Drugs 2000 Apr; 59 (4): 815-827
0012-6667/00/0004-0815/$25.00/0

Linezolid

Delyth Clemett and *Anthony Markham*

Adis International Limited, Auckland, New Zealand

Contents

Abstract

▲ Linezolid is an oxazolidinone antibacterial agent that acts by inhibiting the initiation of bacterial protein synthesis. Cross-resistance between linezolid and other inhibitors of protein synthesis has not been demonstrated.

▲ Linezolid has a wide spectrum of activity against Gram-positive organisms including methicillin-resistant staphylococci, penicillin-resistant pneumococci and vancomycin-resistant *Enterococcus faecalis* and *E. faecium*. Anerobes such as *Clostridium* spp., *Peptostreptococcus* spp. and *Prevotella* spp. are also susceptible to linezolid.

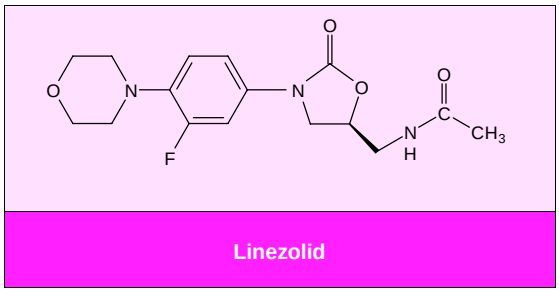
▲ Linezolid is bacteriostatic against most susceptible organisms but displays bactericidal activity against some strains of pneumococci, *Bacteroides fragilis* and *C. perfringens*.

▲ In clinical trials involving hospitalised patients with skin/soft tissue infections (predominantly *S. aureus*), intravenous/oral linezolid (up to 1250mg mg/day) produced clinical success in >83% of individuals. In patients with community-acquired pneumonia, success rates were >94%.

▲ Preliminary clinical data also indicate that twice daily intravenous/oral linezolid 600mg is as effective as intravenous vancomycin 1g in the treatment of patients with hospital-acquired pneumonia and in those with infections caused by methicillin-resistant staphylococci. Moreover, linezolid 600mg twice daily produced >85% clinical/microbiological cure in vancomycin-resistant enterococcal infections.

▲ Linezolid is generally well tolerated and gastrointestinal disturbances are the most commonly occurring adverse events. No clinical evidence of adverse reactions as a result of monoamine oxidase inhibition has been reported.

Features and properties of linezolid (U-100766, PNU-100766)	
Indications	
Complicated and uncomplicated skin and soft tissue infections, community- and hospital-acquired pneumonia, drug-resistant Gram-positive infections	
Mechanism of action	
Oxazolidinone antibacterial agent	Inhibitor of the initiation of bacterial protein synthesis
Dosage and administration	
Usual dosage in clinical trials	600mg
Frequency	Twice daily
Administration	Intravenous/oral
Pharmacokinetic profile (625mg oral dose)	
Peak/trough plasma concentration	18/≥4 mg/L
Time to peak plasma concentration	1 to 2h
Bioavailability	103%
Renal clearance	50 mL/min
Total clearance	120 mL/min
Elimination half-life	4.5 to 5.5h
Adverse events	
Most frequent	Gastrointestinal disturbances



Linezolid

Linezolid is a member of the oxazolidinone class of synthetic antibacterial agents that inhibit bacterial protein synthesis through a unique mechanism. In contrast to other inhibitors of protein synthesis, the oxazolidinones act early in translation by preventing the formation of a functional initiation complex.[1] Consequently, linezolid is not expected to show cross-resistance with existing antibacterial agents. The proposed mechanism of action of linezolid is indicated in figure 1.

1. Antibacterial Activity

Mechanism of Action

Effects on Protein Synthesis

- In a membrane-permeable strain of *Escherichia coli*, linezolid 30 μmol/L inhibited protein synthesis by 90%. Linezolid effectively inhibited cell-free transcription-coupled translation in *E. coli*, with a concentration producing half maximal inhibition (IC_{50}) of 1.8 μmol/L. Following uncoupling of the transcription-translation reaction, linezolid also demonstrated effective inhibition of translation alone.[4]

- Radioligand binding studies in isolated bacterial ribosomes demonstrated that the oxazolidinone eperezolid binds specifically to the 50S ribosomal subunit, and linezolid (1 to 1000 μmol/L) competitively inhibits [^{14}C]eperezolid ribosomal binding in a concentration-dependent manner.[3] Although chloramphenicol and lincomycin also competed for the ribosomal binding site, functional studies indicated that the oxazolidinones act via a distinct mechanism. In contrast to the marked actions of chloramphenicol and lincomycin on elongation (peptidyl transferase activity) and termination of translation, linezolid and eperezolid had little effect on these processes.[3,4]

- Linezolid inhibited the formation of ribosomal initiation complexes involving 30S and 70S ribosomes isolated from *E. coli* (IC_{50} 110 and 130 μmol/L, respectively) and 70S ribosomes from *Staphylococcus aureus* (116 μmol/L). In contrast, other steps in the initiation process were not affected by linezolid. At concentrations of up to 200 μmol/L, linezolid did not inhibit the binding of messenger RNA or *N*-formylmethionyl-transfer RNA ($tRNA^{fMet}$) to isolated 30S ribosomal subunits, nor did it prevent the formation of the initiation factor(IF)-$tRNA^{fMet}$ binary complex. The investigators postulated that binding of oxazolidinones to the 50S subunit distorts the $tRNA^{fMet}$ binding site which overlaps both ribosomal subunits, preventing initiation complex formation (fig. 1).[2]

Effects on Virulence Factors

- *In vitro* experiments indicated that linezolid inhibits the expression of *S. aureus* [minimum inhibitory concentration (MIC) 1.5 mg/L] and *Streptococcus pyogenes* (MIC 0.5 mg/L) virulence factors. Production of α-haemolysin, δ-haemolysin and coagulase by *S. aureus* was considerably reduced in the presence of linezolid at concentrations of 12.5 to 50% of MIC. Additionally, linezolid (25 to 50% of MIC) attenuated streptolysin O and DNAase production by *S. pyogenes*.[5]

In Vitro Activity

Tentative breakpoint criteria for linezolid (supported by preliminary pharmacokinetic data[6,7]) are MICs of ≤4 mg/L for susceptibility and ≥16 mg/L for resistance.[8]

Gram-Positive Bacteria

- Linezolid showed good activity against *S. aureus* (no isolates had MICs >2 mg/L) which was generally equivalent to that of vancomycin. *S. epidermidis* and *S. haemolyticus* had similar susceptibilities to linezolid and vancomycin (all MICs 1 to 2 mg/L).[9] MICs of linezolid were not affected

by resistance to penicillin, methicillin or ciprofloxacin in *S. aureus*, or methicillin in coagulase-negative staphylococci (fig. 2).[9,10]

• In particular, linezolid was highly effective against penicillin-sensitive, -intermediate and -resistant *Streptococcus pneumoniae*, the concentration required to inhibit 90% of strains (MIC_{90}) being 1 mg/L (MIC range ≤0.016 to 4 mg/L).[11,14] In comparison, MIC_{90} values for vancomycin were 0.25 to 0.5 mg/L. Additionally, linezolid remained active against strains of pneumococci resistant to ceftriaxone,[14] erythromycin, clindamycin and tetracycline.[15]

