

ZYVOXTM (linezolid)

Brochure

for the

Anti-Infective Drug Products Advisory Committee Meeting

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Pharmacia and Upjohn

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Appendix A: Preclinical Summary**Appendix B: Study Synopses and Safety Data**

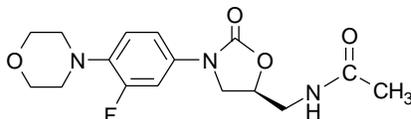
1 INTRODUCTION

Nosocomial infections caused by gram-positive bacteria have become increasingly prevalent. There have been significant increases in the percentages of infections caused by *Staphylococcus aureus*, coagulase-negative staphylococci, streptococci, and enterococci. These infections are of epidemiological and clinical importance because of their capacity to cause serious and life-threatening diseases in both healthy and debilitated individuals. In addition, antimicrobial resistance is a significant problem and is of increasing importance in community-acquired infections, particularly with gram-positive pathogens. The development of gram-positive agents with new mechanisms of action would provide an important option to current therapies for the treatment of serious infections and represents one approach to overcoming resistance.

The (*S*)-3-aryl-5-acetamidomethyl-2-oxazolidinones, first discovered and reported in 1987, are a novel class of totally synthetic antibacterial agents. Oxazolidinones have a number of intriguing attributes, including: (1) a unique mechanism of action that involves inhibition of protein synthesis at a very early stage, providing a lack of cross-resistance with existing antimicrobials; (2) a spectrum of activity that includes a number of important bacterial species; (3) activity in animal models of human infection when administered by either oral or parenteral routes; and (4) sufficient structural latitude to allow for activity and/or toxicity modifications.

The potential of this new antibacterial drug class stimulated an exploratory chemical analog program at Pharmacia & Upjohn. Linezolid (Figure 1) emerged as one of the compounds with the best overall combination of positive attributes, and therefore was advanced to phase I human trials for assessment of safety and pharmacokinetics. The safety and pharmacokinetic profile demonstrated by linezolid in the phase I program resulted in its advancement to phase II, and ultimately phase III clinical trials.

Figure 1. Linezolid (PNU-100766)



The linezolid clinical development program included investigations into the safety and effectiveness of the antibiotic in the treatment of community-acquired pneumonia, nosocomial pneumonia, uncomplicated and complicated skin and soft tissue infections, and infections due to methicillin-resistant *Staphylococcus* species and vancomycin-resistant enterococci (VRE). In addition, special population studies were conducted, including pediatric pneumonia and otitis media. The program goal was to establish linezolid as a

antibacterial agent for the treatment of infections caused by gram-positive organisms, including resistant strains. The positive results of the clinical investigations did indeed establish linezolid as a safe and effective antibacterial agent, resulting in New Drug Applications (NDAs) submitted by Pharmacia & Upjohn to the Food and Drug Administration (FDA) on 18 October 1999. NDAs were submitted for three linezolid formulations: an isotonic solution for intravenous infusion (ZYVOX IV Injection), a compressed tablet formulation (ZYVOX Tablets), and a powder for constitution into a suspension for oral administration (ZYVOX Oral Suspension). The linezolid clinical data are the same for all three formulations.

This brochure summarizes information pertinent to the assessment of the efficacy and safety of linezolid. Unless otherwise noted, all of the analyses presented in this brochure are derived from data contained in the NDA submissions.

2 PROPOSED THERAPEUTIC INDICATIONS AND DOSING RECOMMENDATIONS

As will be summarized in the remainder of this brochure, the results of the preclinical and clinical programs support the use of linezolid for the treatment of the following infections, when caused by susceptible strains of the designated microorganisms:

- **Nosocomial pneumonia**, including cases with concurrent bacteremia, caused by *Staphylococcus aureus* (methicillin-sensitive and –resistant strains) or *Streptococcus pneumoniae* (penicillin-sensitive and –resistant strains).
- **Community-acquired pneumonia**, including cases with concurrent bacteremia, caused by *S pneumoniae* (penicillin-sensitive and –resistant strains) or *S aureus* (methicillin-sensitive and –resistant strains).
- **Complicated skin and skin structure infections**, including cases with concurrent bacteremia, caused by *S aureus* (methicillin-sensitive and –resistant strains), *Staphylococcus epidermidis* (methicillin-sensitive and –resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*.
- **Uncomplicated skin and skin structure infections** caused by *S aureus* (methicillin-sensitive and –resistant strains), *S pyogenes*, or *S agalactiae*.
- **Vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium* infections**, including cases with concurrent bacteremia.

Combination therapy may be indicated if a concomitant gram-negative pathogen is documented or suspected.

All three formulations may be used as initial therapy. Patients who need to commence treatment on the parenteral formulation may be switched to either oral formulation when clinically indicated. In such circumstances, no dose adjustment is required, as linezolid has an oral bioavailability of approximately 100%.

Recommended durations of treatment and dosages for adults are shown in Table 1.

Table 1. Recommended Linezolid Dosage Guidelines for Adults

Infection†	Recommended Duration of Treatment (consecutive days)	Dosage and Route of Administration
Community-acquired pneumonia, including concurrent bacteremia	10 to 14	600 mg intravenous or oral‡ twice daily
Nosocomial pneumonia, including concurrent bacteremia		
Complicated skin and soft tissue infections, including concurrent bacteremia		
VRE infections, including concurrent bacteremia	14 to 28	
Uncomplicated skin and soft tissue infections	10 to 14	400 mg oral‡ twice daily

† Due to the designated pathogens.

‡ Oral dosing using either the tablet or oral suspension formulations.

Elderly Patients: No dose adjustment is necessary.

Patients with Impaired Renal Function: The pharmacokinetics of linezolid are not altered in patients with any degree of renal insufficiency. Therefore, dose adjustment for patients with renal insufficiency is not necessary. In patients undergoing dialysis, the dose should be given after a dialysis session, as hemodialysis is a source of elimination of linezolid (approximately 30% of a dose was eliminated in a 3-hour dialysis session beginning 3 hours after the dose of linezolid was administered).

The two primary metabolites of linezolid have been found to accumulate in the plasma of subjects with severe renal impairment or with end-stage renal disease who are being maintained on hemodialysis. This accumulation is higher than in subjects with normal or moderately impaired renal function. The safety of these two metabolites at accumulated levels has not been established in patients with severe renal impairment. Like linezolid, the two metabolites are dialyzable.

Patients with Impaired Hepatic Function: No dose adjustment is required.

Use During Pregnancy: The safety of linezolid for use in human pregnancy has not been established. Therefore, it should be used during pregnancy only if the potential benefit outweighs the potential risk.

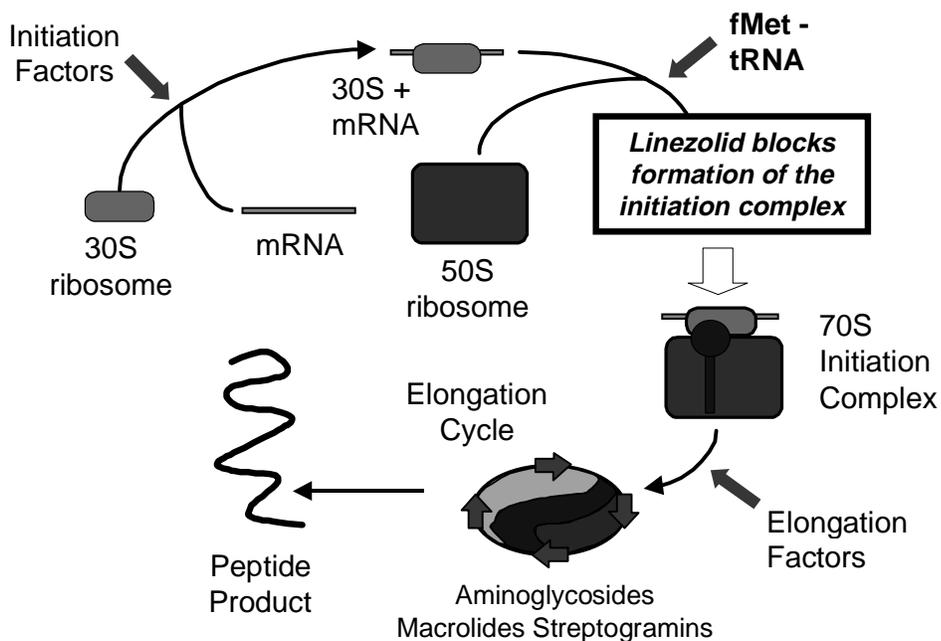
3 MICROBIOLOGY SUMMARY

3.1 Mechanism of Action

Mechanistic studies have been conducted with several different oxazolidinones (including linezolid), ribosomes from different sources, and a variety of assay methods. Conclusions regarding oxazolidinone mechanism of action in general, and linezolid mechanism of action in particular, can be summarized as follows:

- Linezolid targets an early event in translation involving the binding of N-formylmethionyl-tRNA to the ribosome (see Figure 2), a mechanism different from that of other translation inhibitors.
- Binding of linezolid to ribosomes involves a primary interaction with the 50S subunit, most likely within domain V of the 23S rRNA peptidyl transferase center, and a secondary interaction with the 30S subunit. Binding of linezolid to the 50S subunit prevents the binding of N-formylmethionyl-tRNA but does not inhibit peptidyl transferase activity.
- Elongation using polysomes or first peptide bond synthesis is not inhibited. Therefore, oxazolidinones are not classic peptidyl transferase inhibitors.

Figure 2. The Ribosome Cycle, Showing Point of Inhibition by Linezolid



3.2 In Vitro Spectrum and Potency

The in vitro evaluation of the spectrum and potency of linezolid against bacterial clinical isolates has been extensive. It includes the initial studies conducted by Pharmacia & Upjohn and numerous studies conducted in academic, clinical, and contract laboratories in both the US and Europe.

Linezolid demonstrates a primarily gram-positive spectrum of activity, inhibiting nearly all strains of staphylococci (including methicillin-resistant *S aureus* (MRSA) and methicillin-resistant *Staphylococcus epidermidis*), enterococci (including vancomycin-resistant strains), and pneumococci (including penicillin-intermediate and penicillin-resistant strains) at a concentration of 4 µg/mL or less. This compound also demonstrates significant activity against *Corynebacterium* spp, *Bacillus* spp, *Listeria monocytogenes*, *Staphylococcus* spp, *Streptococcus* spp, *Moraxella catarrhalis*, *Chlamydia pneumoniae*, and mycobacteria. Linezolid demonstrates a moderate level of activity (MIC₉₀s of 8 to 16 µg/mL) against *Haemophilus influenzae*, *Neisseria gonorrhoeae*, and *Legionella* spp. Linezolid is relatively inactive against the Enterobacteriaceae. Against anaerobic bacteria, linezolid demonstrates a significant level of in vitro activity. It is a potent inhibitor of gram-positive anaerobes (MIC range of 0.5 to 4 µg/mL), and also has significant activity against gram-negative anaerobes (eg, MICs of 2 to 8 µg/mL for *Bacteroides* spp). A summary of linezolid's activity against key target species is shown in Table 2.

The in vitro results from the linezolid phase III clinical program were compared with the larger Sentry* database with respect to the key species of *S aureus*, *S pneumoniae*, and enterococci. The results are displayed in Figure 3, Figure 4, and Figure 5, irrespective of the underlying resistances for other antibiotics. Overall, the MIC population distributions were comparable.

*The Sentry Program was established in 1997 to measure the predominant pathogens and antimicrobial resistance patterns of nosocomial and community-acquired infections over a broad network of sentinel hospitals in the United States, Canada, South America, and Europe. In 1998, linezolid was added to the Sentry test panel. Briefly, at each institution patient isolates were characterized using standard methods, and MICs were determined using a standard broth microdilution method according to the recommendations of the National Committee for Clinical Laboratory Standards (NCCLS).

