterials in the local treatment of infections mainly of the skin and mouth.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Codetricine†; ***Ger.:*** Tyrosur; ***Gr.:*** Triciderm; ***Hong Kong:*** Tyrosur†; ***Ital.:*** Faringotricina; Hydrotricine; Rinotricina; ***Port.:*** Hydrotricine; ***Turk.:*** Hydrotricine.

Multi-ingredient: ***Arg.:*** Algiodent; Aseptobron Caramelos; Bagociletas; Biotaer an Caramelos; Biotaer Gamma†; Biotaer Nebulizable; Biotaer Ultrason Nebulizable†; Bucotricin; Caramelos Antibioticos; Caramelos Antibioticos Bucoangin†; Caramelos Antibioticos Lefmar; Collubiazol; Fanaletas; Filotricin A; Fonergine; Gineseptina†; Oralsone C; Pulmosan Caramelos; Solumerin; Suavisan†; Sulfanoral T; Tavinex; Vagicural; Vagisan; Vagisan Compuesto; Vulnofilin Compuesto†; ***Austria:*** Dorithricin; Gingivan; Lemocin; Limexx; Neocones; Tyrothricin comp; Tyrothricin compositum; ***Belg.:*** Lemocin; Pantricine†; Tricidine†; Tyro-Drops; ***Braz.:*** Amidalin†; Amigdagen; Amigdalol; Amigdamicin†; Anginotricin; Auritricin; Colpagex N; Colpolase; Dermosed†; Gargotan†; Gynax-N; Gyrol†; Lacto Vagin†; Larintil†; Malvatricin; Malvatricin Ginecologico; Malvatricin Pastilhas; Malvatricin Pronto; Malvatricin Solucao para diluir; Malvatricin Spray; Mentozil†; Otovix†; Oturga; Passilin†; Tirotrin†; Trivagel N; Vagitrin-N; ***Canad.:*** Antibiotic Cold Sore Ointment; Soropon; ***Cz.:*** Dr Rentschler Halstabletten†; ***Fr.:*** Broncorinol rhinites†; Codetricine vitamine C†; Collunovar†; Ergix†; Veybirol-Tyrothricine†; ***Ger.:*** Anginomycin†; Dorithricin Limone†; Dorithricin Original; Inspirol Halsschmerztabletten†; Lemocin; Nordathricin N†; Trachisan†; Tyrosur; ***Gr.:*** Oulogram; Trachisan; ***Hong Kong:*** Deq; Trachisan†; Tyricine; Tyrocaine; Tyrothricin Co; ***Hung.:*** Dorithricin; Tyrosur; ***India:*** Tytin; ***Indon.:*** Lemocin; ***Irl.:*** Tyrozets; ***Israel:*** Acnex†; Kalgaron; Lemocin; Rafathricin with Benzocaine; ***Ital.:*** Bio-Arscolloid; Deltavagin; Furotricina; Golamixin; Kinogen; Rinocidina; ***Malaysia:*** Deq; Trachisan†; Upha Lozenges; ***Mex.:*** Angenovag; ***Port.:*** Afonina; Mebocaina; Medifon; Mentocaina R; Oralbiotico; ***Singapore:*** Beathricin; Deq; Dorithricin; Trachisan; ***Spain:*** Anginovag; Bucometasana; Cicatral; Cohortan; Denticelso; Diformiltricina; Gradin Del D Andreu†; Hemodren Compuesto†; Miozets; Neocones; Otosedol Biotico; Pastillas Koki Ment Tiro; Piorlis; Roberfarin; Sedofarin; Viberol Tirotricina; ***Switz.:*** Gem; Lemocin; Mebucaine; Mebucasol f; Otothricinol; Rhinothricinol; Sangerol; Solmucaine; Trachisan†; Tyrocombine; Tyroqualine; Tyrothricin; Tyrothricine + Gramicidine; ***Thai.:*** Deq; Iwazin; Sigatricin; Trocacin; Troneo†; ***Turk.:*** Neolet; ***UAE:*** B-Cool; ***UK:*** Tyrozets; ***Venez.:*** Otan.

Valnemulin *(BAN, rINN)*

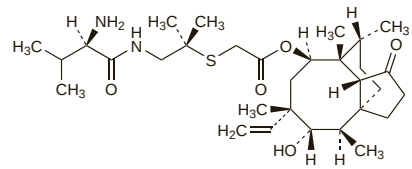
Valnemuliini; Valnemulina; Valnémuline; Valnemulinum. ({2-[(*R*)-2-Amino-3-methylbutyramido]-1,1-dimethylethyl}thio)acetic acid 8-ester with (3a*S*,4*R*,5*S*,6*S*,8*R*,9*R*,9a*R*,10*R*)-octahydro-5,8-dihydroxy-4,6,9,10-tetramethyl-6-vinyl-3a,9-propano-3a*H*-cyclopentacycloocten-1(4*H*)-one.