• Linezolid demonstrated activity against all enterococcal isolates tested, regardless of vancomycin resistance pattern. Against vancomycin-susceptible strains of *Enterococcus faecalis* and *E. faecium*, linezolid and vancomycin had similar effects (MIC 1 to 2 mg/L and 0.25 to 8 mg/L, respectively). Importantly, linezolid also had good activity against vancomycin-resistant strains of enterococci.[13,16] For class A and class B glycopeptide-resistant (VanA and VanB) strains of *E. faecium* (having MIC_{90}s of 512 and ≥128 mg/L for vancomycin and ampicillin, respectively), the MIC_{90} of linezolid was in the range 2 to 4 mg/L. Linezolid had an MIC_{90} or 4 mg/L against vancomycin-resistant *E. faecalis*, compared with a value of 2 mg/L for ampicillin.[13]

• Activity of linezolid was also demonstrated against 8 taxa of *Nocardia*, including the multidrug-resistant strains *N. farcinica* and *N. transvalensis*. With the exception of *N. farcinica* and *N. otitidiscavarium* which had MIC_{50}s of 4 mg/L, all other *Nocardia* taxa had MIC_{50}s of 2 mg/L. MIC_{90}s were in the range 2 to 8 mg/L for all species tested.[17]

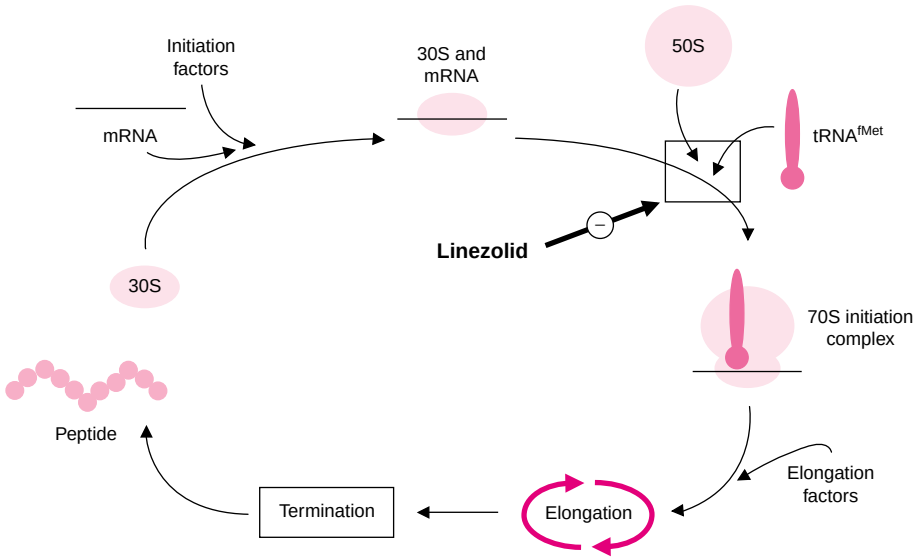


Fig. 1. Schematic representation of the proposed mechanism of action of linezolid. The oxazolidinones appear to prevent an early step in bacterial protein synthesis by preventing formation of the $tRNA^{fMet}$-mRNA-70S or -30S initiation complex. Collective data suggest that the ribosomal interaction of oxazolidinones is partitioned between the 2 subunits. Oxazolidinone binding to the 50S subunit distorts the binding site for $tRNA^{fMet}$, inhibiting ternary initiation complex formation and thus preventing initiation of translation.[2,3] **30S** = 30S ribosomal subunit; **50S** = 50S ribosomal subunit; **70S** = 70S ribosomal complex; **mRNA** = messenger RNA; **$tRNA^{fMet}$** = *N*-formylmethionine-transfer RNA complex.

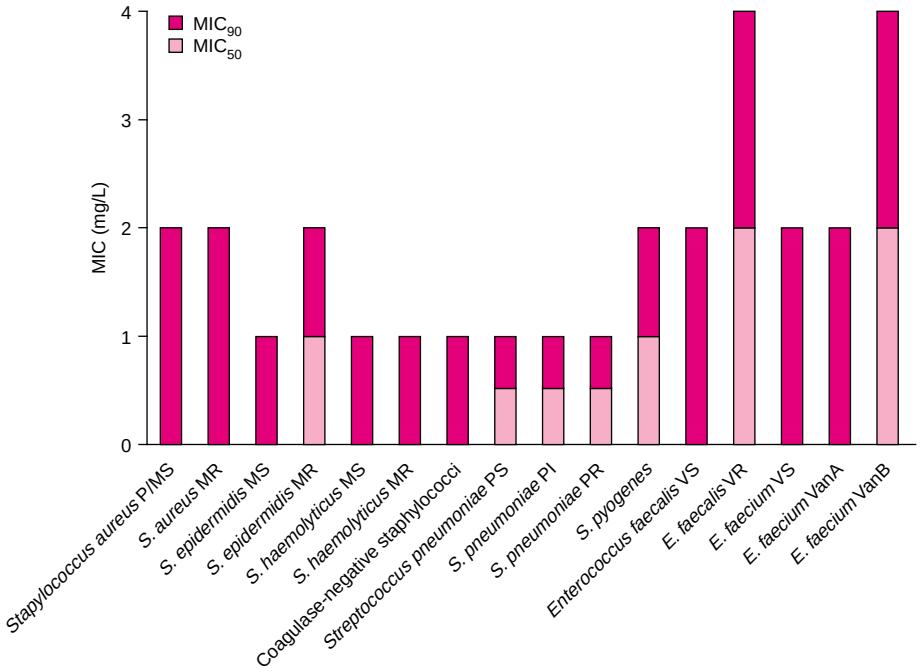


Fig. 2. *In vitro* activity of linezolid against Gram-positive organisms. Data compiled from Von Eiff & Peters,[9] Spangler et al.,[11] Zurenko et al.[12] and Eliopoulos et al.[13] for staphylococci, pneumococci, *S. pyogenes* and enterococci, respectively. **MIC_{50}** and **MIC_{90}** = minimum inhibitory concentration required to inhibit 50% and 90% of strains; **MR** = methicillin-resistant; **MS** = methicillin-susceptible; **PI** = penicillin-intermediate; **P/MS** = penicillin/methicillin-susceptible; **PR** = penicillin-resistant; **PS** = penicillin-susceptible; **VanA** = class A glycopeptide-resistant strain; **VanB** = class B glycopeptide-resistant strain; **VR** = vancomycin-resistant; **VS** = vancomycin-susceptible.