Table 2. Summary of Weighted Average MIC₅₀ and MIC₉₀ Values for Linezolid and Key Target Species

Organism	US Studies				European Studies			
	Total Number		Weighted Average		Total Number		Weighted Average	
	Studies	Isolates	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	Studies	Isolates	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)
<i>S aureus</i> (oxacillin/methicillin-susceptible)	9	916	1.8	2.5	11	488	1.4	1.7
<i>S aureus</i> (oxacillin/methicillin-resistant)	9	973	1.7	3.2	10	535	1.4	1.7
<i>S aureus</i> (miscellaneous isolates)	2	125	1.8	3.4	-	-	-	-
<i>S epidermidis</i> (oxacillin/methicillin-susceptible)	6	183	1.3	2.4	2	87	1.0	1.0
<i>S epidermidis</i> (oxacillin/methicillin-resistant)	6	216	1.2	2.1	2	54	1.5	2.9
<i>S epidermidis</i> (mixed resistance)	-	-	-	-	4	239	≤0.6	≤0.6
<i>S haemolyticus</i>	2	20	0.8	1.0	2	78	1.0	1.2
Coagulase-negative staphylococci (mixed resistance)	4	321	1.3	1.9	5	269	0.9	1.6
<i>E faecalis</i> (vancomycin-susceptible)	4	476	1.2	2.0	5	402	1.1	1.3
<i>E faecalis</i> (vancomycin-resistant)	7	148	1.7	3.1	3	141	≤1.7	≤1.7
<i>E faecium</i> (vancomycin-susceptible)	4	68	1.9	2.0	2	57	1.2	1.2
<i>E faecium</i> (vancomycin-resistant)	6	252	1.3	2.4	2	29	1.3	1.3
<i>E faecium</i> (multiply-resistant)	3	118	2.4	2.4	4	180	1.7	1.9
<i>S agalactiae</i> /Group B Streptococcus	2	164	1.9	2.0	2	65	1.2	1.2
<i>S pneumoniae</i> (penicillin-susceptible)	5	303	0.6	1.0	5	229	1.2	1.6
<i>S pneumoniae</i> (penicillin-intermediate)	4	242	0.6	1.0	4	122	1.5	2.0
<i>S pneumoniae</i> (penicillin-resistant)	6	266	0.6	0.9	5	252	1.0	1.6
<i>S pneumoniae</i> (mixed resistance)	3	432	1.0	1.9	1	113	0.3	0.5
<i>S pyogenes</i>	3	182	1.1	2.2	3	103	1.8	1.8
<i>H influenzae</i>	2	19	12.2	16.0	-	-	-	-
<i>M catarrhalis</i>	3	33	5.3	6.8	-	-	-	-

Figure 3. Comparison of Sentry and Phase III Data: *S aureus*

Staphylococcus aureus, Total No. = 5868 (Sentry: 4498; Phase III: 1370)

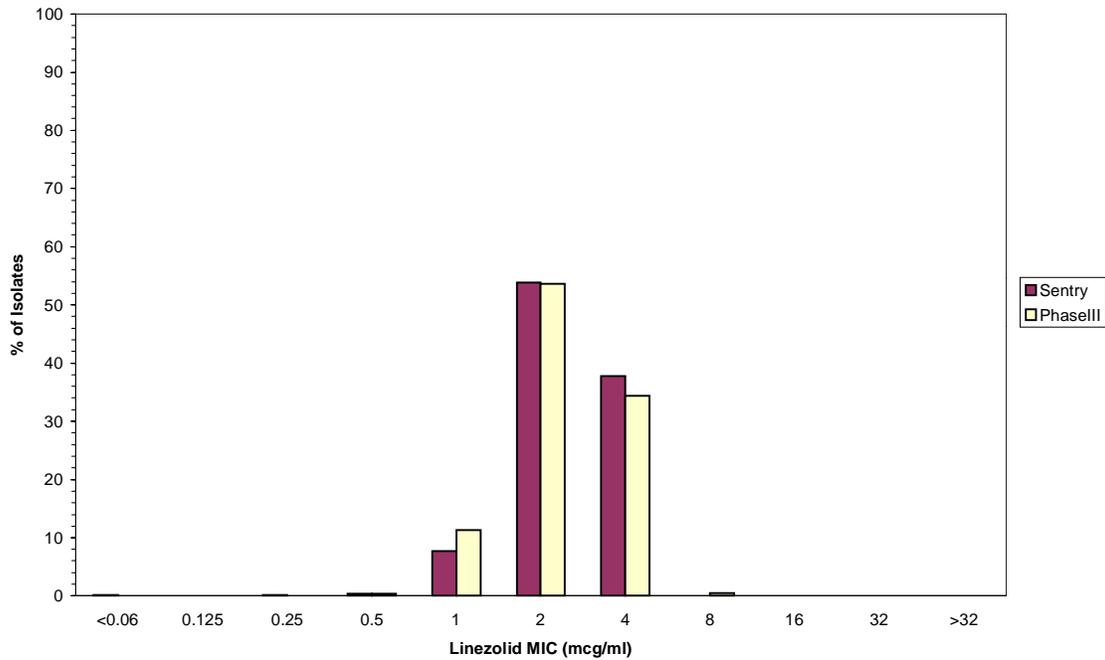


Figure 4. Comparison of Sentry and Phase III Data: *S pneumoniae*

Streptococcus pneumoniae, Total No. = 664 (Sentry: 318; Phase III: 346)

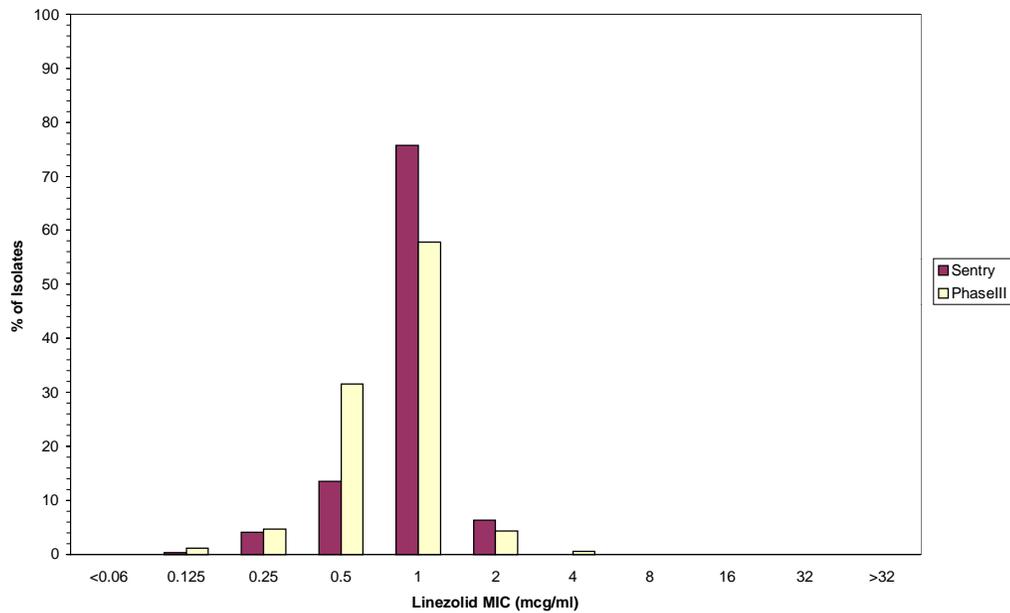
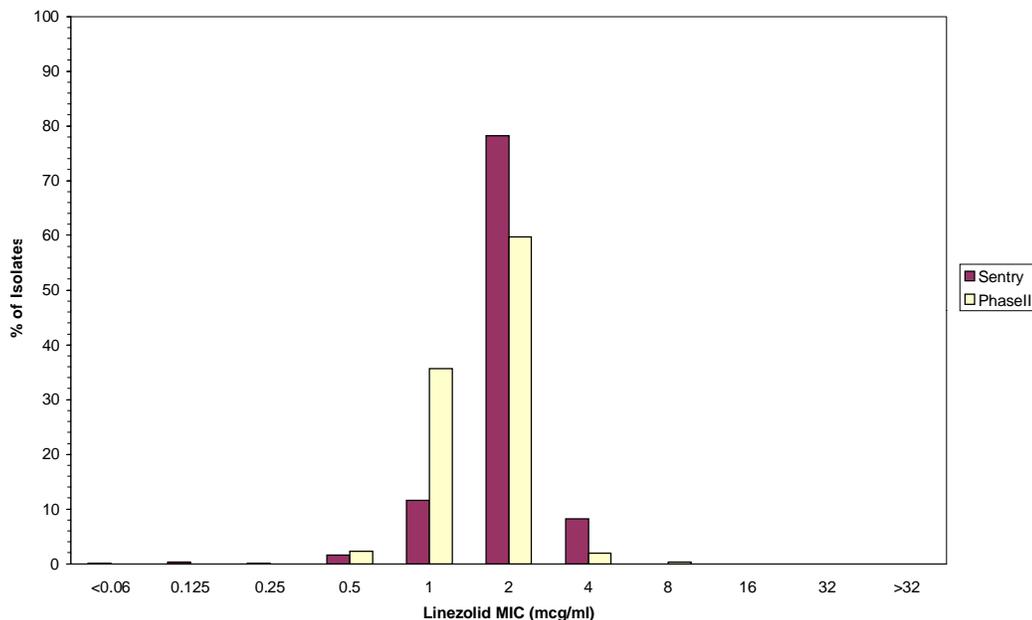


Figure 5. Comparison of Sentry and Phase III Data: Enterococci

Enterococci, Total No. = 1720 (Sentry: 1417; Phase III: 303)



In vitro minimal bactericidal concentration and time-kill assessments have demonstrated that while linezolid exposure results in a significant amount of bacterial killing in most instances, for staphylococci and enterococci it does not satisfy the conventional definitions for a bactericidal agent. For many species of streptococci (including pneumococci), as well as some species of anaerobic bacteria, linezolid exerts a bactericidal effect. Time-kill assays demonstrated \log_{10} cfu/mL reductions in the range of 2.9 to >4.1 for pneumococci (n=5), 0.1 to >2.9 for staphylococci (n=26^{*}), and 0 to 1.6 for enterococci (n=16[†]). However, the demonstrated efficacy of linezolid in a staphylococcal rabbit endocarditis model, and in an enterococcal bacteremia model in neutropenic mice (both described in section 3.3), indicates that in vitro assays do not fully predict the agent's in vivo activity.

Since some antimicrobial agents are known to penetrate host cells or may even be accumulated in certain cell types, the accumulation of linezolid by human neutrophils, human peripheral blood mononuclear cells, or murine J744A cells was evaluated. Linezolid was able to penetrate all three cell types but was not accumulated against a concentration gradient. Linezolid, at sub-MIC levels (1/2-, 1/4-, 1/8-MIC) was able to impair the in vitro

* 16 strains yielding >1 \log_{10} cfu/mL reduction, 6 strains yielding > 2 \log_{10} cfu/mL reduction.

† 15 of 16 strains yielding reductions of less than 1 \log_{10} cfu/mL.

expression of certain soluble and structural virulence factors of *S aureus* and *S pyogenes*. Linezolid significantly inhibited virulence factor expression as measured by a decrease in α -hemolysin, δ -hemolysin, and coagulase in *S aureus*. Linezolid significantly impaired streptolysin O and DNAase production in *S pyogenes*. Potentiation of opsonophagocytosis was demonstrated for both *S aureus* and *S pyogenes* when grown in sub-MIC levels of linezolid.

The in vitro postantibiotic effect (PAE) of linezolid was dependent upon both duration of exposure and drug concentration. Exposure of several gram-positive organisms to linezolid for 1 hour at 1-fold MIC produced a minimal PAE (0.3 to 0.5 h). Increasing the drug concentration to 4-fold MIC while maintaining the exposure time at 1 hour generally resulted in a significant increase in PAE (0.6 to 1.1 h). Increasing both the exposure period (to 2 hours) and the drug concentration (to 4-fold MIC) resulted in further increases in the duration of the PAE (1.7 to 2.0 h), producing an effect comparable to that seen for ciprofloxacin. The PAE of linezolid was also assessed in an animal model for *S aureus* (3.7 to 3.9 h) and *S pneumoniae* (3.6 to 3.8 h), or approximately 2-fold longer than that measured in vitro. The demonstration that linezolid produces serum levels in humans well in excess of the MICs of susceptible organisms indicates that the full PAE of linezolid (as measured in vitro and in vivo) should be realized in clinical practice. However, it should be noted that the pharmacokinetic/pharmacodynamic profile of linezolid does not depend upon PAE as justification for the twice daily dosing interval.

Purulent infections remain a challenging problem, partly due to the suppressive effect of the suppurative environment on antimicrobial action. The activity of linezolid in whole pus was comparable to the results found in broth, indicating that pus has no influence on the activity of linezolid. Linezolid was stable in pus over an extended period of time and produced a bactericidal effect for *S aureus* after incubation for 168 hours.

Linezolid combined with other common antibacterial drugs produced primarily an additive/indifferent response when tested in vitro against multiple strains of staphylococci, pneumococci, enterococci, *Flavobacterium meningosepticum*, and enteric bacteria. Strain-specific examples of synergism and antagonism were also demonstrated, but at very low frequencies.

3.3 Animal Therapeutic Studies

The activity of linezolid was assessed in numerous animal models in studies conducted both by Pharmacia & Upjohn and by outside investigators. Both systemic and localized infection models were employed. In these studies, the predominant route of linezolid administration was oral; however, parenteral administration was employed in some specific instances. The selection of models was intended to support specific clinical claims being sought for linezolid. In addition, linezolid has been challenged in a variety of other models that are not associated with the current linezolid claims, but serve to profile the in vivo activity of the agent. Linezolid was highly efficacious in lethal mouse infection models of gram-positive infection, demonstrating activity against staphylococci, enterococci, and streptococci,

including strains resistant to key therapeutic agents. The compound was active in a neutropenic mouse pneumonitis model, demonstrating efficacy against all six *S pneumoniae* isolates tested, independent of their penicillin susceptibility. Linezolid demonstrated oral activity in mouse soft tissue infection models due to *S aureus*, *E faecalis*, and *Bacteriodes fragilis*, and was very effective in the treatment of Group A *Streptococcus*-induced necrotizing fasciitis. Linezolid was also efficacious in the treatment of a lethal vancomycin-resistant *E faecium* infection in neutropenic mice, a model refractory to nearly all antibiotics.

While in vitro assessments have defined linezolid as a bacteriostatic agent for *S aureus*, linezolid demonstrated excellent activity in the treatment of catheter-induced staphylococcal endocarditis in the rabbit, a model considered to require an in vivo bactericidal effect to achieve efficacy. Both linezolid and vancomycin significantly reduced bacterial vegetation counts compared with control. Valvular vegetations were culture-negative in a similar proportion of rabbits treated with vancomycin or linezolid, demonstrating that the efficacy of 5-day oral linezolid (50 or 75 mg/kg) was equal to that of intravenous vancomycin (25 mg/kg).

To test the efficacy of linezolid in the treatment of otitis media, the chinchilla model was chosen. In this model, oral linezolid achieved middle ear concentrations that were 80% of serum concentrations. Linezolid was efficacious in the treatment of otitis media due to *S pneumoniae*, but not *H influenzae*. Especially important was the finding that linezolid eradicated nasopharyngeal carriage.

The key pharmacodynamic relationship for linezolid with *S aureus* and *S pneumoniae*, as assessed in the mouse thigh infection model, is the amount of time the serum concentration exceeds the MIC. Efficacy was achieved when drug concentrations were maintained above the MIC for 40% of the dosing interval. The pharmacokinetic goal of 40% time above MIC was well within the pharmacokinetic profile of linezolid in humans.