Вальнемулин

$C_{31}H_{52}N_2O_5S$ = 564.8.

CAS — 101312-92-9 (valnemulin); 133868-46-9 (valnemulin hydrochloride).

ATC Vet — QJ01XQ02.



Pharmacopoeias. *Eur.* (see p.vii) includes the hydrochloride for veterinary use.

Profile

Valnemulin is an antibacterial used as the hydrochloride in veterinary medicine.

Vancomycin *(BAN, rINN)*

Vancomicina; Vancomycine; Vancomycinum; Vankomycin; Vankomysiini. (S_a)-(3*S*,6*R*,7*R*,22*R*,23*S*,26*S*,36*R*,38a*R*)-44-{[2-*O*-(3-Amino-2,3,6-trideoxy-3-*C*-methyl-α-L-*lyxo*-hexopyranosyl)-β-D-glucopyranosyl]oxy}-3-(carbamoylmethyl)-10,19-dichloro-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tetradecahydro-7,22,28,30,32-pentahydroxy-6-[(2*R*)-4-methyl-2-(methylamino)valeramido]-2,5,24,38,39-pentaoxo-22*H*-8,11:18,21-dietheno-23,36-(iminomethano)-13,16:31,35-dimetheno-1*H*,16*H*-[1,6,9]oxadiazacyclohexadecino[4,5-*m*][10,2,16]-benzoxadiazacyclotetracosine-26-carboxylic acid.

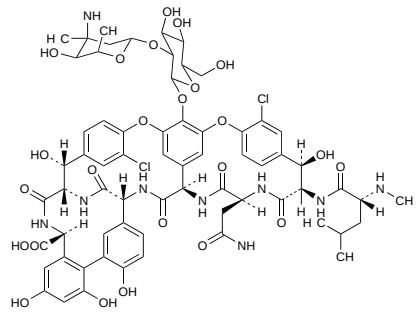
Ванкомицин

$C_{66}H_{75}Cl_2N_9O_{24}$ = 1449.3.

CAS — 1404-90-6.

ATC — A07AA09; J01XA01.

ATC Vet — QA07AA09; QJ01XA01.



Description. A glycopeptide antimicrobial substance or mixture of glycopeptides produced by the growth of certain strains of *Amycolatopsis orientalis* (*Nocardia orientalis*, *Streptomyces orientalis*), or by any other means.

Pharmacopoeias. In *US*.

USP 31 (Vancomycin). Store in airtight containers.

Vancomycin Hydrochloride *(BANM, rINNM)*

Hidrocloruro de vancomicina; Vancomycine, chlorhydrate de; Vancomycin-hydrochlorid; Vancomycini hydrochloridum; Vankomicinhidroklorid; Vankomicino hidrochloridas; Vankomisin Hidroklorür; Vankomycinhydrokloridi; Vankomysiinihydrokloridi; Wankomycyny chlorowodorek.

Ванкомицина Гидрохлорид

$C_{66}H_{75}Cl_2N_9O_{24}$,HCl = 1485.7.

CAS — 1404-93-9.

ATC — A07AA09; J01XA01.

ATC Vet — QA07AA09; QJ01XA01.

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

Ph. Eur. 6.2 (Vancomycin Hydrochloride). A mixture of related glycopeptides, consisting principally of vancomycin B, a substance produced by certain strains of *Amycolatopsis orientalis* or obtained by any other means. A white or almost white, hygroscopic powder. Freely soluble in water; slightly soluble in alcohol. A 5% solution in water has a pH of 2.5 to 4.5. Store in air-

tight containers. Protect from light.

USP 31 (Vancomycin Hydrochloride). A substance or mixture of substances produced by the growth of *Streptomyces orientalis*. A tan to brown, odourless, free-flowing powder. Freely soluble in water; insoluble in chloroform and in ether. A 5% solution in water has a pH of 2.5 to 4.5. Store in airtight containers.

Incompatibility. Solutions of vancomycin hydrochloride have an acid pH and incompatibility may reasonably be expected with alkaline preparations, or with drugs unstable at low pH. Reports of incompatibility are not always consistent, and other factors such as the strength of solution, and composition of the vehicles used, may play a part.