• Linezolid has potent activity (MIC_{90} ≤2 mg/L) against other Gram-positive organisms, including *S. pyogenes*, *Bacillus* spp., *Corynebacterium* spp., *Listeria monocytogenes*, *Mycobacterium tuberculosis* and *Rhodococcus* spp.[12,18]

Gram-Negative Bacteria

• Linezolid lacked significant effects against most Gram-negative pathogens but had *in vitro* activity against *Moraxella catarrhalis* (MIC_{90} 4 mg/L), *Haemophilus influenzae* (MIC_{50} 4 mg/L),[12] *Legionella* spp. (MIC_{90} 4 mg/L),[19] *Neisseria gonorrhoeae* (MIC_{90} 16 mg/L),[20] and *Bordatella pertussis* (MIC_{90} 4 mg/L).[21] Additionally, linezolid exhibited MICs of 2 and 4 mg/L against *Flavobacterium meningosepticum* and *Pasteurella multocida*, respectively.[22,23] *Pseudomonas aeruginosa* and enterobacteriaceae, including *E. coli*, *Klebsiella pneumoniae*, and *Proteus penni*, were not susceptible to linezolid.[12,20]

Anaerobes

• Linezolid demonstrated similar activity to vancomycin (MIC 1 to 2 mg/L for both agents) against *Clostridium difficile* and *C. perfringens* (fig. 3). Additionally, linezolid had good activity against Gram-negative anaerobes including *Bacteroides* spp. (MIC 4 mg/L), *Fusobacterium nucleatum* (MIC 0.5 mg/L) and *Prevotella* spp. (MIC 1 to 2 mg/L).[12,23,24]

Bactericidal Activity

• In time-kill assays, linezolid demonstrated consistent bacteriostatic effects against *S. aureus*, coagulase-

negative staphylococci and enterococci.[12,25-27] Significant concentration-dependent bactericidal activity against staphylococcal and enterococcal strains was not demonstrated at concentrations of 2 to 16 × MIC.[20]

• Linezolid was bactericidal against 3 of 5 streptococcal strains tested, and reduced bacterial counts of the remaining strains by 2.5 to 2.9 $\log_{10}$ colony forming units (cfu)/ml. Bactericidal activity was also demonstrated against *B. fragilis* and *C. perfringens*.[12]

• Serum samples drawn from 10 volunteers receiving multiple doses of oral linezolid 400 or 625mg inhibited test strains of *S. aureus*, *E. faecalis* and *S. pneumoniae*. 6 hours after the final administration, samples from 5 of 6 volunteers receiving linezolid 625mg were bactericidal for *S. pneumoniae*.[28]

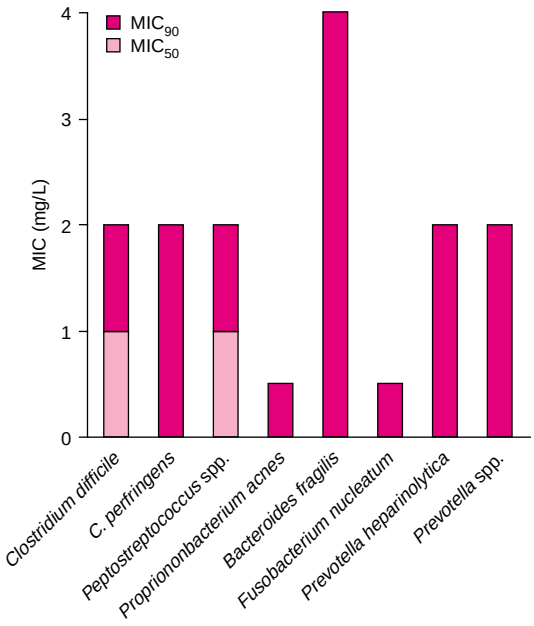


Fig. 3. *In vitro* activity of linezolid against anaerobes.[23,24] **MIC_{50}** and **MIC_{90}** = minimum inhibitory concentration required to inhibit 50% and 90% of strains.

Postantibiotic Effects

• At 4 × MIC, linezolid showed *in vitro* postantibiotic effects (PAE) of 0.6, 1.1 and 1.4 hours, respectively, for methicillin-resistant *S. aureus*, methicillin-susceptible *S. epidermidis* and vancomycin-resistant *E. faecium*.[29] In a mouse thigh infection model, linezolid at dosages of 20 and 80 mg/kg produced PAEs of 3.6 and 3.8 hours for penicillin-sensitive pneumococci, and 3.9 and 3.7 hours for methicillin-sensitive *S. aureus*.[30]

In Vivo Activity

Staphylococci

• In a mouse intraperitoneal model of systemic infection, linezolid was more active than vancomycin against methicillin-susceptible *S. aureus* [50% effective dose (ED_{50}) 2.9 *vs* 13.2 mg/kg/day, and displayed comparable activity against methicillin-resistant strains (2.8 to 15 *vs* 2 to 7 mg/kg/day). Against methicillin-susceptible *S. epidermidis*, linezolid was slightly less active than vancomycin (ED_{50} 4.7 *vs* 1.8 mg/kg/day).[31] Linezolid was not active in a rat model of methicillin-susceptible *S. aureus* experimental osteomyelitis.[32]

• The activity of linezolid 40 mg/kg was compared with that of vancomycin 60 mg/kg and rifampicin 10 mg/kg in a rat model of experimental (methicillin-resistant *S. aureus*) endocarditis (n = 6 to 7 in each group). After 5 days' treatment (twice daily intramuscular injections), bacterial vegetation counts (6.6 $\log_{10}$ cfu/g at the start of therapy) fell by 2.9 and 3.6 $\log_{10}$ cfu/g for linezolid and rifampicin, respectively. Bacterial counts remained unchanged or increased by 4.1 $\log_{10}$ cfu/g in the vancomycin and control groups, respectively.[33]

• However, in a study of experimental endocarditis in rabbits (methicillin-susceptible *S. aureus*), both oral linezolid 50 mg/kg 3 times daily and intravenous vancomycin 25 mg/kg twice daily significantly reduced vegetation counts from control values (2.8, 2.7 and 8.4 $\log_{10}$ cfu/g for linezolid, vancomycin and control, respectively).[34]

Streptococci

• Linezolid was at least as effective as clindamycin against *S. pyogenes* systemic infections (ED_{50} 5 *vs* 8.6 mg/kg/day) and as effective as amoxicillin against *S. pneumoniae* (2.5 *vs* 3.4 mg/kg/day). Additionally, linezolid demonstrated consistent activity (ED_{50} 2.7 to 3.8 mg/kg/day) against 3 strains of pneumococci resistant to clindamycin and penicillin/cephalosporin.[31]

• In a rabbit experimental model of *S. pneumoniae* meningitis, intravenous linezolid (18% central nervous system penetration) reduced both penicillin-sensitive and -resistant CSF bacterial counts (–0.25 and –0.41 $\log_{10}$ cfu/ml · h, respectively). However, linezolid (2 × 20 mg/kg infusions) was less active ($p < 0.05$) than ceftriaxone 125 mg/kg against infection caused by a penicillin-susceptible strain.[35]

• Oral twice daily linezolid 25 mg/kg for 5 days was effective in producing sterile middle ear fluid cultures and eradicating amoxicillin- and erythromycin-resistant *S. pneumoniae* from the nasopharynx in a chinchilla model of otitis media. The concentration of linezolid in middle ear fluid was 81% of that reached in serum.[36]

• Linezolid reduced morbidity associated with severe group A streptococcal myonecrosis in experimental animals. After infection with 10^8 cfu/ml (causing 100% mortality within 115 hours in untreated animals), 12-day survival rates were 80% in animals treated with 20 to 40 mg/kg twice daily. In comparison, the 9-day mortality rate was 100% in animals treated with penicillin G 98 mg/kg.[37]

Enterococci

• In a neutropenic mouse model, linezolid was curative against vancomycin-resistant *E. faecium* (ED_{50} 24 mg/kg/day) and also demonstrated activity against aminoglycoside-resistant *E. faecalis* (ED_{50} 10 mg/kg/day *vs* 0.5 mg/kg/day for vancomycin). Moreover, linezolid had similar efficacy to vancomycin in curing *E. faecalis* soft tissue infections (ED_{50} 11.0 *vs* 16.3 mg/kg/day).[31]