When linezolid was combined in vivo with a variety of other antimicrobial agents (such as piperacillin/tazobactam, vancomycin, imipenem/cilastatin, rifampin, gentamicin, and aztreonam) for the treatment of monomicrobial or polymicrobial infections, no antagonistic interactions were detected. The overall interaction was one of additivity or indifference, supporting the use of linezolid in combination with these agents.

3.4 Assessment of Resistance

3.4.1 Cross-Resistance

Since linezolid is the first member of the class, it was impossible to assess cross-resistance to structurally related agents. It was felt that the most likely scenario for cross-resistance would occur with other agents that target bacterial protein synthesis, and specifically those agents that target the 50S ribosome. Isogenic pairs of strains, differing only by the presence or absence of a known resistance determinant (transconjugants or cured derivatives), and expressing both inducible and constitutive mechanisms, were evaluated for cross-resistance with linezolid. The spectrum of antimicrobial resistance determinants covered all of the

major classes of agents that target the ribosome, including chloramphenicol, fusidic acid, macrolides and related antibiotics, and tetracycline. No cross-resistance between linezolid and major inhibitors of protein synthesis was observed. In addition, in vitro susceptibility studies demonstrated that linezolid is not cross-resistant with other key agents for clinically significant pathogens, including methicillin or ciprofloxacin for staphylococci; vancomycin for enterococci; and penicillins, cephalosporins, lincosamides, and macrolides for pneumococci. Susceptibility (or resistance) to linezolid cannot be predicted from the susceptibility test result for any other marketed agent; therefore, specific susceptibility testing of linezolid (as the first agent in a new class of agents) is required.

3.4.2 Resistance Development

The linezolid spontaneous mutation frequency has been reported in the range of $<1 \times 10^{-9}$ to $<1 \times 10^{-11}$. In vitro, laboratory-derived linezolid-resistant mutants of *S aureus* and *E faecalis* were isolated using a spiral-gradient, serial-passage method. This technique is capable of capturing subtle changes in antibiotic susceptibility resulting from prolonged selective pressure from antibiotics. While this technique was extremely efficient in inducing resistance to ciprofloxacin and streptomycin among susceptible strains of *S aureus* and *E faecalis*, it was less efficient in inducing resistance to linezolid. Sequence analysis of the genomic ribosomal RNA genes of the laboratory-derived mutants demonstrated that resistance to linezolid was correlated with specific 23S rRNA mutations.

Three clinical case reports of enterococcal resistance development during linezolid treatment were reported at the 39th Interscience Conference of Antimicrobial Agents and Chemotherapy (ICAAC); two of the three isolates were available for analysis. Based on the laboratory-derived mutants, and the two analyzed clinical case reports, resistance to linezolid appears to be mediated by previously undescribed mutations in the 23S rRNA of the 50S ribosomal subunit (other mechanisms have not been excluded, however). Transversions of guanine to uracil (G2447U or G2576U) in the 23S rRNA apparently confer resistance by altering the ribosome's affinity for linezolid. The MICs of resistant organisms appear to increase incrementally, suggesting that serial accumulation of the G-to-U mutations, in multiple copies of the 23S rRNA gene, ultimately leads to full resistance. The presence of the G2576U mutation in the two clinical isolates also suggests that the in vitro experiments accurately predicted the mechanism of clinical resistance.

As of 31 December 1999, in the entire phase II/III linezolid clinical program (both completed and ongoing studies), linezolid resistance had developed in 15* clinical isolates of enterococci from two studies: nine from ongoing Study 25 (compassionate-use program) and six from Study 54A/54 (VRE; includes patients from completed Study 54A as well as from the extension Study 54).

* Includes the three isolates that were described at the 39th ICAAC meeting.

A total of 705 patients have been enrolled in the compassionate-use program, of whom 501 had enterococcal infections (VRE faecium = 442; VRE faecalis = 24; VRE other = 12; VRE unspiciated = 2; VSE faecium = 6; VSE faecalis = 13; VSE other = 2). Of the 501 patients with enterococcal infections, Pharmacia & Upjohn is aware of only nine resistant enterococcal isolates, yielding a resistance rate of 1.8%. The isolates had ≥ 4 -fold increases in MICs. All nine patients had received 600 mg of linezolid twice daily, and seven of the nine had infections which would not ordinarily be expected to respond to medical therapy alone (ie, infected prostheses (n = 4) and abdominal abscesses/enterocutaneous fistulae (n = 3)). Two other patients had persistent bacteremia.

A total of 331 patients have been enrolled in Study 54A/54, a randomized dose-comparison study. Pharmacia & Upjohn is aware of only six resistant isolates from this study, four from the 200-mg dose group and two from the 600-mg dose group. However, since the blind on extension Study 54 has not yet been broken, the exact numbers of patients who have received the 200- and 600-mg doses is not available. Assuming random assignment of patients into each treatment group, about 165 patients should have been enrolled in each dose group, yielding resistance rates of 2.4% in the 200-mg dose group and 1.2% in the 600-mg dose group. Of the two isolates in the 600-mg dose group, one patient had multiple undrained abdominal abscesses and the other was found to be colonized with a linezolid-resistant strain of *E faecium* after a 30-day course of therapy.

All but one of the 15 resistant isolates were *E faecium*. The remaining isolate was *E faecalis*, and it was recovered from a patient with a chronic draining surgical site infection (s/p femoral/popliteal bypass). Each linezolid-resistant isolate appears to have developed de novo.

The mean duration of therapy (\pm standard deviation) in patients who had received 600 mg of linezolid twice daily, and from whom resistant organisms had been recovered, was 32 ± 9.9 days (range 22 to 57 days). The patient who developed linezolid-resistant *E faecalis* had been treated for 57 days.

The initial isolates from the 15 patients were resistant to nearly all marketed antimicrobials but were susceptible to linezolid at baseline (MICs of 1 to 2 $\mu\text{g/mL}$). Subsequent isolates, however, had developed resistance to linezolid (defined as an MIC of $\geq 8 \mu\text{g/mL}$). In six isolates the MIC had increased to 8 $\mu\text{g/mL}$, in eight isolates the MIC had increased to 16 $\mu\text{g/mL}$, and in one isolate the MIC had increased to 32 $\mu\text{g/mL}$. As stated previously, the G2576U mutation previously described in laboratory-derived mutants has been documented in two of the these resistant clinical isolates. Sequence analysis of the remainder of the resistant strains is in progress.

Pharmacia & Upjohn recognizes that with the introduction of a new class of antibiotics, it will be important to monitor bacterial susceptibility. Accordingly, the activity of linezolid is being monitored in an ongoing global surveillance study. This study is targeted to be performed at more than 1500 hospitals and to include an analysis of more than 150,000 bacterial isolates, which will be tested against 14 antibiotics. The results of this study will allow linezolid susceptibility rates to be tracked and compared to other antibiotics.

3.5 Proposed MIC Breakpoints

The linezolid clinical program demonstrated the efficacy of the compound in pneumonia, skin and soft tissue infections, and VRE infections. Key target species included *S aureus* (methicillin-susceptible and -resistant strains), *E faecium* (vancomycin-susceptible and -resistant strains), *E faecalis* (vancomycin-susceptible and -resistant strains), *S pneumoniae* (penicillin-susceptible and -resistant strains), *Streptococcus agalactiae*, and *S pyogenes*.

Multicenter laboratory studies defined MIC quality control ranges as follows: *S aureus* ATCC 29213, 1 to 4 µg/mL; *E faecalis* ATCC 29212, 1 to 4 µg/mL; and *S pneumoniae* ATCC 49619, 0.50 to 2 µg/mL. Acceptable zone diameter ranges were defined as follows: *S aureus* ATCC 25923, 27 to 31 mm; and *S pneumoniae* ATCC 49619, 28 to 34 mm.

The provisional MIC susceptibility breakpoint defined by organism population distributions, pharmacokinetics, pharmacodynamics, and microbiological outcome in the human trials was ≤4 µg/mL for staphylococci, enterococci, *S pneumoniae*, and *Streptococcus* spp other than *S pneumoniae*. The provisional zone diameter susceptibility breakpoints were defined as ≥21 mm for staphylococci and enterococci, ≥24 mm for *S pneumoniae*, and ≥20 mm for *Streptococcus* spp other than *S pneumoniae*. Intermediate and Resistant categories for MIC and zone size were not defined due to the absence of a significant number of phase III Microbiological Evaluable patients with target pathogen MIC values of 8 µg/mL or greater. The rare isolate that yields a nonsusceptible lab result would require retesting, and if confirmed, submission to a reference laboratory.

4 NONCLINICAL PHARMACOLOGY, ADME, AND TOXICOLOGY SUMMARY

Linezolid was shown to have superior pharmacokinetic characteristics, and the nonclinical species were extensively exposed to linezolid and its metabolites. The pharmacokinetic behavior of linezolid was similar across nonclinical species, and, overall, mice, rats, and dogs were considered to be good models of the behavior of linezolid in humans. The dose-limiting toxicities of linezolid were well defined. In repeated-dose toxicity studies reversible hematopoietic and gastrointestinal effects were observed in rats and dogs, and reversible reproductive effects were observed in male rats. Linezolid and its metabolites were excreted in the milk of lactating rats and crossed the placenta in pregnant rats. No evidence of teratogenicity was seen, but effects on male fertility, mild fetal toxicity, and reproductive effects on the F1 generation were observed in rats. Linezolid showed no evidence of genotoxicity. Additionally, linezolid was shown to be a weak, reversible monoamine oxidase (MAO) inhibitor.

For a more detailed summary of the preclinical information, please see Appendix A.

5 SCOPE OF THE CLINICAL PROGRAM

5.1 Phase I Studies

Phase I studies elucidated linezolid pharmacokinetics in healthy subjects, in subjects with renal or hepatic impairment, and in studies stratified by age or sex. Bioavailability, MAO inhibitory (MAOI) assessments, and drug-drug interaction studies were also conducted. The scope of the phase I studies is summarized in Table 3.

Table 3. Completed Phase I Studies: Scope of Clinical Investigations

Study Category Protocol Numbers *	Types of Phase I Studies	Total Subjects	Type of Control
PK/dose ranging 1, 2, 3, 4, 15, 16, 18	Single & multiple doses, oral & IV dosing, three times daily vs twice daily regimens	170	Placebo
Metabolism/Excretion 13	Radiolabeled comparison of tablets & oral suspension	15	None
Bioavailability 7, 8, 43	Comparison of 4 formulations, effect of food on absorption, bioavailability of oral suspension	48	None
Special Populations 14, 21, 28, 47	Age/sex, renal/hepatic impairment, pediatric PK	125	None
MAOI Effects 12, 22, 23, 24, 27	Tyramine, pseudoephedrine, phenylpropanolamine, dextromethorphan	99	Placebo
Other Drug Interactions 19, 20, 44	Companion antibiotics (aztreonam, gentamicin), Warfarin	37	None
TOTAL PHASE I	23 STUDIES	494 SUBJECTS	

* All protocol numbers begin with the project code M/1260/00.

5.2 Phase II Studies

Data from the phase I studies were used to design and modify phase II studies that explored proof-of-concept and dose-ranging in patients with pneumonia, skin and soft tissue infections, and bacteremia. These studies led to the choice of dosing regimens used in phase III studies: 400 mg twice daily for uncomplicated skin and soft tissue infections and 600 mg twice daily for patients with community-acquired pneumonia, hospital-acquired pneumonia, complicated skin and soft tissue infections, and infections with associated bacteremia. The scope of the phase II studies is summarized in Table 4.

Table 4. Completed Phase II Studies: Scope of Clinical Investigations

Protocol Number * & Indication	LZD BID Dose	LZD Route	Control	No. Pts LZD	No. Pts Control	Total Patients
Dose-Finding Studies						
09-CAP	Low High †	IV-PO	None	62 116	None	178
10-SST	Low High †	IV-PO	None	148 191	None	339
11-Bacteremia	600 mg	IV-PO	None	164	None	164
26-Low-Dose SST	100 mg 200 mg	IV-PO	None	103 86	None	189
Compassionate Use Study						
25-Compassionate Use ‡	600 mg	IV-PO	None	230	None	230
Pediatric Studies						
45-Pediatric CAP	10 mg/kg	IV-OS	None	78	None	78
49-Pediatric Otitis Media	10 mg/kg	OS	None	65	None	65
Nasal/Fecal Carriage Studies						
29- <i>S aureus</i> Nasal Carriage	§	PO	Placebo	52	9	61
30-VRE Fecal Carriage	**	PO	Placebo	27	7	34
TOTAL PHASE II		9 STUDIES		1322	16	1338

* All protocol numbers begin with the project code M/1260/00.

† Low Dose = 250 mg three times daily or 375 mg twice daily. High Dose = 375 mg three times daily or 600/625 mg twice daily.

‡ Interim report for patients with data available as of the 30 June 1999 NDA cutoff date.

§ Six twice daily linezolid regimens were used: 200, 400, or 600 mg for either 3 or 5 days.

** Four twice daily linezolid regimens were used: 400 or 600 mg for either 3 or 5 days.

CAP = community-acquired pneumonia; SST = skin/soft tissue; VRE = vancomycin-resistant *Enterococcus* spp; IV = intravenous; PO = oral; OS = oral suspension; LZD = linezolid

5.3 Phase III Studies

The phase III program studied patients according to the epidemiology and severity of pneumonia or the complexity of skin infection. In addition, some of the phase III protocols were designed to collect data on infections caused by specific drug-resistant pathogens (eg, MRSA or VRE). A total of nine phase III studies were conducted, in which 4196 patients were enrolled and 2193 were treated with linezolid. The scope of the phase III studies is summarized in Table 5.