Stability. Although licensed product information recommends storage at 2° to 8°, solutions of vancomycin hydrochloride in various diluents (sodium chloride 0.9%, glucose 5%, and peritoneal dialysis solution) have been found to be stable for at least 14 days at room temperature.[1-3]

The stability of vancomycin in ophthalmic solution has also been studied.[4]

1. Das Gupta V, *et al.* Stability of vancomycin hydrochloride in 5% dextrose and 0.9% sodium chloride injections. *Am J Hosp Pharm* 1986; **43:** 1729–31.
2. Walker SE, Birkhans B. Stability of intravenous vancomycin. *Can J Hosp Pharm* 1988; **41:** 233–8.
3. Mauhinuey WM, *et al.* Stability of vancomycin hydrochloride in peritoneal dialysis solution. *Am J Hosp Pharm* 1992; **49:** 137–9.
4. Fuhrman LC, Stroman RT. Stability of vancomycin in an extemporaneously compounded ophthalmic solution. *Am J Health-Syst Pharm* 1998; **55:** 1386–8.

Adverse Effects

The intravenous use of vancomycin may be associated with the so-called 'red-neck' or 'red-man' syndrome, characterised by erythema, flushing, or rash over the face and upper torso, and sometimes by hypotension and shock-like symptoms. The effect appears to be due in part to the release of histamine and is usually related to rapid infusion.

Hypersensitivity reactions may occur in about 5% of patients and include rashes, fever, chills, and rarely, anaphylactoid reactions, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and vasculitis. Many reactions have become less frequent with the availability of more highly purified preparations. Reversible neutropenia, eosinophilia, and rarely thrombocytopenia and agranulocytosis have been reported; neutropenia is stated to be more common in patients who have received a total dose of 25 g or more. Nephrotoxicity, including rare cases of interstitial nephritis, may occur, particularly at high doses or in patients with predisposing factors, but has declined in frequency with greater awareness of the problem and appropriate monitoring of plasma concentrations and renal function.

Ototoxicity is also associated with vancomycin, and is more likely in patients with high plasma concentrations, or with renal impairment or pre-existing hearing loss.. It may progress after drug withdrawal, and may be irreversible. Hearing loss may be preceded by tinnitus, which must be regarded as a sign to stop treatment.

Vancomycin is irritant; intravenous use may be associated with thrombophlebitis, although this can be minimised by the slow infusion of dilute solutions, and by using different infusion sites. Extravasation may cause tissue necrosis.

Because of its poor absorption, relatively few adverse effects have been reported after the oral use of vancomycin, although mild gastrointestinal disturbances have occurred.

Effects on the ears. Reviews[1,2] of ototoxicity associated with vancomycin therapy have indicated that the actual number of cases is quite small, and close examination suggests that in most cases where hearing loss occurred patients had also received an aminoglycoside. The degree, and the reversibility, of ototoxicity associated with vancomycin alone is uncertain.

1. Bailie GR, Neal D. Vancomycin ototoxicity and nephrotoxicity: a review. *Med Toxicol* 1988; **3:** 376–86.
2. Brummett RE, Fox KE. Vancomycin- and erythromycin-induced hearing loss in humans. *Antimicrob Agents Chemother* 1989; **33:** 791–6.

Effects on the gastrointestinal tract. A 25-year-old woman developed *Clostridium difficile* colitis after a course of vancomycin and metronidazole, both orally, for pelvic inflammatory disease.[1] The condition resolved after treatment with vancomycin given alone.

1. Bingley PJ, Harding GM. Clostridium difficile colitis following treatment with metronidazole and vancomycin. *Postgrad Med J* 1987; **63:** 993–4.

Effects on the heart. A report[1] of cardiac arrest associated with an inadvertent rapid intravenous dose of vancomycin 150 mg in a neonate.

1. Boussemart T, *et al.* Cardiac arrest associated with vancomycin in a neonate. *Arch Dis Child* 1995; **73:** F123.

Effects on the kidneys. In a study,[1] nephrotoxicity was seen in 14 of 101 patients assigned to vancomycin 1 g before and after vascular surgery for infection prophylaxis compared with 2 of 99 assigned to saline placebo, suggesting that even short regimens of vancomycin can affect renal function. In another study involving 224 patients, nephrotoxicity was seen in 8 of 168 given vancomycin alone, 14 of 63 given vancomycin with an aminoglycoside, and 11 of 103 given an aminoglycoside without vancomycin.[2] This latter study found that use with aminoglycosides, trough serum concentrations of vancomycin greater than 10 micrograms/mL, and prolonged vancomycin therapy (for more than 21 days) were associated with an increased risk of nephrotoxicity. In both studies nephrotoxicity was defined in terms of increased serum creatinine.

1. Gudmundsson GH, Jensen LJ. Vancomycin and nephrotoxicity. *Lancet* 1989; **i:** 625.
2. Rybak MJ, *et al.* Nephrotoxicity of vancomycin, alone and with an aminoglycoside. *J Antimicrob Chemother* 1990; **25:** 679–87.