Mycobacteria

• Oral linezolid 25, 50 and 100 mg/kg (n = 8 for each group) reduced organ bacterial counts in a murine model of *Mycobacterium tuberculosis* infection. After 4 weeks of 5 days' treatment per week, starting 1 week postinfection, bacterial counts were significantly reduced ($p < 0.05$) in the spleen (5.85, 5.34 and 8.06 $\log_{10}$ cfu/organ in 25 and 100 mg/kg and control groups, respectively) and lung (6.64, 5.52 and 8.17 $\log_{10}$ cfu/organ). However, 4 deaths occurred in the lower dose group. When treatment was started 1 day postinfection, all doses of linezolid reduced ($p < 0.01$) organ bacterial counts. However, the activity of the highest dose of linezolid was less than half that of isoniazid 25 mg/kg ($p < 0.01$).[38]

Polymicrobic and Gram-Negative Infections

• Polymicrobic (gentamicin-resistant *S. aureus* and gentamicin-susceptible *E. coli*) soft tissue infections were effectively cured by treatment with linezolid-aztreonam and vancomycin-aztreonam combinations (ED_{50} 5.6 *vs* 3.7 mg/kg/day). However, linezolid alone was ineffective against the Gram-negative pathogens *E. coli*, *Klebsiella pneumoniae* and *Moraxella catarrhalis* in a mouse systemic infection model.[31]

• In a chinchilla model of otitis media, experimental infection and nasopharyngeal colonisation with nontypeable *H. influenzae* was not eradicated by linezolid, despite achieving middle ear fluid concentrations above the MIC (8 mg/L).[36]

Resistance

• In Gram-positive bacteria, *in vitro* resistance to linezolid was not easily induced. When exposed to a drug concentration of twice the MIC, no resistant mutants were found in 12 strains of methicillin-susceptible and -resistant *S. aureus* and *S. epidermidis* (spontaneous mutation frequency $<1 \times 10^{-9}$ for each organism).[39] In another study in *S. aureus*, development of spontaneous resistance did not occur at 2, 4 or 8 times the MIC of linezolid, yielding a spontaneous mutation frequency of $<8 \times 10^{-11}$. Additionally, serial passage of staphylococci and

enterococci produced no evidence of rapid development of resistance.[12]

• Cross-resistance between linezolid and other inhibitors of protein synthesis targeting the 50S ribosomal subunit did not develop in staphylococcal, enterococcal and streptococcal strains containing genes conferring resistance to chloramphenicol, fusidic acid, lincosamides, macrolides, streptogramins and tetracyclines.[40]

2. Pharmacokinetic Profile

Absorption and Distribution

• Linezolid is rapidly and completely absorbed after oral administration, reaching peak plasma concentrations (C_{max}) within 1 to 2 hours (t_{max}), and having a mean absolute bioavailability of 103%.[6,41] C_{max} was 23% lower ($p = 0.0014$) in the presence of food, although the area under the plasma concentration-time curve (AUC), t_{max} and bioavailability were unchanged.[41] Linezolid has a steady-state volume of distribution (V_{ss}) of 50L and is 31% bound to plasma proteins.[42]

• At steady state, C_{max} values were 12 and 18 mg/L, respectively, after 14.5 days' twice daily oral administration of linezolid 375 and 625mg in 24 volunteers. Minimum plasma concentrations (C_{min}) were ≥4 mg/L (i.e. above the MIC_{90} for susceptible pathogens) for both doses.[6] After twice daily intravenous administration (n = 17), linezolid 500 and 625mg for 7.5 days produced steady-state C_{min} values of 3.51 and 3.84 mg/L, respectively. Plasma concentrations remained above 4 mg/L for 9 to 10 hours of the 12-hour dose interval.[7]

• In rats treated with a single oral dose of [^{14}C]linezolid 25 mg/kg, brain levels of radioactivity were 14 to 23% of plasma levels 0.3 to 4 hours postdose. Mineral bone concentrations were similarly low. With the exception of the eye and testis (≈40%) most other tissues contained concentrations of radioactivity that were ≥70% and ≥60% of plasma concentrations at 20 minutes and 4 hours, respectively (data on file, Pharmacia & Upjohn).

• After 5 days' treatment with linezolid 40 mg/kg twice daily in a rat model of endocarditis, mean trough vegetation concentrations of linezolid were 2.2 μg/g. Simultaneous serum concentrations were similar, suggesting no accumulation of linezolid in vegetations. In contrast, trough concentrations of vancomycin (administered at 60 mg/kg twice daily) in vegetations were 7-fold higher than those in serum. After a single dose of linezolid, both serum and vegetation concentrations remained above the MIC for 7 to 8 hours postdose.[33]

Metabolism and Elimination

• Metabolism studies indicated that linezolid undergoes slow nonenzymatic oxidation, mediated by reactive oxygen species *in vivo*,[43] resulting in the formation of carboxylic acid metabolites with low antibacterial potency (MIC against *S. aureus* of >16 mg/L).[44] Unchanged drug accounted for 90% of the circulating dose of linezolid, and the metabolite with the highest circulating concentration accounted for <6%. Involvement of the cytochrome P450 (CYP) system in the metabolism of linezolid has not been demonstrated, and linezolid neither induces nor inhibits rat and human CYP isoforms.[43]

• After a single 500mg oral dose in healthy volunteers, urinary and faecal recoveries were 80 to 85% and 7 to 12% over 7 days, respectively, of the administered dose. At steady state, 30% of the dose was excreted intact in the urine.[44]

• Total (CL) and renal clearances (CL_R) of linezolid were 120 and 50 mL/min, respectively, after oral or intravenous administration. The elimination half-life ($t_{½z}$) was 4.5 to 5.5 hours under single dose and steady-state conditions.[6,7]

Influence of Age, Gender and Disease on Pharmacokinetics

• The pharmacokinetic properties of a single oral dose of linezolid 600mg were not influenced by age after administration in young (mean 30 years, n = 15) and elderly (mean 70 years, n = 14) volunteers. CL was lower in female than in male volun-

teers in both age groups, although $t_{½z}$ values were similar. Consequently, dose adjustments in adults are not warranted on the grounds of age or gender.[45]

• In children and adolescents, the pharmacokinetic properties of intravenous linezolid 1.5 mg/kg did not differ among age groups (12 months to 2 years, 3 to 6, 7 to 12, and 13 to 18 years). Although CL was somewhat higher in paediatric than in adult patients receiving similar doses on a mg/kg basis (125mg = 1.7 mg/kg for a typical 70kg adult), V_{ss} values were similar. Additionally, $t_{½z}$ (3 to 3.7 hours) was shorter in paediatric than in adult patients.[46]

• In 24 individuals with varying degrees of renal function [creatinine clearance (CL_{CR}) 10 to 39 ml/min, 40 to 79 ml/min and >80 ml/min], CL of linezolid 600mg was not altered as a function of CL_{CR}. However, an 80% increase in CL_R was observed in patients receiving dialysis (8.8 *vs* 5.8 ml/min in patients with normal renal function). Thus dosage adjustment is unnecessary in individuals with mild to moderately impaired renal function, although supplemental or postdialysis doses may be necessary for those on haemodialysis.[47]

• The disposition of linezolid did not appear to be affected by mild to moderate hepatic impairment. Pharmacokinetic parameters were not significantly altered in 7 patients with liver disease compared with 8 matched controls receiving a single oral dose of 600mg. Hence, dosage adjustment is not necessary in patients with mild to moderate liver disease.[48] The pharmacokinetics of linezolid have not been investigated in patients with severe hepatic impairment.