Table 5. Completed Phase III Studies: Scope of Clinical Investigations

Protocol Number * & Indication	LZD BID Dose	LZD Route	Control	No. Pts LZD	No. Pts Control	Total Patients
Pneumonia						
33-Inpatient CAP	600 mg	IV-PO	CRO-CPD	381	366	747
51-Outpatient CAP	600 mg	PO	CPD	274	266	540
48A-Inpatient HAP	600 mg	IV	VAN	203	193	396
SUBTOTAL				856	827	1683
Skin and Soft Tissue Infections						
39A-Uncomplicated SST	400 mg	PO	CLR	382	371	753
39-Uncomplicated SST	400 mg	PO	CLR	166	166	332
55-Complicated SST	600 mg	IV-PO	OX-DX	400	419	819
37-Complicated SST	600 mg	IV-PO	NAF-DX	2	2	4
SUBTOTAL				950	958	1908
Resistant Pathogens						
31-Methicillin-resistant <i>Staphylococcus</i> species	600 mg	IV-PO	VAN	240	220	460
54A-VRE	600 mg 200 mg	IV-PO	LZD	79 66	(LZD)	145
SUBTOTAL				385	220	605
TOTAL PHASE III				2193	2003	4196
				9 STUDIES		

* All protocol numbers begin with the project code M/1260/00.

CAP = community-acquired pneumonia; HAP = hospital-acquired (nosocomial) pneumonia; SST = skin/soft tissue; VRE = vancomycin-resistant *Enterococcus* species; BID = twice daily; IV = intravenous; PO = oral; CLR = clarithromycin; CRO = ceftriaxone; CPD = cefpodoxime; DX = dicloxacillin; LZD = linezolid; NAF = nafcillin; OX = oxacillin; VAN = vancomycin

6 PHARMACOKINETICS SUMMARY

6.1 Introduction

The pharmacokinetics of linezolid have been assessed in 431 healthy male and female volunteers in 23 clinical pharmacology studies following oral or intravenous dosing. About 250 subjects received one or more single doses of linezolid and about 175 subjects received multiple doses. Pharmacokinetic studies have been conducted to assess dose proportionality, metabolism and excretion, absolute bioavailability after oral dosing, the effect of food on bioavailability, the pharmacokinetics in special populations (such as subjects of various ages, and subjects with renal or hepatic impairment), and potential drug interactions. Linezolid is available in three formulations: an intravenous solution (2 mg/mL), tablets (400 and 600 mg strengths), and an oral suspension (20 mg/mL).

Linezolid concentrations were quantitated in human plasma, urine, sweat, saliva, and dialysate fluid by validated, sensitive, specific high-pressure liquid chromatographic methods. A validated, sensitive, and specific LC/MS/MS method was used to quantitate linezolid in samples with limited volumes of plasma and cerebrospinal fluid.

The proposed clinical dosing regimen is 400 or 600 mg of linezolid twice daily intravenously or orally. The following doses of linezolid have been studied as part of safety, tolerance, and pharmacokinetic studies: single oral doses of 50 to 500 mg; multiple oral doses of 100 to 750 mg given every 8 hours for up to 10 days; multiple oral doses of 125 to 625 mg given every 12 hours for 14 days; single intravenous doses (30-minute infusion) of 250 to 750 mg; multiple intravenous doses of 250 to 500 mg given every 8 hours for up to 7 days; and multiple intravenous doses of 500 and 625 mg given every 12 hours for 7 days.

6.2 Absorption, Distribution, Metabolism, and Excretion

A summary of the pharmacokinetic parameters of linezolid in healthy volunteers dosed every 12 hours either intravenously or orally is provided in Table 6. Pharmacokinetic steady state is achieved after two to four doses of linezolid. The average steady-state minimum plasma concentration (C_{min}) values were 3.1 and 6.2 $\mu\text{g/mL}$ for the 400- and 600-mg oral doses, respectively; the corresponding average maximum plasma concentration (C_{max}) values were 11.0 and 21.2 $\mu\text{g/mL}$, respectively. The time course of steady-state plasma concentration data for a 400- or 600-mg oral dose of linezolid is shown in Figure 6. After oral or intravenous administration, mean linezolid plasma concentrations exceed or approximate the MIC_{90} values (~ 4 mg/mL) for the susceptible pathogens throughout the 12-hour dosing interval for the 600-mg dose and for about 70% of the dosing interval for the 400-mg dose.

Table 6. Pharmacokinetic Parameters of Linezolid in Adult Subjects (Mean \pm SD, (Range))

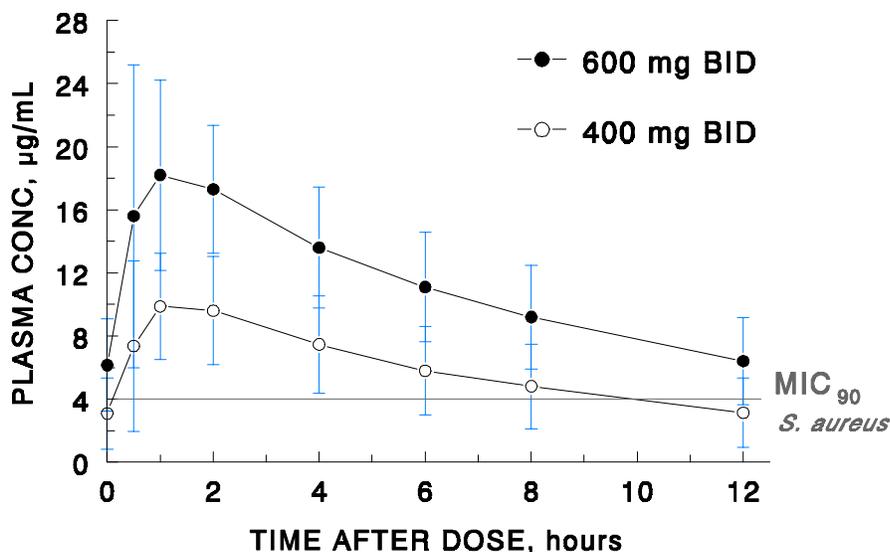
Dose of Linezolid	C _{max} , $\mu\text{g/mL}$	C _{min} , $\mu\text{g/mL}$	t _{max} , h	AUC* $\mu\text{g h/mL}$	t _{1/2} , h	CL, mL/min
400 mg Oral						
single dose [†] (N=12)	8.10 \pm 1.83 (5.4-10.3)	NA	1.52 \pm 1.01 (0.25-3.0)	55.1 \pm 25.0 (23-102)	5.2 \pm 1.5 (3.2-8.1)	146 \pm 67 (66-292)
twice-daily dose (N=16)	11.0 \pm 4.4 (5.9-24)	3.08 \pm 2.25 (0.5-7.1)	1.12 \pm 0.47 (0.5-2.0)	73.4 \pm 33.5 (34-152)	4.7 \pm 1.7 (2.6-7.9)	110 \pm 49 (44-198)
600 mg Oral						
single dose (N=16)	12.7 \pm 4.0 (6.6-21)	NA	1.28 \pm 0.66 (0.5-3.0)	91.4 \pm 39.3 (42-176)	4.3 \pm 1.7 (2.9-7.2)	127 \pm 48 (57-240)
twice-daily dose (N=16)	21.2 \pm 5.8 (10-32)	6.15 \pm 2.94 (2.0-12.3)	1.03 \pm 0.62 (0.5-2.0)	138 \pm 42 (68-209)	5.4 \pm 2.1 (2.7-9.6)	80 \pm 29 (48-146)
600 mg Oral Suspension						
single dose (N=16)	11.0 \pm 2.8 (6.7-16)	NA	0.97 \pm 0.88 (0.5-4.0)	80.8 \pm 35.1 (50-166)	4.6 \pm 1.7 (2.9-7.8)	141 \pm 45 (60-200)
600 mg IV[‡]						
single dose (N=6)	12.9 \pm 1.66 (10-14)	NA	0.50 \pm 0.10 (0.5-0.75)	80.2 \pm 33.3 (57-146)	4.4 \pm 2.4 (2.3-7.6)	138 \pm 39 (69-176)
twice-daily dose (N=6)	15.1 \pm 2.5 (13-19)	3.68 \pm 2.36 (1.1-3.5)	0.51 \pm 0.03 (0.5-0.58)	89.7 \pm 31.0 (55-142)	4.8 \pm 1.7 (3.1-7.8)	123 \pm 40 (70-183)

* AUC for single dose=AUC_{0- ∞} ; AUC for multiple doses=AUC₀₋₁₂.

[†] Data normalized from 375-mg dose.

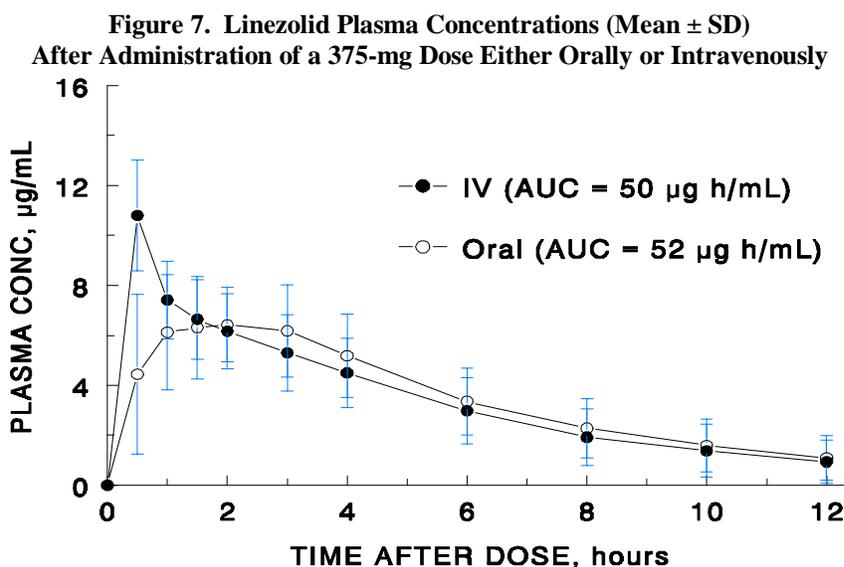
[‡] Data normalized from 625-mg dose.

NA=Not applicable

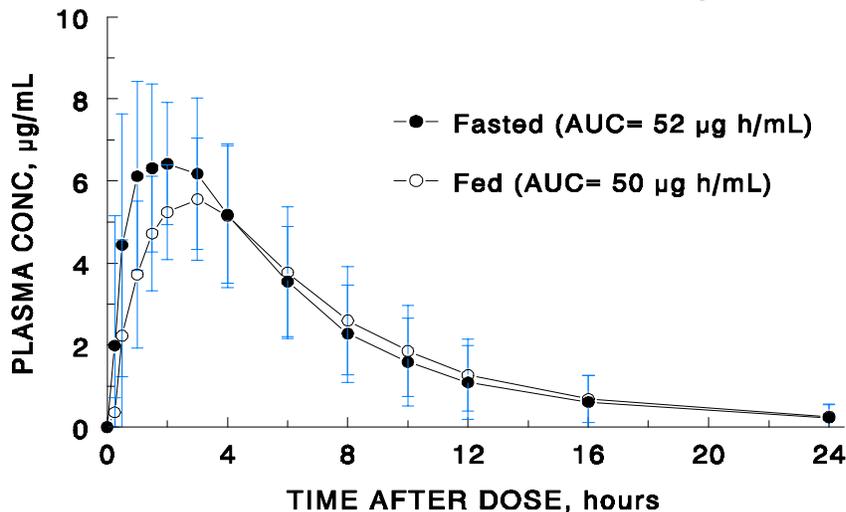
Figure 6. Linezolid Plasma Concentrations at Steady State (Mean \pm SD) After Oral Dosing

6.2.1 Absorption

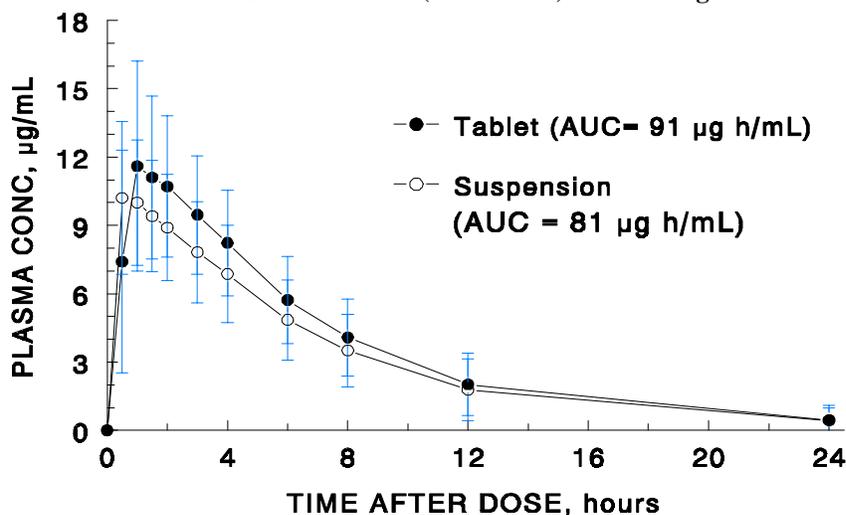
Linezolid is rapidly and extensively absorbed after oral dosing, with C_{max} usually achieved between 1 to 2 hours after dosing. Based on AUC (area under the concentration versus time curve), a marker of the overall extent of absorption, the absolute bioavailability of an oral dose is approximately 100%. Mean single-dose concentration-time profiles are shown for an intravenous and oral linezolid dose in Figure 7. The high oral bioavailability demonstrates that linezolid can be administered by either the intravenous or oral route without the need for a dosage adjustment.