Effects on the liver. A 57-year-old man with multiple medical conditions developed raised liver enzyme values, on 5 different occasions, while being treated with oral vancomycin for episodes of *Clostridium difficile*-associated enterocolitis; liver enzymes returned to normal values each time the vancomycin was stopped.[1]

1. Cadle RM, *et al.* Vancomycin-induced elevation of liver enzyme levels. *Ann Pharmacother* 2006; **40:** 1186–9.

Effects on the nervous system. Reports of encephalopathy[1] (associated with high CSF concentrations after oral doses) and peripheral neuropathy[2] associated with vancomycin.

1. Thompson CM, *et al.* Absorption of oral vancomycin—possible associated toxicity. *Int J Pediatr Nephrol* 1983; **4:** 1–4.
2. Leibowitz G, *et al.* Mononeuritis multiplex associated with prolonged vancomycin treatment. *BMJ* 1990; **300:** 1344.

Effects on the skin. Rashes, erythema, or pruritus are the most common skin reactions associated with vancomycin but there have also been reports of linear IgA dermatosis,[1-4] Stevens-Johnson-like reaction,[5] bullous eruption,[6] local skin necrosis,[7] and exfoliative dermatitis.[6] In an analysis, risk factors for adverse cutaneous reactions were suggested to be age under 40 years and duration of therapy greater than 7 days.[6]

1. Piketty C, *et al.* Linear IgA dermatosis related to vancomycin. *Br J Dermatol* 1994; **130:** 130–1.
2. Nousari HC, *et al.* Vancomycin-associated linear IgA bullous dermatosis. *Ann Intern Med* 1998; **129:** 507–8.
3. Bernstein EF, Schuster M. Linear IgA bullous dermatosis associated with vancomycin. *Ann Intern Med* 1998; **129:** 508–9.
4. Danielsen AG, Thomsen K. Vancomycin-induced linear IgA bullous disease. *Br J Dermatol* 1999; **141:** 756–7.
5. Laurencin CT, *et al.* Stevens-Johnson-like reaction with vancomycin treatment. *Ann Pharmacother* 1992; **26:** 1520–1.
6. Korman TM, *et al.* Risk factors for adverse cutaneous reactions associated with intravenous vancomycin. *J Antimicrob Chemother* 1997; **39:** 371–81.
7. Hoelen DW, *et al.* Severe local vancomycin induced skin necrosis. *Br J Clin Pharmacol* 2007; **64:** 553–4.

Red-man syndrome. References[1-3] to the 'red-man syndrome', and evidence that pretreatment with an antihistamine can provide significant protection against it.[4,5] Similar reactions appear to be much less of a problem with teicoplanin and substitution of teicoplanin for vancomycin may be a viable alternative in patients at risk.[2,3,6] Skin tests are reported[7] to be of little value in predicting the severity of 'red-man syndrome'.

1. Wallace MR, *et al.* Red man syndrome: incidence, etiology, and prophylaxis. *J Infect Dis* 1991; **164:** 1180–5.
2. Polk RE. Anaphylactoid reactions to glycopeptide antibiotics. *J Antimicrob Chemother* 1991; **27** (suppl B): 17–29.
3. Rybak MJ, *et al.* Absence of "red man syndrome" in patients being treated with vancomycin or high-dose teicoplanin. *Antimicrob Agents Chemother* 1992; **36:** 1204–7.
4. Renz CL, *et al.* Oral antihistamines reduce the side effects from rapid vancomycin infusion. *Anesth Analg* 1998; **87:** 681–5.
5. Renz CL, *et al.* Antihistamine prophylaxis permits rapid vancomycin infusion. *Crit Care Med* 1999; **27:** 1732–7.
6. Smith SR. Vancomycin and histamine release. *Lancet* 1990; **335:** 1341.
7. Polk RE, *et al.* Vancomycin skin tests and prediction of "red man syndrome" in healthy volunteers. *Antimicrob Agents Chemother* 1993; **37:** 2139–43.

After oral administration. Reports of rash[1] and 'red-man syndrome'[2,3] after oral vancomycin.

1. McCullough JM, *et al.* Oral vancomycin-induced rash: case report and review of the literature. *DICP Ann Pharmacother* 1991; **25:** 1326–8.
2. Killian AD, *et al.* Red man syndrome after oral vancomycin. *Ann Intern Med* 1991; **115:** 410–11.
3. Bergeron L, Boucher FD. Possible red-man syndrome associated with systemic absorption of oral vancomycin in a child with normal renal function. *Ann Pharmacother* 1994; **28:** 581–4.

Precautions

Vancomycin should not be given to patients who have experienced a hypersensitivity reaction to it. It should not be given intramuscularly, and care should be taken when it is given intravenously to avoid extravasation, because of the risk of tissue necrosis. The adverse effects of infusion may be minimised by dilution of each 500 mg of vancomycin in at least 100 mL of fluid, and by infusion of doses over not less than 60 minutes.