Drug Interactions

• No clinically significant pharmacokinetic interactions were noted during coadministration of linezolid 375mg and aztreonam 1g as a single intravenous infusion in 12 volunteers. Concentrations of linezolid remained ≥4 mg/L for approximately 5 hours postinfusion. Consequently, dosage adjustment is not required when addition of aztreonam to the treatment regimen is indicated for Gram-negative coverage.[49]

3. Therapeutic Profile

Oral and intravenous linezolid have been evaluated in open-label studies of the treatment of community-acquired pneumonia (including one study in paediatric patients) and skin/soft tissue infections. A further 7 studies (6 versus comparator drugs, 1 dose-ranging) involving >2900 patients aged >18 years have investigated the clinical efficacy of linezolid in pneumonia and skin/soft tissue infections and against strains of methicillin-resistant *S. aureus* and vancomycin-resistant *E. faecium* (patients aged ≥13 years were included in the latter study). Studies were presented in abstract or preliminary form, and in some instances the infecting organism was not specified. In general, clinical success rates were based on combined cure and improvement.

Open-Label Studies

• Hospitalised patients (n = 273) with skin/soft tissue infections (predominantly caused by *S. aureus*, although *S. epidermidis*, *S. pyogenes* and enterococci were also isolated) participated in an open-label study of intravenous/oral linezolid. Patients received either low (250mg three times daily or 375mg twice daily[1]) or high dose linezolid (375mg three times daily or 625mg twice daily) for at least 3 days before switching to oral treatment until the end of therapy (mean total duration 10 days). At long term follow-up (15 to 28 days after termination of therapy) clinical success rates were 83.3 and 87.7% for the low and high dose groups, respectively. Similarly, 90 and 82.5% achieved treatment success in terms of microbiological outcome.[50]

• The efficacy of linezolid in hospitalised patients with community-acquired pneumonia was evalu-

1 Both low and high dosage regimens were switched from three times daily to twice daily, maintaining the same total daily dosage, after interim pharmacokinetic data became available.

ated using a similar dosage and treatment protocol. A total of 44 patients received low dose linezolid, while 76 were treated with the high dose regimen. Pneumonia was predominantly due to *S. pneumoniae* (68%), although isolates also included *S. aureus*, *Haemophilus* spp. and group B streptococci. At follow-up (15 to 28 days after the end of treatment) 93.2% and 94.4% of patients in the low dose group achieved clinical and microbiological success, respectively. In the high dose group, success rates were 94.4% and 97.4%.[51]

• 64 paediatric patients (aged 12 months to 6 years) with community-acquired pneumonia (causal organism unspecified) were treated with twice daily intravenous/oral linezolid at a dosage of 10 mg/kg for 7 to 14 days. Clinical cure was achieved in 95.3% of patients.[52]

Comparative Studies

• Linezolid 400 and 600mg twice daily produced clinical success rates of ≥89% in patients with complicated and uncomplicated skin/soft tissue infections, and in outpatients and hospitalised patients with community-acquired pneumonia (fig. 4).[52] The efficacy of linezolid did not differ from that of standard treatments. However, linezolid was significantly ($p = 0.022$) more effective than the comparator treatment in a subset of hospitalised patients with community-acquired pneumonia and associated bacteraemia (93.3 *vs* 69.9%, respectively).[52]

• Preliminary publication of results from 2 studies indicated comparable efficacy of twice daily intravenous linezolid 600mg and vancomycin 1g in methicillin-resistant staphylococcal infections (including pneumonia, bacteraemia and urinary or skin/soft tissue infections with *S. aureus* and coagulase negative stapylococci) and hospital-acquired pneumonia (fig. 5). Step-down to oral treatment occurred in some patients in with methicillin-resistant staphylococcal infections.[52,53]

• Intravenous linezolid at twice daily dosages of 200 or 600mg effected clinical cure in 73.7% and 88.6% of patients (fig. 5) with vancomycin-resis-

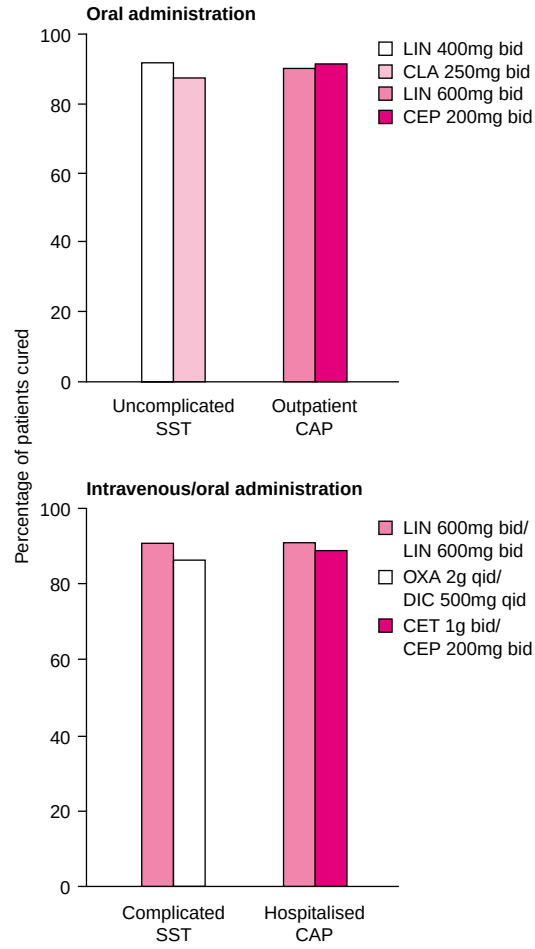


Fig. 4. Clinical success rates in patients with pneumonia and skin/soft tissue (SST) infections receiving oral, or intravenous followed by oral, administration of linezolid (LIN) in 4 studies. The duration of treatment was 7 to 14 days in patients with uncomplicated SST (n = 611) and 10 to 21 days in those with complicated SST (n = 591). Outpatients (n = 407) and hospitalised patients (n = 526) with CAP received 10 to 14 and 7 to 21 days' treatment, respectively. For each type of infection, patients were randomised to receive LIN or the appropriate standard treatment. Data from clinically evaluable patients are presented.[52] **bid** = twice daily; **CAP** = community-acquired pneumonia; **CEP** = cefpodoxime; **CET** = ceftriaxone; **CLA** = clarithromycin; **DIC** = dicloxacillin; **OXA** = oxacillin; **qid** = 4 times daily.