Oral absorption of linezolid is not affected by food; only a slight decrease in C_{max} (about 18%) and a slightly later T_{max} (about 2 hours versus about 1.5 hours) were observed. Linezolid plasma concentrations after an oral dose taken with a meal or in a fasted state are shown in Figure 8. Meals were not restricted with regard to timing of doses in the phase III efficacy trials.

Figure 8. Linezolid Plasma Concentrations (Mean \pm SD) After a Single Oral 375-mg Dose

The oral suspension of linezolid is bioequivalent to the tablet based on AUC and C_{max} . The time course of plasma linezolid concentrations are shown in Figure 9 for the tablet and suspension formulations.

Figure 9. Linezolid Plasma Concentrations (Mean \pm SD) After a Single Oral 600-mg Dose

6.2.2 Distribution

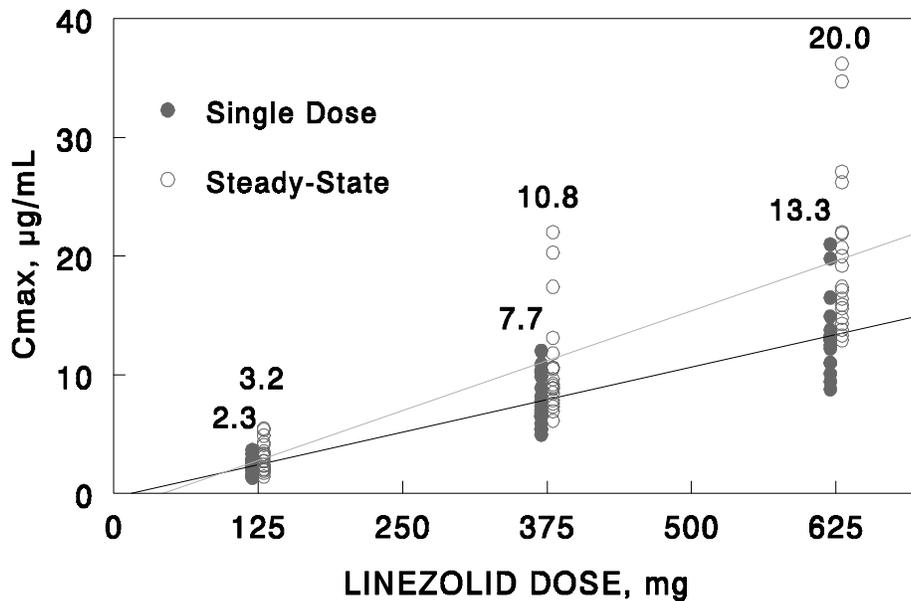
The plasma protein binding of linezolid is relatively low (31%), indicating that measurement of total plasma concentrations of linezolid is appropriate for calculating the pharmacokinetic

parameters. The distribution of linezolid is approximately that of total body water, as the steady-state volume of distribution averaged 40 to 50 L. Consistent with this observation, fluid-to-plasma ratios of linezolid concentrations were 4.5:1, 0.55:1, 1.2:1, and 0.7:1 for lung epithelial lining fluid, sweat, saliva, and cerebrospinal fluid, respectively. The red blood cell-to-plasma ratio is about 0.7, suggesting a slight exclusion of linezolid from the cell.

6.2.3 Dose Proportionality

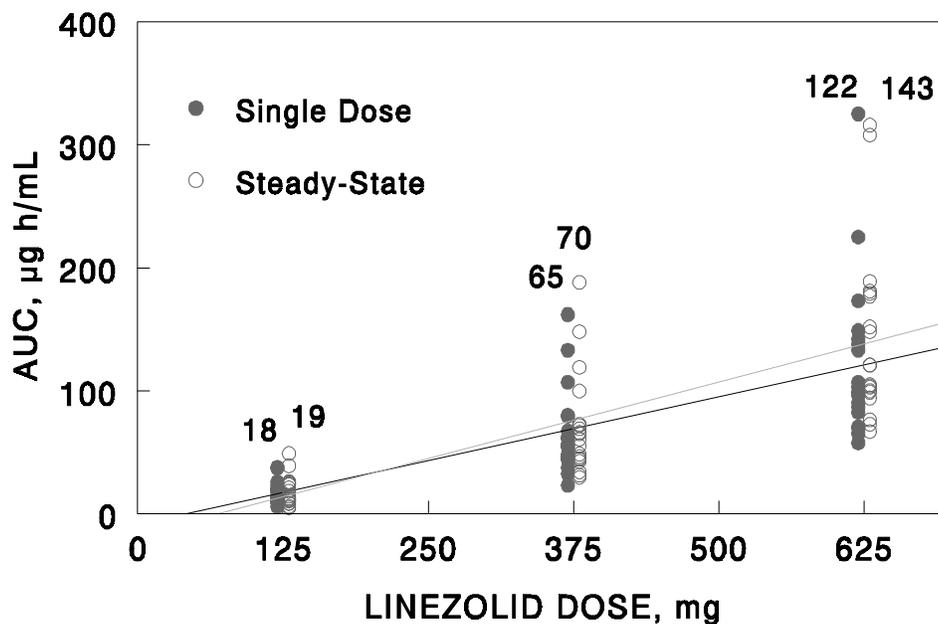
The dose proportionality of orally administered linezolid was assessed for single-dose and steady-state administration of 125, 375, and 625 mg in a crossover study. The results indicate that there is a small degree of disproportional increase with higher doses of linezolid (AUC and C_{max} increase slightly more than would be proportional to dose). The relationship between C_{max} and AUC after single and multiple doses of linezolid in individual subjects are shown in Figure 10 and Figure 11.

Figure 10. Individual Subject C_{max} Values After Oral Linezolid



Mean values are above each data column; lines = linear regression of the data

Figure 11. Individual Subject AUC Values After Oral Linezolid



Mean values are above each data column; lines = linear regression of the data

Total oral clearance among subjects (CL) is variable, as evidenced by a coefficient of variation of about 40%. CL for the 625-mg dose is about 30% lower than would be predicted from the 125-mg dose. The slight decrease in CL was accounted for by small decreases in both renal (CL_R) and nonrenal (CL_{NR}) clearance. The degree of disproportional pharmacokinetics is small relative to the overall variability among subjects, and clearance is relatively constant within a subject between a 400- and 600-mg dose, such that dose adjustments in the clinical use of linezolid are not considered necessary.

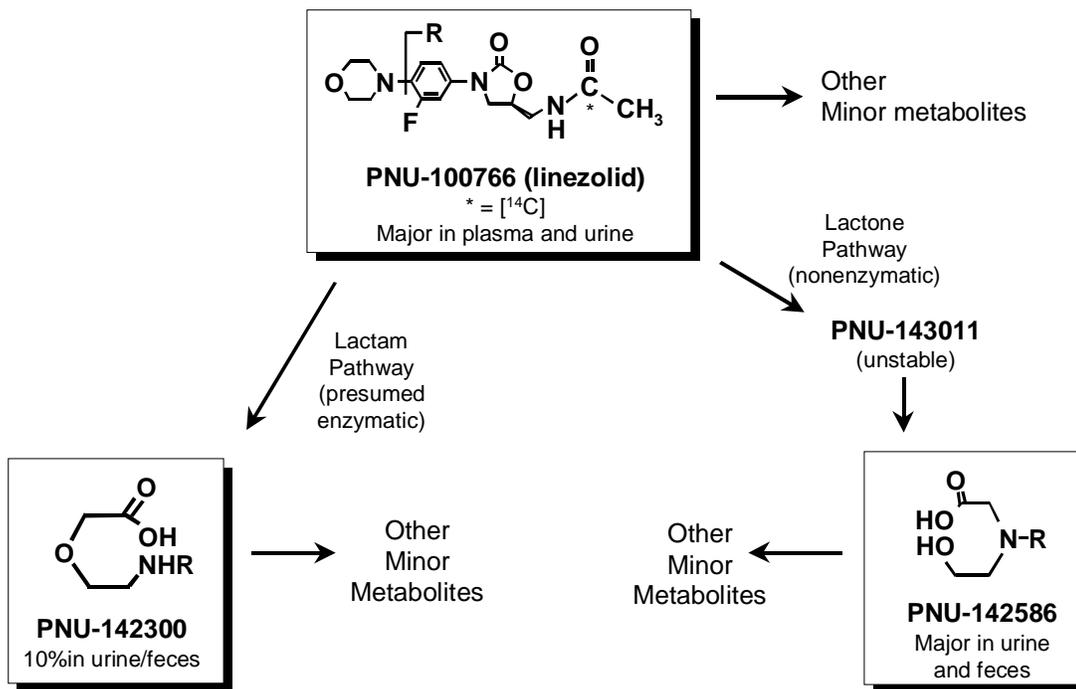
6.2.4 Metabolism

Linezolid circulates mainly as parent drug. Under steady-state conditions, plasma concentrations of the most abundant metabolite account for only 20% to 30% of the linezolid AUC, indicating that systemic exposure of patients to linezolid will exceed that of its metabolites. The metabolites do not have significant antibacterial activity.

There are three main pathways in the clearance of linezolid: excretion of intact linezolid in urine, and two distinct nonrenal pathways that form metabolites PNU-142300 and PNU-142586, respectively (Figure 12). Of these two major nonrenal elimination pathways, PNU-142300 represents a relatively constant and low 9% to 11% of dose. In vitro studies on the possible roles of the major oxidases involved in drug metabolism (P450, FMO and MAO), showed that formation of the major metabolite, PNU-142586, is not mediated by major human isoforms of these enzymes. In vitro studies using human liver microsomes also showed that the formation of PNU-142586 is initiated by a chemical oxidation that is a

nonenzymatic (noncatalytic) process. The enzymes or oxidants that contribute to PNU-142586 formation *in vivo* have not been elucidated.

Figure 12. Metabolic Pathways for Linezolid in Mouse, Rat, Dog, and Human



6.2.5 Excretion

After single or multiple intravenous doses, the total systemic clearance (CL) of linezolid was approximately 100 to 200 mL/min. Renal clearance (CL_R) averaged about 30 to 50 mL/min, which suggests net tubular reabsorption. The nonrenal clearance, calculated as the difference between CL and CL_R , averaged about 70 to 150 mL/min. The elimination half-life averaged from 5 to 7 hours. The absorption, metabolism, and excretion of a 500-mg dose of ^{14}C -linezolid (100 μCi) was assessed under single- and multiple-dose conditions. Mass balance measurements accounted for approximately 94% of the dose in urine and feces. Approximately 35% of the dose was accounted for as parent drug in the urine, and approximately 50% of the dose was accounted for as the two major metabolites in the urine (approximately 40% as PNU-142586 and 10% as PNU-142300). Approximately 10% of the dose was found as the two major metabolites in the feces.

6.3 Linezolid Pharmacokinetics in Special Populations

6.3.1 Pediatric Subjects

The pharmacokinetic parameters of linezolid in pediatric patients is discussed in section 15.2.

6.3.2 Age and Sex

The effects of age and sex on the pharmacokinetics of linezolid were assessed in a study of 6 elderly males (ages 65-75 years; mean = 70 years), 8 elderly females (ages 65-75 years; mean = 70 years), 8 young males (ages 21-38 years; mean = 29 years), and 7 young females (ages 21-38 years; mean = 30 years). The pharmacokinetics of linezolid were determined for each subject after receiving a single, 600-mg, oral dose (see Table 7). Except for renal clearance, which was correlated with creatinine clearance, there were no significant differences in pharmacokinetic parameters between the young and elderly groups. Females had approximately a 20% lower weight-adjusted clearance and volume of distribution of linezolid than males. Both groups had a similar half-life. A dosing adjustment based on sex is not warranted due to the wide range of linezolid concentrations that are well tolerated and the small difference in disposition between males and females.

Table 7. Linezolid Pharmacokinetic Parameters in Young and Elderly Males and Females (mean ± SD)

Parameter	Young Males	Elderly Males	Young Females	Elderly Females
Subject Age, years	30 ± 7	70 ± 3	30 ± 6	70 ± 3
C _{max} , µg/mL	12 ± 2	12 ± 3	16 ± 1	16 ± 2
T _{max} , h	1.0 ± 0.5	1.2 ± 0.9	1.4 ± 0.5	1.4 ± 0.7
AUC, µg h/mL	80 ± 18	74 ± 16	128 ± 29	125 ± 59
Total CL, mL/min/kg	1.7 ± 0.3	1.6 ± 0.4	1.3 ± 0.3	1.3 ± 0.4
Half-life, h	5.3 ± 1.7	4.6 ± 1.3	4.8 ± 1.5	5.3 ± 2.2

6.3.3 Renal Impairment

Linezolid pharmacokinetics were evaluated in patients with varying degrees of renal function. These groups, as defined by creatinine clearance (CL_{Cr}) were CL_{Cr} >80 mL/min (normal), CL_{Cr} 30-79 mL/min (moderate impairment), CL_{Cr} 10-29 mL/min (severe impairment), and CL_{Cr} <10 mL/min (hemodialysis patients). Linezolid plasma concentrations were similar regardless of renal function (see Figure 13). Total clearance of linezolid did not change as a function of creatinine clearance, but renal clearance decreased with decreasing renal function (see Figure 14). These results indicate that no change in dose is necessary for patients with decreased renal function to achieve and maintain similar

concentrations of linezolid. The dose timing for linezolid, however, may need alteration to accommodate the hemodialysis schedule. Currently it is recommended that the dose of linezolid be given after a hemodialysis session, as about 30% of a dose may be removed during a 3-hour hemodialysis session.