Because the risk of ototoxicity and nephrotoxicity is thought to be increased at high plasma concentrations it may be desirable to adjust dosage requirements according to plasma-vancomycin concentrations. It has been suggested that dosage should be adjusted to avoid peak plasma concentrations above 30 to 40 micrograms/mL and trough concentrations exceeding 10 micrograms/mL, although uncertainty about the optimum methods and sampling times for monitoring, as well as some uncertainty about the degree of risk, means that there is less general agreement than for the aminoglycosides. It is generally agreed, however, that vancomycin should be avoided in patients with a history of impaired hearing and that particular care is necessary in patients with renal impairment, in neonates (especially if premature), and in the elderly, all of whom may be at increased risk of toxicity. Renal function and blood counts should be monitored regularly in all patients, and monitoring of auditory function is advisable, especially in high-risk patients. Vancomycin should be stopped in patients who develop tinnitus.

Since vancomycin is poorly absorbed, toxicity is much less of a problem after oral use than with the intravenous route, but care is required in patients with inflammatory gastrointestinal disorders, including antibiotic-associated colitis, in whom absorption may be enhanced.

Interactions

Other ototoxic or nephrotoxic drugs, such as aminoglycosides, polymyxins, cisplatin, and loop diuretics, markedly increase the risk of toxicity and should be given with vancomycin only with great caution.

Some of the adverse effects of vancomycin may be enhanced by the use of general anaesthetics; it has been suggested that, where patients require both, vancomycin infusions should be completed before the induction of anaesthesia.

Vancomycin may increase neuromuscular blockade produced by drugs such as suxamethonium or vecuronium.

Antimicrobial Action

Vancomycin is a glycopeptide antibiotic with a primarily bactericidal action against a variety of Gram-positive bacteria.

Mechanism of action. Vancomycin exerts its action by inhibiting the formation of the peptidoglycan polymers of the bacterial cell wall. Unlike penicillins, which act primarily to prevent the cross-linking of peptidoglycans which gives the cell wall its strength, vancomycin prevents the transfer and addition of the muramylpentapeptide building blocks that make up the peptidoglycan molecule itself. Vancomycin may also exert some effects by damaging the cytoplasmic membrane of the protoplast, and by inhibiting bacterial RNA synthesis.

Spectrum of activity. Staphylococci, notably *Staph. aureus* and *Staph. epidermidis* (including meticillin-resistant strains), *Streptococcus pneumoniae*, *Str. pyogenes*, and some strains of Group B streptococci are reported to be susceptible to vancomycin. The viridans streptococci, and enterococci such as *Enterococcus faecalis*, are often 'tolerant', i.e. inhibition, but no bactericidal effect, can be achieved at usual plasma concentrations (but see Activity with other Antimicrobials and Resistance, below).

Clostridium difficile is usually highly susceptible as are most other clostridia. *Actinomyces* spp., *Bacillus anthracis*, *Corynebacterium* spp., some lactobacilli, and

Listeria are usually susceptible. Virtually all Gram-negative organisms, as well as mycobacteria and fungi, are intrinsically resistant.

Activity with other antimicrobials. Vancomycin exhibits synergy with the aminoglycosides against enterococci; such combinations are usually bactericidal, even against vancomycin-tolerant strains. The synergistic effect is reported to be greater with gentamicin than with streptomycin. Combinations with an aminoglycoside are also reported to show synergy against *Staph. aureus*; however, variable results, including antimicrobial antagonism, or lack of synergy, have been reported against strains of *Staph. aureus* when vancomycin was combined with rifampicin. Synergy has been reported with the third-generation cephalosporins against *Staph. aureus* and enterococci.

Resistance to vancomycin in normally susceptible organisms has until recently remained relatively uncommon, although high-level intrinsic resistance has been seen in some species of *Lactobacillus*, *Leuconostoc*, and *Erysipelothrix*. However, there are an increasing number of reports of high-level acquired resistance amongst enterococci, apparently plasmid-mediated and transferable to other Gram-positive organisms, notably *Staph. aureus*, which are causing considerable concern. Organisms exhibiting high-level vancomycin resistance demonstrate cross-resistance to teicoplanin. Low-level resistance has also been reported in enterococci, but these organisms remain sensitive to teicoplanin, and this form of resistance does not appear to be transferable. Low-level vancomycin resistance has also been seen rarely among some staphylococcal strains: in contrast to the enterococci, these are often cross-resistant to teicoplanin. The mechanism of acquired resistance is uncertain, although it appears to be associated with the development of novel cell-membrane proteins.