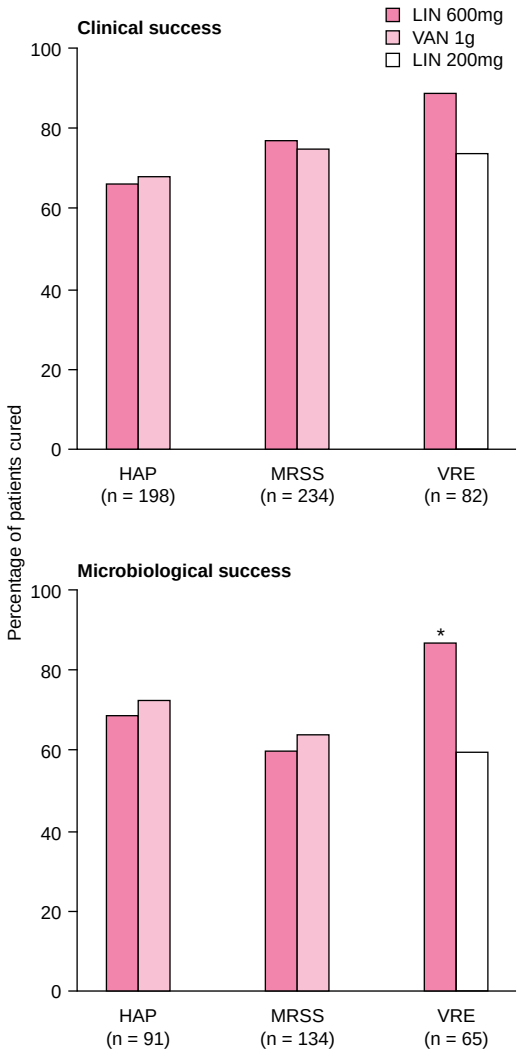


Fig. 5. Clinical and microbiological success rates in patients receiving intravenous (± oral treatment in MRSS) linezolid (LIN) in 3 studies. Patients with HAP or infections of MRSS were randomised to receive (7 to 21 and 7 to 28 days' treatment, respectively) twice daily LIN 600mg or vancomycin (VAN) 1g. The efficacy of 7 to 28 days' twice daily LIN 200 and 600mg was compared in patients with VRE infections.[52,53] Data for clinically and microbiologically evaluable patients are presented. **HAP** = hospital-acquired pneumonia; **MRSS** = methicillin-resistant staphylococcal species; **VRE** = vancomycin-resistant enterococci. * p = 0.015 *vs* LIN 200mg.

tant enterococcal infections (positive cultures of urine, wound, abscess, respiratory secretions, or peritoneal or pleural fluid). The higher dosage was significantly (p = 0.015) more effective in producing microbiological cure (85.7 *vs* 58.6%).[52,53]

Compassionate Use

In the US, linezolid is available for compassionate use in patients (aged >28 days) with significant infection caused by a cultured Gram-positive organism not able to be treated otherwise (i.e. due to resistance or poor tolerability of other therapies). Patients received twice daily intravenous or oral dosages of linezolid 600mg, or 10 mg/kg/day in paediatric patients.

- As of October 1999, this programme had enrolled 596 patients with various infections, predominantly bacteraemia, and also including intra-abdominal abscesses and peritonitis, skin/soft tissue infections, osteomyelitis, and lower and upper respiratory tract infections. Overall, most infections (65.7%) were caused by vancomycin-resistant *E. faecium*; other causal organisms included methicillin-resistant *S. aureus* and *S. epidermidis* (17.4% and 2.3%, respectively) and vancomycin-resistant *E. faecalis* (3.7%). In bacteraemic patients (42.6% of those enrolled), 81.4% of infections were due to vancomycin-resistant *E. faecium*.[54,55]

- In patients for whom data are available, 75.3% and 74.5% achieved clinical and microbiological cure, respectively, at short term follow-up (7 to 10 days or 1 month after drug discontinuation).[54] In bacteraemic patients (42.1% in intensive care units, 54.4% on a general ward, 3.5% outpatients), treatment with linezolid produced 82.5% and 85.9% clinical and microbiological cure rates, respectively. Organisms were eradicated from the bloodstream by day 2 to 2.5 in 50% of patients, and by day 5 to 5.5 in 75%.[55]

- To date, 65 patients with neutropenia (87.7% with vancomycin-resistant *E. faecium* infections) have been treated in the compassionate use programme. Clinical and microbiological cure was achieved in 69.6 and 83.3% of patients, respec-

tively. The mean time to eradication in patients with microbiological cure was 3.3 days.[56]

• Development of resistance to linezolid has been reported in 2 patients during the compassionate use protocol. Patients received 4 or 6 weeks' treatment for *E. faecium* infection of complicated clinical course, were bacteraemic, and had long-standing indwelling devices that could not be removed. Initial MICs were 2 mg/L in both patients and final isolate MICs were 16 and 32 mg/L. With the exceptions of nitrofurantoin (6 of 6 isolates in patient 1 had intermediate susceptibility, 3 of 6 had intermediate susceptibility in patient 2) and chloramphenicol (3 of 6 susceptible in patient 1; 2 of 6 susceptible in patient 2), the isolates were resistant to every agent (n = 32) tested.[57]

4. Tolerability

• Linezolid was well tolerated after oral or intravenous administration of daily dosages up to 1250mg.[6,7,42] In volunteers, the most common adverse events were those involving the gastrointestinal tract. With the exception of tongue discoloration, these events had a similar incidence among linezolid- and placebo-treated individuals.[7]

• Tolerability data are available for >500 patients (with Gram-positive skin/soft tissue infections or who required hospitalisation for presumed pneumococcal pneumonia) who received daily dosages of intravenous/oral linezolid 750 or 1250mg for 5 to 14 days in open-label multicentre studies. Drug-related adverse events occurred in 32.7% of patients, were generally of mild to moderate intensity, resolved during continuous linezolid treatment, and were not dose-related. The most commonly occurring drug-related adverse events were nausea (5.4%), diarrhoea (5.2%), tongue discolouration (2.5%), oral monilia (2.3%), taste perversion (2.3%) and headache (2.3%). Adverse events necessitated study discontinuation in 3% of patients. Serious drug-related adverse events (one episode each of elevated liver enzymes, atrial fibrillation, worsening renal failure and pancreatitis) occurred in <1% of patients.[58]

• In the linezolid compassionate use protocol (results at September 1999), the overall adverse event rate was 36.3%. Events considered at least possibly related to drug treatment resulted in discontinuation of therapy in 11.4% of patients. The most commonly occurring of these events were thrombocytopenia (2.6%), dermatological reactions (2.5%), reduced haemoglobin/haematocrit (0.8%), leucopenia (0.8%) and allergy (0.3%). Serious adverse events considered to be possibly or probably related to linezolid treatment occurred in 5.6% of patients. At the end of therapy, linezolid was well tolerated by 77.8% of patients and a further 12.6% experienced some problems but continued with treatment.[54]

• *In vitro* studies have indicated that linezolid is a weak, competitive inhibitor of human monoamine oxidase (MAO).[59] However, no clinical evidence of adverse events due to MAO inhibition has been reported during linezolid treatment.[54,55,58]

5. Linezolid: Current Status

Linezolid is an oxazolidinone antibacterial agent that inhibits the initiation of translation and has activity against many Gram-positive organisms. Linezolid has shown efficacy in the treatment of skin/soft tissue infections, pneumonia and bacteraemia. In particular, linezolid is effective against infections caused by methicillin-resistant *S. aureus*, penicillin-resistant *S. pneumoniae* and vancomycin-resistant *E. faecium*.