The disposition of the two primary metabolites of linezolid (PNU-142300 and PNU-142586) has been evaluated in these subjects with varying degrees of renal impairment. Plasma and urine samples were assayed for the metabolites. These metabolites have been found to accumulate in plasma in the subjects with severe renal impairment and in those subjects with end stage renal disease maintained on hemodialysis. The accumulation in plasma in these two groups are higher than those with normal or moderately impaired renal function. In this single dose study, linezolid was well tolerated and there were no drug-related adverse effects reported; however, the safety of these two metabolites at accumulated levels during multiple dosing has not been established in patients with severe renal impairment.

Figure 13. Mean Linezolid Plasma Concentrations After a Single 600-mg Oral Dose in Patients with Varying Degrees of Renal Impairment

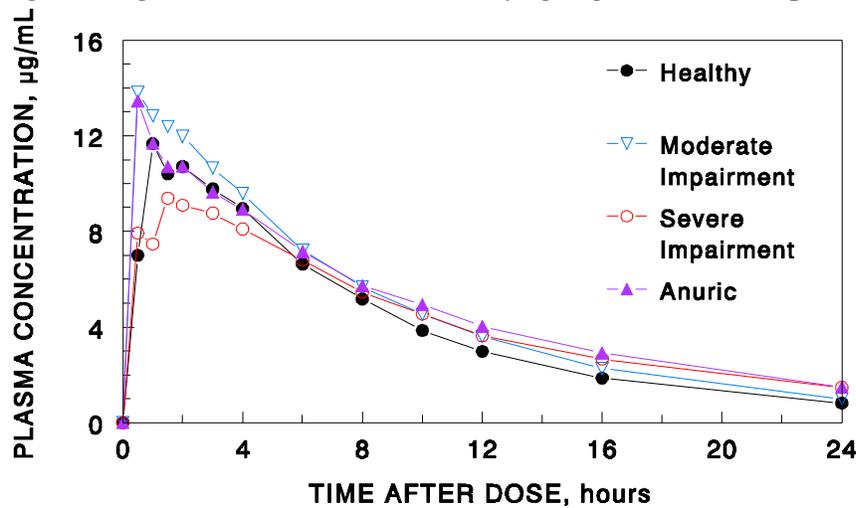
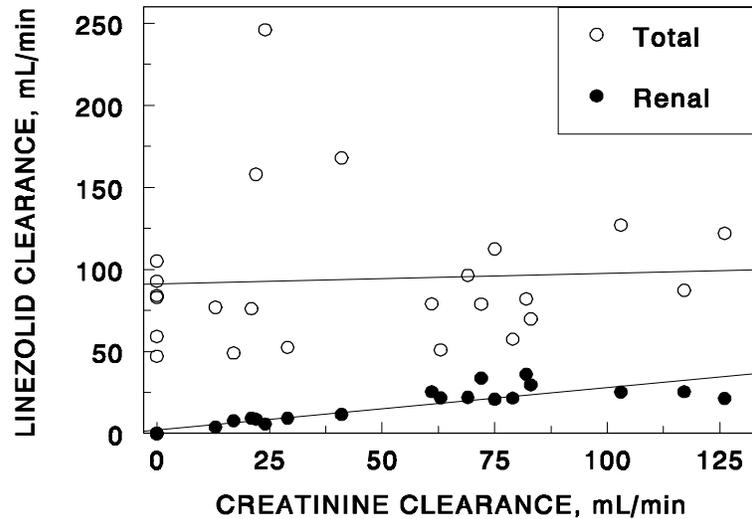


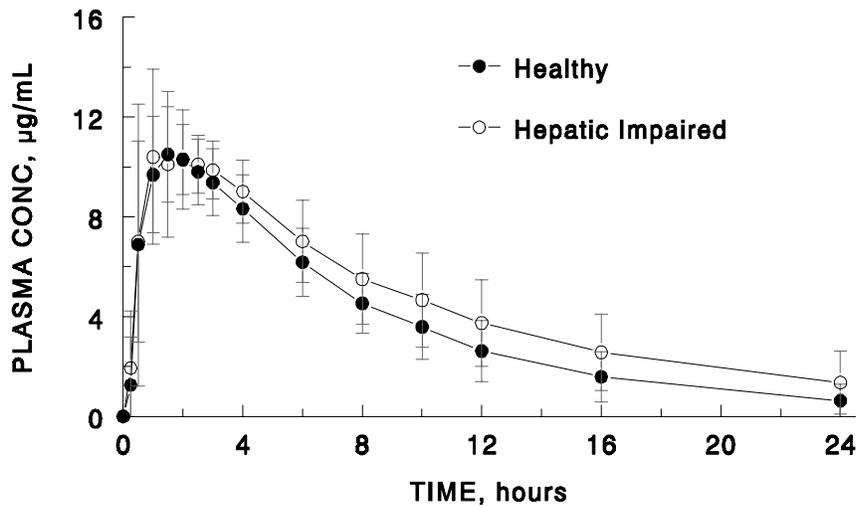
Figure 14. Individual Patient Total and Renal Clearance of Linezolid as a Function of Creatinine Clearance



6.3.4 Hepatic Impairment

A study was conducted to determine the effect of hepatic disease (biopsy-proven mild-to-moderate impairment by the Child-Pugh Score) on linezolid pharmacokinetics. Similar plasma linezolid concentrations were observed (see Figure 15), and no statistically significant differences in linezolid pharmacokinetic parameters were observed for patients with mild to moderate liver disease relative to healthy volunteers. No dosage adjustment of linezolid appears necessary in patients with mild to moderate hepatic impairment.

Figure 15. Linezolid Plasma Concentrations (Mean \pm SD) in Healthy Volunteers and Subjects with Hepatic Impairment After a 600-mg Oral Dose



6.4 Drug Interactions

6.4.1 Cytochrome P-450 Considerations

In vitro investigations into the effects of linezolid on human cytochrome P450 isoforms, and vice versa, were undertaken to identify any potential cytochrome P450-mediated drug interactions. In vitro metabolism studies using specific probe substrates and cDNA expressed human cytochrome P450 isoforms showed that linezolid did not inhibit the activities of clinically significant human cytochrome P450 isoforms CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. No evidence for induction of CYP2C9 was observed in vivo in humans, using warfarin as the probe. No meaningful induction of CYP1A, CYP2B, CYP2C, CYP2E, CYP3A, and CYP4A was observed in studies of rat livers from the 90-day oral toxicology study. Linezolid was not a substrate of any of the major human CYP450 isoforms. Therefore, clinically significant drug interactions mediated through inhibition or induction of major isoforms of CYP P450 are not expected.

6.4.2 Antibiotic Combinations

A second antibacterial agent, which provides gram-negative coverage, may be required in patients who have mixed gram-positive and gram-negative infections. Therefore, the pharmacokinetics of linezolid were evaluated when linezolid was administered in combination with aztreonam or gentamicin. The pharmacokinetics of linezolid were unaltered following concomitant intravenous administration of aztreonam or gentamicin.

6.4.3 Inhibition of Monoamine Oxidase Activity

Preclinical and in vitro studies have shown that linezolid is a weak, reversible inhibitor of the monoamine oxidase enzymes. Historically, the most common interactions of monoamine oxidase inhibiting (MAOI) agents may result in an exaggerated vasopressor response with sympathomimetic amines or tyramine, and the serotonin syndrome with serotonergic agents. The potential for linezolid to interact with these agents was characterized in four Phase I studies. These studies assessed concomitant administration of either tyramine, pseudoephedrine (PSE), phenylpropanolamine (PPA), or dextromethorphan with and without steady-state linezolid.

The study evaluating tyramine showed that, when linezolid was given at a dose of 625 mg twice daily, a very large dose (100 mg) of tyramine relative to common intake in foods was necessary to raise systolic blood pressure by 30 mmHg in healthy subjects (typical high-tyramine foods contain 1 to 2 mg tyramine per portion).

MAOI potential was further characterized in the three studies evaluating PSE, PPA, or dextromethorphan. These were randomized, double-blind, placebo-controlled studies in healthy volunteers. Details of design and treatments are summarized in Table 8.

Table 8. Study Design of Phase I MAOI Studies

Study Day	Treatment
Day 1	Two doses of active compound* or placebo 4 hours apart
Day 2	No medication administered
Day 3	Two doses of active compound or placebo (whichever was not administered on day 1) 4 hours apart
Days 4-6	Linezolid tablet 600 mg every 12 hours (to attain steady-state levels of linezolid)
Day 7	Linezolid tablet 600 mg every 12 hours Two doses of active compound or placebo 4 hours apart
Day 8	Linezolid tablet 600 mg every 12 hours
Day 9	Linezolid tablet 600 mg every 12 hours Two doses of active compound or placebo (whichever was not administered on day 7) 4 hours apart

* Active compound = pseudoephedrine (PSE) 60 mg, phenylpropanolamine (PPA) 25 mg, or dextromethorphan 20 mg. These represent the maximum labeled over-the-counter doses.

When dextromethorphan was administered with linezolid, no evidence of serotonin syndrome was observed, based on body temperature, cognitive function, sedation, blood pressure, or pulse. This indicates that no restrictions are necessary for coadministration of linezolid and dextromethorphan.

The results of the evaluation of linezolid with two sympathomimetic agents are summarized below. No effect on heart rate was observed. Slightly greater increases in blood pressure were observed when PSE or PPA was administered with linezolid than during individual administration of these agents; however, the blood pressure values remained within the normal range of daily activity. The mean maximum systolic blood pressure (mmHg) in the PSE study for the four treatments were placebo = 130 (range 101 to 152); PSE alone = 133 (range 104 to 161); linezolid alone = 132 (range 103 to 153); and linezolid with PSE = 151 (range 131 to 174). The mean maximum systolic blood pressure (mmHg) in the PPA study for the four treatments were placebo = 121 (range 103 to 158); PPA alone = 125 (range 106 to 139); linezolid alone = 120 (range 107 to 135); and linezolid with PPA = 147 (range 129 to 176). Increases were transient, and returned to baseline within 2 to 3 hours after maximum effect. More detailed study results regarding systolic and diastolic blood pressure and heart rate are presented in Table 9.

Table 9. Summary of Blood Pressure and Heart Rate Following Two Doses of Placebo (PBO) and Two Doses of PSE or PPA With and Without Steady-State Linezolid (LIN)

Treatment	Blood Pressure (mmHg)				Heart Rate (bpm)	
	Systolic		Diastolic		Max Change From t=0	Maximum Value
	Max Change From t=0	Maximum Value	Max Change From t=0	Maximum Value		
Linezolid/Pseudoephedrine Study (N = 13)						
PBO	11±7 (0 to 27)	130±16 (101 to 152)	10±4 (0 to 14)	72±9 (60 to 92)	7±4 (0 to 12)	71±10 (56 to 91)
PSE	18±9 (5 to 39)	133±17 (104 to 161)	10±5 (4 to 19)	73±8 (60 to 85)	11±7 (0 to 25)	75±12 (63 to 94)
LIN+PBO	15±9 (2 to 31)	132±16 (103 to 153)	10±4 (3 to 18)	72±6 (62 to 84)	8±6 (0 to 16)	73±8 (64 to 91)
LIN+PSE	32±10 (20 to 52)	151±15 (131 to 174)	17±8 (8 to 34)	80±8 (66 to 95)	11±7 (0 to 28)	75±8 (60 to 89)
Statistics (p-values)						
PSE vs PBO	NS	NS	NS	NS	NS	NS
LIN vs PBO	NS	NS	NS	NS	NS	NS
LIN+PSE vs PBO	0.0001	0.0015	0.0007	0.0163	NS	NS
LIN+PSE vs PSE	0.0001	0.0082	0.0023	0.0294	NS	NS
Linezolid/Phenylpropranolamine Study (N = 13)						
PBO	8±7 (0 to 26)	121±15 (103 to 158)	6±4 (0 to 16)	72±5 (65 to 78)	7±4 (0 to 13)	74±8 (60 to 91)
PPA	14±11 (0 to 40)	125±12 (106 to 139)	11±6 (3 to 22)	75±8 (65 to 91)	7±4 (0 to 18)	74±8 (58 to 93)
LIN+PBO	11±7 (2 to 22)	120±11 (107 to 135)	10±4 (3 to 17)	72±5 (64 to 81)	6±4 (0 to 15)	77±7 (69 to 89)
LIN+PPA	38±20 (18 to 79)	147±15 (129 to 176)	22±8 (11 to 39)	84±7 (77 to 96)	6±6 (0 to 16)	75±8 (64 to 89)
Statistics (p-values)						
PPA vs PBO	NS	NS	0.0248	NS	NS	NS
LIN vs PBO	NS	NS	NS	NS	NS	NS
LIN+PPA vs PBO	0.0001	0.0001	0.0001	0.0001	NS	NS
LIN+PPA vs PPA	0.0001	0.0001	0.0001	0.0003	NS	NS

PBO = placebo, PSE = pseudoephedrine, LIN = linezolid, PPA = phenylpropranolamine, NS = no significant difference. Data represent maximum increases from baseline and maximum values attained. All data show mean ± SD (range).

Overall, the preclinical and healthy volunteer clinical evaluations of linezolid and potential inhibition of MAO indicate that linezolid is a weak, reversible, competitive inhibitor of

MAO. No serotonin syndrome-like effects were observed. Linezolid alone does not elevate blood pressure or heart rate. Transient increases consistent with changes in normal blood pressure range were observed with large doses of tyramine or with concomitant sympathomimetic agents.

The proposed labeling specifically warns hypertensive patients to avoid sympathomimetics in conjunction with linezolid. Normotensive patients have negligible risk of significant blood pressure elevations with tyramine containing foods or with over-the-counter sympathomimetic agents.