◊ References to increasing resistance to vancomycin amongst enterococci[1,2] and *Staphylococcus aureus*,[3-9] and guidelines to prevent its spread.[10,11]

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4. Johnson AP. Intermediate vancomycin resistance in Staphylococcus aureus: a major threat or a minor inconvenience? *J Antimicrob Chemother* 1998; **42:** 289–91.
5. Ploy MC, *et al.* First clinical isolate of vancomycin-intermediate Staphylococcus aureus in a French hospital. *Lancet* 1998; **351:** 1212.
6. Smith TL, *et al.* Emergence of vancomycin resistance in Staphylococcus aureus. *N Engl J Med* 1999; **340:** 493–501.
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8. Hiramatsu K. Vancomycin-resistant Staphylococcus aureus: a new model of antibiotic resistance. *Lancet Infect Dis* 2001; **1:** 147–55.
9. Chang S, *et al.* Infection with vancomycin-resistant Staphylococcus aureus containing the VanA resistance gene. *N Engl J Med* 2003; **348:** 1342–7.
10. Hospital Infection Control Practices Advisory Committee (HICPAC). Recommendations for preventing the spread of vancomycin resistance. *Infect Control Hosp Epidemiol* 1995; **16:** 105–13.
11. CDC. Investigation and control of vancomycin-intermediate and resistant Staphylococcus aureus (VISA/VRSA): a guide for health departments and infection control personnel (updated September 2006). Available at: http://www.cdc.gov/ncidod/dhqp/pdf/ar/visa_vrsa_guide.pdf (accessed 06/07/08)

Pharmacokinetics

Vancomycin is only poorly absorbed from the gastrointestinal tract, although absorption may be somewhat greater when the gastrointestinal tract is inflamed. Infusion of a 1-g dose intravenously over 60 minutes has reportedly been associated with plasma concentrations of up to about 60 micrograms/mL immediately after completion of the infusion, and about 25 micrograms/mL 2 hours later, falling to under 10 micrograms/mL after 11 hours. However, there may be considerable interindividual variation in the pharmacokinetics of vancomycin: a range of half-lives between 3 and 13 hours has been reported, with an average of about 6 hours, in patients with normal renal function. Half-life may be prolonged in patients with renal impairment, to 7 days or more in anephric patients. About 55% is bound to plasma proteins, although large variations have been reported.

Vancomycin diffuses into extracellular fluid, including pleural, pericardial, ascitic, and synovial fluid. Small amounts are found in bile. However, there is little diffusion into the CSF and even when the meninges are inflamed effective concentrations may not be achieved. Vancomycin crosses the peritoneal cavity; about 60% of an intraperitoneal dose is reported to be absorbed in 6 hours. It is reported to cross the placenta. It is also distributed into breast milk.

Little or no metabolism of vancomycin is thought to take place. It is excreted unchanged by the kidneys, mostly by glomerular filtration. Some 80 to 90% of the dose is excreted in urine within 24 hours. There appears to be a small amount of non-renal clearance, although the mechanism for this has not been determined.

The pharmacokinetics of vancomycin may be altered by conditions which affect renal clearance: clearance of vancomycin has been reported to be enhanced in burn patients, whereas in those with renal impairment, or reduced renal function (such as neonates or the elderly), clearance is reduced and plasma-concentrations and half-lives increased. Dosage adjustment is often necessary in patients with reduced or impaired renal function; ideally, this should be based on plasma-concentration monitoring. Although clearance is also altered in hepatic impairment, it has been suggested that dosage adjustment is not necessary in the absence of other factors.

Plasma concentrations of vancomycin are reported to be little affected by conventional haemodialysis, although the use of high-flux membranes may significantly reduce vancomycin concentrations. Peritoneal dialysis, although it may decrease concentrations, is also thought not to do so by significant amounts, but haemoperfusion or haemofiltration effectively removes vancomycin from the blood.

Uses and Administration

Vancomycin is a glycopeptide antibiotic that is used in the treatment of serious staphylococcal or other Gram-positive infections when other drugs such as the penicillins cannot be used because of resistance or patient intolerance. It is used particularly in the treatment of meticillin-resistant staphylococcal infections (p.195), in conditions such as brain abscess, staphylococcal meningitis, peritonitis associated with continuous ambulatory peritoneal dialysis, and septicaemia. It is used alone, or with another drug such as an aminoglycoside, in the treatment and prophylaxis of endocarditis, for the prophylaxis of surgical infection, and in intensive care and the management of immunocompromised patients. It may be used as part of a multi-drug regimen for the treatment of inhalation and gastrointestinal anthrax. For details of all these infections and their treatment, see under Choice of Antibacterial, p.162. It is also used (by mouth) in the treatment of antibiotic-associated colitis (p.171).

Vancomycin may be used with other antibacterials to extend the spectrum of efficacy or increase effectiveness, notably with gentamicin or other aminoglycosides, or with rifampicin (but see Antimicrobial Action, above).