References

1. Shinabarger D. Mechanism of action of the oxazolidinone antibacterial agents. Expert Opin Invest Drugs 1999; 8: 1195-202
2. Swaney SM, Aoki H, Ganoza MC, et al. The oxazolidinone linezolid inhibits initiation of protein synthesis in bacteria. Antimicrob Agents Chemother 1998; 42: 3251-5
3. Lin AH, Murray RW, Vidmar TJ, et al. The oxazolidinone eperezolid binds to the 50S ribosomal subunit and competes with binding of chloramphenicol and lincomycin. Antimicrob Agents Chemother 1997; 41: 2127-31
4. Shinabarger DL, Marotti KR, Murray RW, et al. Mechanism of action of oxazolidinones: effects of linezolid and eperezolid on translation reactions. Antimicrob Agents Chemother 1997; 41: 2132-6
5. Gemell CG, Ford CW. Expression of virulence factors by gram-positive cocci exposed to sub-MIC levels of linezolid. Proceedings of the 39th Interscience Conference on Antimicrobial

Agents and Chemotherapy; 1999 Sep 26-29; San Francisco, CA, B118
6. Stalker DJ, Wajszczuk CP, Batts DH. Linezolid safety, tolerance, and pharmacokinetics following oral dosing twice daily for 14.5 days [abstract]. 37th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1997 Sep 28; Toronto (ON), 23
7. Stalker DJ, Wajszczuk CP, Batts DH. Linezolid safety, tolerance, and pharmacokinetics after intravenous dosing twice daily for 7.5 days [abstract]. 37th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1997 Sep 28; Toronto (ON), 23-4
8. Biedenbach DJ, Jones RN. Disk diffusion test interpretive criteria and quality control recommendations for testing linezolid (U-100766) and eperezolid (U-100592) with commercially prepared reagents. J Clin Microbiol 1997; 35: 3198-202
9. Von Eiff C, Peters G. Comparative in-vitro activities of moxifloxacin, trovafloxacin, quinpristin/dalfopristin and linezolid against staphylococci. J Antimicrob Chemother 1999; 43: 569-73
10. Jones ME, Visser MR, Klootwijk M, et al. Comparative activities of clinafloxacin, grepafloxacin, levofloxacin, moxifloxacin, ofloxacin, sparfloxacin, and trovafloxacin and nonquinolones linozelid, quinupristin-dalfopristin, gentamicin, and vancomycin against clinical isolates of ciprofloxacin-resistant and -susceptible *Staphylococcus aureus* strains. Antimicrob Agents Chemother 1999; 43: 421-3
11. Spangler SK, Jacobs MR, Appelbaum PC. Activities of RPR 106972 (a new oral streptogramin), cefditoren (a new oral cephalosporin), two new oxazolidinones (U-100592 and U-100766), and other oral and parenteral agents against 203 penicillin-susceptible and -resistant pneumococci. Antimicrob Agents Chemother 1996; 40: 481-4
12. Zurenko GE, Yagi BH, Schaadt RD, et al. In vitro activities of U-100592 and U-100766, novel oxazolidinone antibacterial agents. Antimicrob Agents Chemother 1996; 40: 839-45
13. Eliopoulos GM, Wennersten CB, Gold HS. In vitro activities of new oxazolidinone antimicrobial agents against enterococci. Antimicrob Agents Chemother 1996; 40: 1745-7
14. Mason Jr EO, Lamberth LB, Kaplan SL. In vitro activities of oxazolidinones U-100592 and U-100766 against penicillin-resistant and cephalosporin-resistant strains of *Streptococcus pneumoniae*. Antimicrob Agents Chemother 1996; 40: 1039-40
15. deAzavedo JCS, Trpeski L, Pong-Porter S, et al. Activity of linezolid on antibiotic-resistant and -susceptible strains of *Streptococcus pneumoniae* collected from across Canada. Proceedings of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 27 Sep; San Francisco, E72
16. Noskin GA, Siddiqui F, Stosor V, et al. Successful treatment of persistent vancomycin-resistant *Enterococcus faecium* bacteremia with linezolid and gentamicin. Clin Infect Dis 1999; 28: 689-90
17. Brown BA, Ward SC, Mann L, et al. In vitro activity of linezolid against multiple species of Nocardia: a new drug of choice for a difficult disease? [abstract]. Proceedings of the 5th International Conference on the Macrolides, Azalides, Streptogramins, Ketolides and Oxazolidinones, 2000 Jan 26-28; Seville, 08.15
18. Salmon SA, Portis EL, Case CA. Minimum inhibitory concentration determinations for oxazolidinone antimicrobial agents and comparator agents against strains of *Rhodococcus equi* [abstract]. 38th Interscience Conference on Antimicrobial Agents and Chemotherapy 1998 Sep 24; San Diego (CA), 206
19. Schülin T, Wennersten CB, Ferraro MJ, et al. Susceptibilities of *Legionella* spp. to newer antimicrobials in vitro. Antimicrob Agents Chemother 1998; 42: 1520-3
20. Jones RN, Johnson DM, Erwin ME. In vitro antimicrobial activities and spectra of U-100592 and U-100766, two novel fluorinated oxazolidinones. Antimicrob Agents Chemother 1996; 40: 720-6
21. Hoppe JE. *In vitro* susceptibilities of *Bordetella pertussis* and *Bordetella parapertussis* to the novel oxazolidinones eperezolid (PNU-100592) and linezolid (PNU-100766). J Chemother 1999; 11: 220-1
22. Di Pentima MC, Mason Jr EO, Kaplan SL. In vitro antibiotic synergy against *Flavobacterium meningosepticum*: implications for therapeutic options. Clin Infect Dis 1998; 26: 1169-76
23. Goldstein EJC, Citron DM, Merriam CV. Linezolid activity compared to those of selected macrolides and other agents against aerobic and anaerobic pathogens isolated from soft tissue bite infections in humans. Antimicrob Agents Chemother 1999; 43: 1469-74
24. Edlund C, Oh H, Nord CE. In vitro activity of linezolid and eperezolid against anaerobic bacteria. Clin Microbiol Infect 1999; 5: 51-3
25. Jorgensen JH, McElmeel ML, Trippy CW. In vitro activities of the oxazolidinone antibiotics U-100592 and U-100766 against *Staphylococcus aureus* and coagulase negative Staphylococcus species. Antimicrob Agents Chemother 1997; 41: 465-7
26. Bostic GD, Perri MB, Thal LA, et al. Comparative in vitro and bactericidal activity of oxazolidinone antibiotics against multidrug-resistant enterococci. Diagn Microbiol Infect Dis 1998; 30: 109-12
27. Kaatz GW, Seo SM. In vitro activity of oxazolidinone compounds U100592 and U100766 versus *Staphylococcus aureus* and *Staphylococcus epidermidis* [abstract]. 35th Interscience Conference on Antimicrobial Agents and Chemotherapy 1995: 150
28. Schaadt RD, Batts DH, Daley-Yates PT, et al. Serum inhibitory titers and serum bactericidal titers for human subjects receiving multiple doses of the antibacterial oxazolidinones eperezolid and linezolid. Diagn Microbiol Infect Dis 1997; 28: 201-4
29. Tenover FC, Lancaster MV, Hill BC, et al. Characterization of staphylococci with reduced susceptibilities to vancomycin and other glycopeptides. J Clin Microbiol 1998; 36: 1020-7
30. Andes D, Van Ogtrop ML, Craig WA. Pharmacodynamic activity of a new oxazolidinone, Linezolid, in an animal infection model [abstract]. 38th Interscience Conference on Antimicrobial Agents and Chemotherapy 1998 Sep 24; San Diego, CA, 3
31. Ford CW, Hamel JC, Wilson DM, et al. In vivo activities of U-100592 and U-100766, novel oxazolidinone antimicrobial agents, against experimental bacterial infections. Antimicrob Agents Chemother 1996; 40: 1508-13
32. Piper KE, Rouse MS, Wilson WR, et al. Treatment of methicillin-sensitive *Staphylococcus aureus* experimental osteomyelitis with linezolid of cefazolin. Proceedings of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 Sep 28; San Francisco (CA), A131
33. Gehman MJ, Pitsakis PG, Mallela SV, et al. Linezolid (L) vs methicillin-resistant *Staphylococcus aureus* in experimental rat endocarditis [poster]. Proceedings of the 37th Annual