6.5 Conclusions

Data from the pharmacokinetic studies show the following:

- The pharmacokinetic properties of linezolid assure that pharmacologically active concentrations will be maintained during the recommended dosing interval.
- The excellent oral bioavailability of linezolid eliminates the need for dose adjustment when changing from intravenous to oral therapy and allows initial treatment to be given orally.
- Oral therapy can utilize either a tablet or a suspension formulation.
- No dose adjustments are required based on sex, age, renal function, or hepatic function.
- Based on its weak and reversible MAOI properties, clinically significant interactions between linezolid and other drugs or tyramine-containing foods are unlikely.
- Linezolid is not a substrate of, nor an inducer or inhibitor of, clinically important cytochrome P450 enzymes.

7 DOSE-FINDING STUDIES

The phase I clinical program included studies to assess safety, tolerance, dose finding, and pharmacokinetics. Results of these studies demonstrated that 400 or 600 mg of linezolid, administered intravenously or orally, provides plasma linezolid concentrations in excess of the MICs for most gram-positive pathogens. Administration of linezolid 600 mg twice daily results in plasma concentrations in excess of 8 µg/mL for approximately 70% of the dosing interval and concentrations of approximately 4 µg/mL throughout the dosing interval. The phase I clinical studies showed that doses of up to 625 mg twice daily were well tolerated.

Three nonrandomized, uncontrolled phase II studies provided the foundation for dose selection of linezolid in phase III trials: Study 09 in community-acquired pneumonia, Study 10 in skin and soft tissue infections, and Study 11 in bacteremia. Studies 09 and 10 were nonrandomized, open-label, uncontrolled, dose-comparative studies comparing the efficacy and safety of multiple-dose regimens of linezolid administered intravenously (followed by

oral administration if clinically improved) in adults hospitalized with community-acquired pneumonia or skin and soft tissue infections, respectively. Linezolid was to be administered either twice daily or three times daily for up to 14 days. Patients were broadly grouped by dose regimen into two categories: high dose (1125 to 1250 mg/day) and low dose (750 mg/day).

Study 11 was a nonrandomized, open-label, uncontrolled study investigating the efficacy and safety of linezolid administered intravenously (followed by oral administration if clinically improved) in adults hospitalized with suspected gram-positive bacteremia. Patients were to receive 600-mg linezolid twice daily for up to 21 days. Aztreonam was allowed concomitantly for suspected or proven mixed infections due to gram-negative bacterial pathogens.

Data from the phase II dose-finding studies showed that linezolid was effective for gram-positive community-acquired pneumonia or skin and soft tissue infections. In the pneumonia study (study 09), patients had better clinical outcome when treated with high-dose linezolid than when treated with low-dose linezolid. In the skin and soft tissue infections study (study 10), clinical cure rates were comparable between dose groups.

These results led to the selection of the higher, 600-mg twice-daily dose in patients with more severe infections; in patients with less severe infections, such as outpatients with uncomplicated skin and soft tissue infections, the 400-mg twice-daily dose was selected.

8 STUDIES SUPPORTING THE EFFICACY OF LINEZOLID

8.1 Introduction

Seven comparator-controlled phase III studies (Studies 31, 33, 39A, 39, 48A, 51, 55), one dose-comparison phase III study (Study 54A), and two uncontrolled phase II studies (Studies 45 and 25) comprise the major dataset for the efficacy analyses. The pivotal studies for the pneumonia indications are Studies 51, 33, and 48A, and the pivotal studies for the skin and soft tissue infection indications are Studies 39A and 55.

There were two pathogen-driven studies. Study 54A was conducted in patients with infections due to VRE, and is the pivotal study for the VRE infection indication. Study 31 was conducted in patients with infections due to methicillin-resistant *Staphylococcus* species; it provides supportive data for complicated skin and soft tissue infections and nosocomial pneumonia.

Supportive data are also provided by one phase III comparator-controlled study (Study 39, uncomplicated skin and soft tissue infections) and by two phase II uncontrolled studies (Study 45, pediatric community-acquired pneumonia; and Study 25, a compassionate use study).

Appendix B contains study synopses for the seven comparator-controlled studies, as well as for the dose-comparison Study 54A.

Table 10 presents the studies from which data supporting the therapeutic indication of linezolid were drawn.

Table 10. Pivotal Phase III and Supportive Studies

Diagnosis	Comparator-Controlled		Dose-Comparison	Uncontrolled
	Pivotal	Supportive	Pivotal	Supportive
Pneumonia	33, 48A, 51	31		45
Community-acquired	33, 51			45
Nosocomial	48A	31		
Skin and Soft Tissue Infection	39A, 55	31, 39		
Uncomplicated	39A	39		
Complicated	55	31		
Enterococcal Infections			54A	25

CAP = Community-acquired pneumonia; SST = Skin and soft tissue

8.2 Methods

8.2.1 Definitions of Patient Populations

Analyses of efficacy data were performed for four different patient populations: Intent-to-Treat (ITT), modified Intent-to-Treat (MITT), Clinically Evaluable, and Microbiologically Evaluable. The ITT population included those patients who were randomized and received at least one dose of study medication. The MITT population consisted of those ITT patients who also had a pathogen isolated at baseline.

The Clinically Evaluable population consisted of all ITT patients, unless one or more of the following criteria for clinical nonevaluability applied:

- **Prior Antibiotic Usage** - Prior antibiotic therapy for longer than 24 hours, unless the patient was considered to have failed that regimen.
- **Insufficient Therapy** - Discontinuation of study medication for any reason other than lack of efficacy before the minimum dose requirement was met.
- **Noncompliance with Study Medication Regimen** - Taking less than 80% of the prescribed study medications or missing two or more consecutive doses through treatment day 7.
- **Concomitant Antibiotics** - Usage of a concomitant antibiotic, except as allowed by protocol.

- **No Post-Baseline Assessment** - No assessment (indeterminate was an assessment) in the Test-of-Cure (TOC) analysis window, unless the Investigator's Clinical Outcome was a failure at End of Treatment (EOT).
- **Disease-Specific Criteria** – Patients enrolled in the pneumonia studies (Studies 33, 51, 48A, and 45, and patients with pneumonia in Study 31) were considered clinically nonevaluable if they had a negative chest radiograph at baseline. Patients enrolled in Studies 31 and 54A were considered clinically nonevaluable if the source of their MRSA or VRE infection was endocarditis, meningitis, osteomyelitis, or an infected device.

The Microbiologically Evaluable population consisted of Clinically Evaluable patients who had a pathogen recovered at baseline that was not resistant to the study medications.

8.2.2 Definitions of Outcomes

In this brochure, clinical cure rates (that is, the Sponsor's Assessment of Clinical Outcome) are shown for the ITT, MITT, Clinically Evaluable, and Microbiologically Evaluable populations. Evidence of cure and/or equivalence to comparator was seen for linezolid in all four patient populations; however, the Clinically Evaluable population is considered the most clinically relevant, as it consists of those patients who met disease-specific criteria, received sufficient study drug treatment, complied with the conditions of the protocol, and were assessed within the proper visit windows. Cure rates were determined at the TOC assessment, which occurred at a follow-up (F-U) visit, generally 7 to 28 days after the last dose of study medication.

The Sponsor's Assessment of Clinical Outcome was a conservative modification of the Investigator's Assessment of Clinical Outcome. Patients must have received at least 5 days of study medication to be considered a cure and at least 2 days of study medication to be considered a failure. In addition, the following criteria were applied to the sponsor's assessment:

- If the investigator's assessment was failed at EOT and there was no investigator assessment at TOC, the patient was considered failed.
- If the patient took a concomitant antibiotic due to a lack of efficacy of the study drug, he or she was considered failed.
- If the sponsor's assessment was cured or improved at EOT and there was no investigator's assessment at TOC, the patient was considered indeterminate.

In addition to overall cure rates, clinical cure and eradication rates for individual pathogens are shown for the Microbiologically Evaluable population.

8.2.3 Assignment of Outcomes

Prior to unblinding, the sponsor assigned one of four clinical outcomes to each patient: cured, failed, indeterminate, or missing. In addition to the patient's clinical outcome, pathogens isolated at baseline were also assigned one of four outcomes: eradication, persistence (or noneradication), indeterminate, or missing. If a patient was coinfecting with one or more pathogens, each baseline pathogen was assigned a separate outcome. Therefore, one patient could have more than one pathogen outcome.

8.2.4 Statistical Methods

8.2.4.1 Comparator-Controlled Studies

Each of the comparator-controlled phase III studies (31, 33, 39A, 39, 48A, 51, and 55) was designed to test the equivalence of linezolid and its comparator. The distribution of cured and failed between treatment groups was compared at the TOC assessment by using a Chi-square test for homogeneity of proportions. Confidence intervals (95%) for the difference in cure rates between treatments were calculated based on the normal approximation to the binomial distribution. Linezolid and the comparator were considered to be equivalent if the lower limit of the confidence interval was $\geq -10\%$ ($\geq -20\%$ in Study 48A).

Required sample sizes were based on a test of equivalence described by Blackwelder* and Makuch and Simon,† in conjunction with recommendations given in the Points to Consider document from the Division of Anti-Infective Drug Products at FDA (dated 26 October 1992) and the General Guidelines for the Evaluation of Anti-Infective Drugs in Humans from the Infectious Disease Society of America (final draft, 1992).

8.2.4.2 Dose-Comparison Study 54A

Study 54A was designed to test the superiority of the 600-mg dose of linezolid over the 200-mg dose of linezolid. The distribution of cured and failed between treatment groups was compared at the TOC assessment by using a Chi-square test for homogeneity of proportions. Confidence intervals (95%) for the difference in cure rates between treatments were calculated based on the normal approximation to the binomial distribution.

The design of Study 54A was the result of discussions with the FDA and was based on a planned enrollment of 500 patients (250 patients per treatment group). However, Pharmacia & Upjohn decided to terminate this study after 145 patients had been enrolled and treated in order to include this valuable experience in the NDA submission. The decision to terminate the study was a prospective decision and was not based on an interim analysis of the data.

* Blackwelder WC. Proving the null hypothesis in clinical trials. *Cont Clin Trials* 1982;3:345-53.

† Makuch R, Simon R. Sample size requirements for evaluating a conservative therapy. *Cancer Treat Rep* 1978;62:1037-40.

Although statistically underpowered, the results in the 600-mg dose group were consistently better than those in the 200-mg dose group for all endpoints and in all analysis populations, in the treatment of patients with VRE infections.

8.2.5 Presentation of Data

FDA guidelines for the development of anti-infectives were followed in designing the studies for the indications of community-acquired pneumonia, nosocomial pneumonia, uncomplicated skin and soft tissue infections, and complicated skin and soft tissue infections. The design of Study 54A (VRE infections) was the result of discussions with the FDA.

In general, efficacy data for studies within an indication are presented separately.

9 SUMMARY OF EFFICACY DATA: PNEUMONIA

9.1 Community Acquired Pneumonia

9.1.1 Pivotal Studies 33 and 51

9.1.1.1 Clinical Methodology

9.1.1.1.1 Study Design

Study 33

This phase III, randomized, open-label comparator-controlled, multicenter study was conducted in patients with demonstrated or presumptive *S pneumoniae* pneumonia. The study consisted of a baseline/screening visit; inpatient treatment (if necessary, patients could be hospitalized for the entire study); outpatient treatment, including a study visit at day 7; an EOT visit; and an F-U visit. Patients who returned between 12 and 28 days after the last dose of study medication were included in the TOC assessments. Safety was evaluated throughout the study by clinical observations, vital sign assessments, laboratory evaluations, and assessment of adverse events.

Study 51

This phase III, investigator-blinded, comparator-controlled study was conducted in adult patients with community-acquired pneumonia. The study consisted of five visits: a baseline/screening visit, patient treatment evaluation visits (days 3 and 9) after treatment initiation, an EOT visit within 72 hours of the last dose of study medication, and an F-U visit 15 to 21 days after study medication was stopped. Clinical assessments were performed at each visit; patients who returned between 12 and 28 days after the last dose of study medication were included in the TOC assessments. Safety was evaluated throughout the study by physical examination, vital sign assessments, laboratory assessments, and adverse events.

*9.1.1.1.2 Study Drug Dosage Form and Dosage Regimen*Study 33

- Linezolid IV 600 mg twice daily followed by linezolid oral tablets 600 mg twice daily for 7 to 14 consecutive days
- Ceftriaxone IV 1 g twice daily followed by cefpodoxime proxetil oral tablets 200 mg twice daily for 7 to 14 consecutive days

Study 51

- Linezolid oral tablets 600 mg twice daily for 10 to 14 consecutive days
- Cefpodoxime proxetil oral tablets 200 mg twice daily for 10 to 14 consecutive days

*9.1.1.1.3 Inclusion/Exclusion Criteria*Study 33

Patients at least 13 years of age with community-acquired pneumonia were eligible for enrollment if they had radiographic findings consistent with pneumonia and at least two of the following symptoms: cough; production of purulent sputum or a change (worsening) in character of the sputum, auscultatory findings on pulmonary examination of rales and/or pulmonary consolidation (dullness on percussion, bronchial breath sounds, or egophony); dyspnea, tachypnea, or hypoxemia, particularly if any or all of these were progressive in nature; or an organism consistent with a respiratory pathogen isolated from sputum or blood cultures.

In addition, eligible patients had at least one of the following conditions: fever, elevated total peripheral WBC count $>10,000/\text{mm}^3$, $>15\%$ immature neutrophils (bands) regardless of total peripheral WBC, or leukopenia with total WBC $<4,500/\text{mm}^3$. Eligible patients had to provide a respiratory, blood, or pleural fluid specimen for microbiological evaluation and had to have a survival expectancy of at least 60 days.

Patients were excluded from participation in the study if they had an infection due to organisms known to be resistant to either of the study medication regimens before study entry or had received previous antibiotic treatment for the current episode of pneumonia for more than 24 hours, unless documented to be a treatment failure (72 hours of treatment and not responding).