Administration and dosage. Vancomycin is given as the hydrochloride but doses are expressed in terms of the base. 1.03 g of vancomycin hydrochloride is equivalent to about 1 g of vancomycin. It is given intravenously, preferably by intermittent infusion, although continuous infusion has been used. For intermittent infusion, a concentrated solution containing the equivalent of 500 mg of vancomycin in 10 mL of water is prepared and then added to glucose 5% or sodium chloride 0.9% to produce a diluted solution containing not more than 5 mg/mL; this diluted solution is then infused over at least 60 minutes for a 500-mg dose or 100 minutes for a 1-g dose. Final concentrations of up to 10 mg/mL may be used for patients requiring fluid restriction, although there is an increased risk of adverse events. For continuous intravenous infusion when intermittent infusion is not feasible, the equivalent of 1 to 2 g is added to a sufficiently large volume of glucose or sodium chloride to permit the daily dose to be given over a period of 24 hours.

The usual adult dose is the equivalent of 500 mg of vancomycin every 6 hours or 1 g every 12 hours. Response is generally seen within 48 to 72 hours in sensitive infections. In patients with staphylococcal endocarditis, treatment for at least 3 weeks has been recommended.

For the prophylaxis of endocarditis in high-risk patients undergoing dental or other procedures who are unable to receive penicillin, vancomycin may be given before the procedure in a single dose of 1 g by intravenous infusion over at least 100 minutes followed by intravenous gentamicin.

Doses in infants and children. UK licensed product information states that children and infants over 1 month of age may be given 10 mg/kg every 6 hours. Neonates and infants up to 1 month old may be given an initial dose of 15 mg/kg; this is followed by 10 mg/kg every 12 hours in the first week of life or by 10 mg/kg every 8 hours in those aged 1 week to 1 month. The *BNFC* recommends the following doses:

- neonates less than 29 weeks postmenstrual age, 15 mg/kg every 24 hours;
- 29 to 35 weeks postmenstrual age, 15 mg/kg every 12 hours
- over 35 weeks postmenstrual age, 15 mg/kg every 8 hours
- infants and children 1 month of age and over, 15 mg/kg every 8 hours (to a maximum daily dose of 2 g)

Dose adjustment and monitoring. It has been recommended that dosage should be adjusted if necessary according to plasma-vancomycin concentrations, and this is particularly important where factors such as age or renal impairment (see also below) may predispose to toxicity, or where there is a risk of subtherapeutic concentrations. There has been some dispute about the relationship between plasma concentrations and toxicity, and this, complicated by differences in the sampling time after the end of infusion and by differences in the regimens and assay method used, has meant that suggested peak and trough concentrations have varied considerably. However, in order to avoid toxic concentrations immediately after the end of infusion the consensus appears to be that concentrations of not more than 30 to 40 micrograms/mL should be aimed for 1 to 2 hours after completion of infusion. It is usually recommended that trough concentrations (measured just before the next dose) should be below 10 micrograms/mL. The *BNF* suggests a trough concentration of 10 to 15 micrograms/mL, or 15 to 20 micrograms/mL to treat less sensitive strains of meticillin-resistant *Staph. aureus*.

Other routes. Vancomycin hydrochloride is given by mouth in the treatment of staphylococcal enterocolitis and antibiotic-associated colitis, including pseudomembranous colitis associated with the overgrowth of *Clostridium difficile*. It is given in a dose of 0.5 to 2 g daily in 3 or 4 divided doses for 7 to 10 days; the lowest dose of 500 mg daily is often considered adequate. A suggested dose for children in licensed product information is 40 mg/kg daily in 3 or 4 divided doses; the *BNFC* suggests a dose of 5 mg/kg 4 times daily for infants and children from 1 month of age up to 5 years of age, 62.5 mg 4 times daily for children aged 5 to 12 years, and 125 mg 4 times daily for children over 12 years of age.

In meningitis or other CNS infections, vancomycin has sometimes been given by the intrathecal or intraventricular route in order to ensure adequate CSF concen-

trations of antibiotic. Vancomycin has also been applied topically to the eye or given by subconjunctival or intravitreal injection; it has also been given by inhalation.

◊ Reviews.

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4. Cunha BA. Vancomycin revisited: a reappraisal of clinical use. *Crit Care Clin* 2008; **24:** 393–420.
5. Levine DP. Vancomycin: understanding its past and preserving its future. *South Med J* 2008; **101:** 284–91.

Administration in renal impairment. Various methods, including predictive nomograms based on creatinine clearance and pharmacokinetic methods such as those using Bayesian statistics, have been suggested for calculating vancomycin dosage requirements in patients with reduced renal function. One suggested approach has been a loading dose of 15 mg/kg followed by a daily dose in mg equivalent to about 15 times the glomerular filtration rate in mL/minute; or in anuric patients a dose of 1 g every 7 to 10 days. However, individualised dosage based on plasma concentrations is generally to be preferred.