Meeting of the Infectious Diseases Society of America; 1999 Nov 18-21; Philadelphia, PA, 169
34. Buchanan L, Dileto-Fang C, Dailey C, et al. Antimicrobial effects of linezolid and vancomycin in experimental endocarditis [abstract]. Proceedings of the 37th Annual Meeting of the Infectious Diseases Society of America; 1999 Nov 18-21; Philadelphia (PA), 52
35. Gerber CM, Acosta F, Cottagnoud M, et al. Evaluation of linezolid against penicillin-sensitive and resistant pneumococci in the experimental meningitis model. Proceedings of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 Sep 28; San Fancisco (CA), B109
36. Pelton SI, Figueira M, Albut R, et al. Efficacy of linezolid in experimental otitis media. Antimicrob Agents Chemother 2000; 44: 654-7
37. Bryant AE, Stevens DL. Efficacy of U100766 or HMR3647 in experimental streptococcal myonecrosis [abstract]. Proceedings of the XIV Lancefield Society International Symposium on Streptococci and Streptococcal Diseases; 1999 Oct 11-15; Auckland
38. Cynamon MH, Klemens SP, Sharpe CA et al. Activities of several novel oxazolidinones against *Mycobacterium tuberculosis* in a murine model. Antimicrob Agents Chemother 1999; 43: 1189-91
39. Kaatz GW, Seo SM. In vitro activities of oxazolidinone compounds U100592 and U100766 against *Staphylococcus aureus* and *Staphylococcus epidermidis*. Antimicrob Agents Chemother 1996; 40: 799-801
40. Fines M, Leclercq R. Influence of mechanisms of resistance to antiobiotics that bind to the 50S ribosomal subunit on the activity of linezolid against gram-positive organisms. Proceedings of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 Sep 26-29; San Francisco (CA), C183
41. Welshman IR, Stalker DJ, Wajszczuk CP. Assessment of absolute bioavailability and evaluation of the effect of food on oral bioavailability of linezolid [abstract]. Antiinfect Drugs Chemother 1998; 16 Suppl. 1: 54
42. Pawsey SD, Daley-Yates PT, Wajszczuk CP. U-100766 safety, toleration and pharmacokinetics after oral and intravenous administration [abstract]. 1st European Congress on Chemotherapy 1996 May 14; Glasgow, F151
43. Wienkers LC, Wynalda MA, Feenstra KL, et al. In vitro metabolism of linezolid (PNU-100766): lack of induction or inhibition of cytochrome P450 enzymes and studies on the mechanism of formation of the major human metabolite, PNU-142586. Proceedings of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 Sep 26-29; San Francisco (CA), A68
44. Feenstra KL, Slatter JG, Stalker DJ, et al. Metabolism and excretion of the oxazolidinone antibiotic linezolid (PNU 100766) following oral administration of [^{14}C]PNU 100766 to healthy human volunteers [abstract]. 38th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1998 Sep 24; San Diego (CA), 17
45. Lasher Sisson T, Jungbluth GL, Stalker DJ, et al. Effect of age and gender on the single-dose pharmacokinetics of linezolid. Proceedings of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 Sep 27; San Francisco (CA), 1194
46. Stalker DJ, Kearns GL, James L, et al. Pharmacokinetics of linezolid in paediatric patients [abstract]. Clin Infect Dis 1998 Oct; 27: 1061
47. Brier ME, Stalker DJ, Aronoff GR, et al. Pharmacokinetics of linezolid in subjects with varying degrees of renal function and on dialysis [abstract]. J Invest Med 1998; 46: 276A
48. Hendershot PE, Jungbluth GL, Cammarata SK, et al. Pharmacokinetics of linezolid in patients with liver disease [abstract]. J Antimicrob Chemother 1999; 44 Suppl. A: 55
49. Lasher Sisson T, Jungbluth GL, Hopkins NK. A pharmacokinetic evaluation of concomitant administration of linezolid and aztreonam. J Clin Pharmacol 1999; 39: 1277-82
50. Cammarata SK, Hafkin B, Demke DM, et al. Efficacy of linezolid in skin and soft tissue infections [abstract]. Clin Microbiol Infect 1999; 5 Suppl. 3: 133
51. Cammarata SK, Hafkin B, Todd WM, et al. Efficacy of linezolid in community-acquired S. pneumoniae pneumonia. Am J Respir Crit Care Med 1999; 159 Suppl. Pt 2 (3): A844
52. Anon. First resistance to linezolid reported. Scrip Mag 1999 Oct 6; 2478: 23
53. Pharmacia & Upjohn, 1999. Data on file
54. Birmingham MC, Zimmer GS, Hafkin B, et al. Outcomes with linezolid from an ongoing compassionate use (CU) trial of patients (pts) with significant, resistant Gram-positive infections [abstract]. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 Nov 18-24; Buffalo (NY), 724
55. Birmingham MC, Zimmer GS, Flavin SM, et al. Results of treating bacteraemic patients with linezolid in a compassionate use trial for resistant, gram-positive infections [abstract]. Proceedings of the 37th Annual Meeting of the Infectious Diseases Society of America; 1999 Nov 18-21; Philadelphia (PA), 129
56. Smith PF, Birmingham MC, Zimmer GS, et al. Clinical outcomes (CO), safety and tolerance of linezolid (LZD) for resistant Gram-positive infections in patients with neutropenia (NPS) [abstract]. Clin Infect Dis 1999; 29: 960
57. Zurenko GE, Todd WM, Hafkin B, et al. Development of linezolid-resistant *Enterococcus faecium* in two compassionate use program patients treated with Linezolid [abstract]. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 Sep 24-2; San Francisco (CA), 118
58. Wilks NE, McConnell-Martin MA, Oliphant TH. Safety and tolerance of linezolid in phase II trials [abstract]. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 Sep 24-27; San Francisco (CA), 40
59. Martin JP, Herberg JT, Slatter JG, et al. Although a novel microtiter-plate assay demonstrates that linezolid (PNU-100766) is a weak, competitive (reversible) inhibitor of human monoamine oxidase(MAO A), no clinical evidence of MAO A inhibition in clinical trials has been observed [abstract]. 38th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1998 Sep 24; San Diego (CA), 27

Correspondence: *Delyth Clemett,* Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 10, New Zealand.
E-mail: demail@adis.co.nz