Preparations

BP 2008: Vancomycin Intravenous Infusion;
USP 31: Sterile Vancomycin Hydrochloride; Vancomycin Hydrochloride Capsules; Vancomycin Hydrochloride for Injection; Vancomycin Hydrochloride for Oral Solution; Vancomycin Injection.

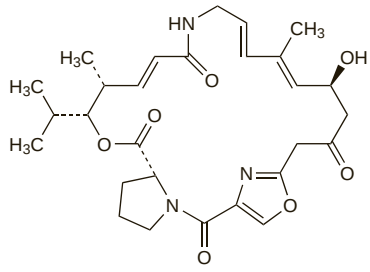
Proprietary Preparations (details are given in Part 3)
Arg.: Fabomicina; Icoplax; Rivervan; Vancocin†; Vancomax†; Vancotenk; Varedet; ***Austral.:*** Vancocin; ***Belg.:*** Vamysin; Vancocin; ***Braz.:*** Biovancomin†; Vanclomin; Vancoabbott; Vancocid†; Vancocina; Vanconorth†; Vancoplus†; Vancoson; Vancotrat; ***Canad.:*** Vancocin; ***Chile:*** Kovan; Vancocina†; ***Cz.:*** Edicin; Vancocin; Vancoled†; ***Denm.:*** Vancocin†; ***Fin.:*** Orivan†; Vancocin†; ***Fr.:*** Vancocine†; ***Ger.:*** Vanco; Vanco-saar; ***Gr.:*** Vamistol†; Voncon; Vondem; Voxin†; ***Hong Kong:*** Lyphocin; Vancocin; ***Hung.:*** Edicin†; Vancocin; ***India:*** Vancocin; Vancogram; Vanlid; ***Indon.:*** Vancep; ***Irl.:*** Vancocin; ***Israel:*** Vanco-Teva; Vancocin†; Vancoled†; ***Ital.:*** Copovan; Farmaciclin; Levovanox; Maxivanil; Vanco; Vancocina; Vancotex; Zengac; ***Malaysia:*** Vancocin†; Vancotex; ***Mex.:*** Estavam; Ifavac; Vanaurus; Vancam†; Vancocin; Vancox; ***Neth.:*** Vancocin; ***Norw.:*** Vancocin†; ***NZ:*** Vancocin†; ***Philipp.:*** Vancocin; ***Pol.:*** Edicin; Vancocin; ***Port.:*** Glipep; Vancocina†; ***Rus.:*** Edicin (Эдицин); Vancocin (Ванкоцин); ***S.Afr.:*** Vancocin; ***Spain:*** Diatracin†; ***Swed.:*** Vancocin; Vancoscand†; ***Switz.:*** Vancocin; ***Thai.:*** Edicin; Vancocin†; Vancogen; ***Turk.:*** Vancorin; ***UAE:*** Vancolon; ***UK:*** Vancocin; ***USA:*** Lyphocin; Vancocin; Vancoled; ***Venez.:*** Vagran; Vancobehr†.

Virginiamycin *(BAN, USAN, rINN)*

Antibiotic 899; SKF-7988; Virgimycin; Virginiamicina; Virginiamycine; Virginiamycinum.

Виргиниамицин

CAS — 11006-76-1; 21411-53-0 (virginiamycin M_1); 23152-29-6 (virginiamycin S_1).
ATC — D06AX10.
ATC Vet — QD06AX10; QJ01FG90.



(virginiamycin M_1)

Profile

Virginiamycin is a streptogramin antibacterial mixture consisting principally of 2 antimicrobial substances, virginiamycin M_1, and virginiamycin S_1, produced by the growth of *Streptomyces virginiae*. It has been used for the treatment of infections due to sensitive organisms, particularly Gram-positive cocci. It has been given orally and applied locally. It may cause gastrointestinal disturbances including diarrhoea and vomiting. A few instances of hypersensitivity have been observed.

Virginiamycin has been used in animal feeding stuffs as a growth promotor.

Preparations

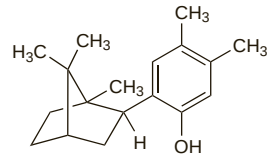
Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Belg.:*** Spitalen†.

Xibornol *(BAN, rINN)*

CP3H; 1HP; 1BX; Xibornolum. 6-(Isoborn-2-yl)-3,4-xylenol; 6-[(1*R*,2*S*,4*S*)-Born-2-yl]-3,4-xylenol.

Ксиборнол

$C_{18}H_{26}O$ = 258.4.
CAS — 38237-68-2; 13741-18-9.
ATC — J01XX02.
ATC Vet — QJ01XX02.



Profile

Xibornol is an antibacterial that is reported to have a bacteriostatic action on Gram-positive organisms such as staphylococci and streptococci, as well as activity against *Haemophilus influenzae*. It has been given orally, as an oral spray, and rectally.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Bornilene.