Study 51

Patients at least 18 years of age who developed pneumonia while living in the community, with radiographic findings consistent with pneumonia and at least two of the following symptoms, were eligible for participation in the study: cough; production of purulent sputum or a change (worsening) in character of the sputum; auscultatory findings on pulmonary examination of rales and/or pulmonary consolidation (dullness on percussion, bronchial breath sounds, or egophony); dyspnea, tachypnea, or hypoxemia, particularly if any or all of these were progressive in nature; or organism consistent with a respiratory pathogen isolated from respiratory, sputum, or blood cultures. In addition, eligible patients had at least one of

the following: fever, elevated total peripheral white blood cell (WBC) count $>10,000/\text{mm}^3$ or $>15\%$ immature neutrophils (bands) regardless of total peripheral WBC.

Patients were excluded from participation in the study if they had an infection due to organisms known to be resistant to either of the study medication regimens before study entry or had received previous antibiotic treatment for the current episode of pneumonia for more than 24 hours, unless documented to be a treatment failure (72 hours of treatment and not responding).

9.1.1.2 Results

9.1.1.2.1 Patient Disposition and Evaluability/Demographics

Study 33

The evaluability/disposition of patients in Study 33 are summarized in Table 11 and Table 12.

Table 11. Summary of Patient Evaluability (Study 33)

Population	Linezolid		Ceftriaxone/Cefpodoxime	
	No.	%†	No.	%†
ITT Patients	381	100.0	366	100.0
MITT Patients	128	33.6	126	34.4
Clinically Evaluable Patients	276	72.4	258	70.5
Microbiologically Evaluable Patients	90	23.6	95	26.0

† Percentages based on ITT population.

ITT = Intent-to-Treat; MITT = Modified Intent-to-Treat

Table 12. Summary of Patient Disposition - ITT Patients (Study 33)

Population	Linezolid N = 381		Ceftriaxone/Cefpodoxime N = 366	
	No.	%	No.	%
Completed Treatment	320	84.0	301	82.2
Discontinued During Treatment	61	16.0	65	17.8
-Lack of Efficacy	14	3.7	26	7.1
-Death	4	1.0	4	1.1
-Adverse Event	19	5.0	16	4.4
-Ineligible but Started Study Medication	8	2.1	7	1.9
-Protocol Noncompliance	3	0.8	3	0.8
-Subject's Personal Request	4	1.0	1	0.3
-Lost to Follow-Up	4	1.0	2	0.5
-Other†	5	1.3	6	1.6

† Not specified.

ITT = Intent-to-Treat

Patients in both treatment groups were comparable at baseline with respect to age, vital signs, weight, sex, race, medical history, physical examination data, clinical signs and symptoms, and safety laboratory parameters. Approximately 59% of the patients were male, and the distribution of patient ages was approximately 33% <45 years, 30% 45-64 years, and 37% ≥65 years.

Study 51

The evaluability/disposition of patients in Study 51 are summarized in Table 13 and Table 14.

Table 13. Summary of Patient Evaluability (Study 51)

Population	Linezolid		Cefpodoxime	
	No.	%†	No.	%†
ITT Patients	274	100.0	266	100.0
MITT Patients	61	22.3	59	22.2
Clinically Evaluable Patients	207	75.5	210	78.9
Microbiologically Evaluable Patients	51	18.6	46	17.3

† Percentages based on ITT population.

ITT = Intent-to-Treat; MITT = Modified Intent-to-Treat

Table 14. Summary of Patient Disposition - ITT Patients (Study 51)

Population	Linezolid N = 274		Cefpodoxime N = 266	
	No.	%	No.	%
Completed Treatment	219	79.9	237	89.1
Discontinued During Treatment	55	20.1	29	10.9
-Lack of Efficacy	15	5.5	9	3.4
-Death	2	0.7	0	0
-Adverse Event	20	7.3	2	0.8
-Ineligible but Started Study Medication	5	1.8	8	3.0
-Subject's Personal Request	5	1.8	2	0.8
-Lost to Follow-Up	5	1.8	7	2.6
-Other†	3	1.1	1	0.4

† Not specified.

ITT = Intent-to-Treat

Patients in both treatment groups were comparable at baseline with respect to age, vital signs, weight, sex, race, medical history, physical examination data, clinical signs and symptoms, and safety laboratory parameters. Approximately 50% of the patients were male, and the distribution of patient ages was approximately 46% <45 years, 33% 45-64 years, and 21% ≥65 years.

9.1.1.2.2 Clinical Cure Rates

An overview of the Clinical cure rates for pivotal studies 51 and 33 in community-acquired pneumonia is presented in Table 15. Clinical cure rates were consistent and very similar between Study 33 (hospitalized patients) and Study 51 (outpatients). In both studies, the treatment groups were statistically equivalent with respect to the Sponsor's Assessment of Clinical Outcome for Clinically Evaluable patients (Study 33 95% CI for difference = -3.0%, 7.4%; Study 51 95% CI for difference = -6.8%, 4.8%;).

Table 15. Clinical Cure Rates for Patients With Community-Acquired Pneumonia (Studies 33 and 51)

Sponsor's Assessment of Clinical Outcome	Linezolid		Comparator†		95% CI
	n/N	%‡	n/N	%‡	
Study 33					
ITT Patients	268/323	83.0	240/314	76.4	0.3, 12.8
MITT Patients	91/107	85.0	89/115	77.4	-2.5, 17.9
Clinically Evaluable Patients	247/272	90.8	225/254	88.6	-3.0, 7.4
Microbiologically Evaluable Patients	80/89	89.9	81/93	87.1	-6.5, 12.0
Study 51					
ITT Patients	188/229	82.1	191/223	85.7	-10.3, 3.2
MITT Patients	47/56	83.9	41/51	80.4	-11.0, 18.1
Clinically Evaluable Patients	182/203	89.7	185/204	90.7	-6.8, 4.8
Microbiologically Evaluable Patients	45/50	90.0	38/46	82.6	-6.4, 21.1

† Oral cefpodoxime proxetil in Study 51; IV ceftriaxone/oral cefpodoxime proxetil in Study 33.

‡ Percentages are based on the total number of patients reporting, excluding indeterminate and missing.

ITT = Intent-to-Treat; MITT = Modified Intent-to-Treat; CI = confidence interval for difference

9.1.1.2.3 Pathogen Eradication Rates

Individual pathogen eradication rates are presented for the Microbiologically Evaluable population in Table 16.

Table 16. Pathogen Eradication Rates in Microbiologically Evaluable Patients With Community-Acquired Pneumonia (Studies 33 and 51)

Pathogen	Linezolid		Comparator†	
	n/N	%‡	n/N	%‡
Study 33				
<i>Streptococcus pneumoniae</i>	63/71	88.7	62/69	89.9
Penicillin-intermediate§	7/9	77.8	9/9	100.0
Penicillin-resistant§	3/4	75.0	1/1	100.0
<i>Staphylococcus aureus</i>	18/20	90.0	13/17	76.5
Methicillin-resistant§	1/1	100.0	0	0
<i>Haemophilus influenzae</i> *	2/2	100.0	10/11	90.9
<i>Moraxella catarrhalis</i>	1/1	100.0	3/4	75.0
<i>Streptococcus pyogenes</i>	0	0	0	0
Study 51				
<i>Streptococcus pneumoniae</i>	25/27	92.6	19/21	90.5
Penicillin-intermediate§	2/3	66.7	3/4	75.0
Penicillin-resistant§	0	0	0	0
<i>Staphylococcus aureus</i>	11/12	91.7	11/12	91.7
Methicillin-resistant§	1/1	100.0	1/1	100.0
<i>Haemophilus influenzae</i>	10/12	83.3	13/15	86.7
<i>Moraxella catarrhalis</i>	3/3	100.0	1/1	100.0
<i>Streptococcus pyogenes</i>	1/1	100.0	1/1	100.0

† Oral cefpodoxime proxetil in Study 51; IV ceftriaxone/oral cefpodoxime proxetil in Study 33.

‡ Percentages are based on the total number of patients reporting, excluding indeterminate and missing.

§ Data for intermediate and resistant organisms are subsets of the pathogen total.

* Excluding linezolid patients in Study 33 who received concomitant aztreonam.

9.1.2 Supportive Study 45

Efficacy results for Study 45 (pediatric pneumonia) are presented in section 15.3.1, and are consistent with the results seen in Studies 33 and 51.

9.1.3 Pooled Pathogen Eradication Rates

Pooled pathogen eradication rates for the community-acquired pneumonia studies (Studies 33, 51, and 45) are presented in Table 17.

Table 17. Pooled Pathogen Eradication Rates in Microbiologically Evaluable Patients With Community-Acquired Pneumonia (Studies 33, 45, 51)

Pathogen	Linezolid		Comparator†	
	n/N	%‡	n/N	%‡
<i>Streptococcus pneumoniae</i>	93/103	90.3	81/90	90.0
Penicillin-intermediate§	9/12	75.0	12/13	92.3
Penicillin-resistant§	5/6	83.3	1/1	100.0
<i>Staphylococcus aureus</i>	29/32	90.6	24/29	82.8
Methicillin-resistant§	2/2	100.0	1/1	100.0
<i>Haemophilus influenzae</i> *	12/14	85.7	23/26	88.5
<i>Moraxella catarrhalis</i>	4/4	100.0	4/5	80.0
<i>Streptococcus pyogenes</i>	2/2	100.0	1/1	100.0

† Oral cefpodoxime proxetil in Study 51; IV ceftriaxone/oral cefpodoxime proxetil in Study 33.

‡ Percentages are based on the total number of patients reporting, excluding indeterminate and missing.

§ Data for intermediate and resistant organisms are subsets of the pathogen total.

* Excluding linezolid patients in Study 33 who received concomitant aztreonam.

9.1.4 Conclusions

- Linezolid 600 mg twice daily IV/oral is equivalent to ceftriaxone/cefpodoxime for the treatment of adult community-acquired pneumonia. Linezolid cured 90.3% of the Clinically Evaluable patients versus 89.5% of those treated with comparators.
- Linezolid 10 mg/kg twice daily cured 95.3% of the Clinically Evaluable children (12 months to 17 years of age) with community-acquired pneumonia.
- The recommended duration of therapy is 10 to 14 days.
- Linezolid eradicated *S pneumoniae* (including PRSP), *S aureus*, and *H influenzae* at rates comparable to ceftriaxone and cefpodoxime.
- Linezolid is effective in eradication of PRSP and MRSA in community-acquired pneumonia.

9.2 Nosocomial Pneumonia

9.2.1 Pivotal Study 48A

9.2.1.1 Clinical Methodology

9.2.1.1.1 Study Design

This phase III, randomized, double-blind, multicenter study was designed to compare the efficacy, safety, and tolerance of linezolid and vancomycin in the treatment of nosocomial pneumonia. The study consisted of a baseline/screening visit, patient treatment evaluation visits every 3 days while on study medication, an EOT visit within 72 hours of the last dose of study medication, and an F-U visit 15 to 21 days after completion of treatment. Clinical and/or microbiological assessments were performed at each visit; patients who returned between 12 and 28 days after the last dose of study medication were included in the TOC assessments. Safety was evaluated throughout the study by physical examination, vital sign assessments, laboratory assessments, and monitoring of adverse events.

9.2.1.1.2 Study Drug Dosage Form and Dosage Regimen

- Linezolid IV 600 mg twice daily for 7 to 21 consecutive days. Aztreonam use was allowed for gram-negative coverage.
- Vancomycin IV 1 g twice daily for 7 to 21 consecutive days. Aztreonam use was allowed for gram-negative coverage.

9.2.1.1.3 Inclusion/Exclusion Criteria

Adult patients with a clinical picture compatible with pneumonia (acquired in an in-patient health care facility or chronic care facility) were required to satisfy at least two of the following criteria: cough; production of purulent sputum or a change (worsening) in character of the sputum; auscultatory findings on pulmonary examination of rales and/or pulmonary consolidation; dyspnea, tachypnea, or hypoxemia, particularly if any or all of these were progressive in nature; organism consistent with a respiratory pathogen isolated from respiratory, sputum, or blood cultures; and expected to survive at least 7 days.

Each patient should also have had at least two of the following: fever; respiratory rate >30 breaths per minute; systolic hypotension; pulse rate ≥ 120 beats per minute; altered mental status; requirement for mechanical ventilation; elevated total peripheral WBC $>10,000/\text{mm}^3$; $>15\%$ immature neutrophils (bands) regardless of total peripheral WBC; leukopenia with total WBC $<4,500/\text{mm}^3$. Patients also had a chest radiograph at baseline/screening or within 48 hours of initiation of treatment consistent with a diagnosis of pneumonia (new or progressive infiltrates, consolidation, or pleural effusion); provided a suitable invasive respiratory specimen and a sputum specimen for Gram's stain and culture; had venous access for intravenous dosing; and were willing to complete all study-related activities and F-U visit.

An expectorated sputum specimen or endotracheal suction specimen was obtained from all patients. In addition, investigators were to obtain a respiratory specimen from one or more of the following sources, as clinically appropriate:

- Bronchoalveolar lavage (BAL)
- Protected specimen brush (PSB)
- Transthoracic aspiration
- Transtracheal aspiration
- Thoracentesis

Patients were to be excluded for the following reasons: infection due to organisms known to be resistant to either of the study medication regimens before study entry; known or suspected meningitis, endocarditis, or osteomyelitis; CD4 cell count < 200 cells/mm³ secondary to Human Immunodeficiency Virus (HIV) infection; previous antibiotic treatment received for more than 24 hours, unless documented to be a treatment failure (72 hours of treatment and not responding) or if the isolated pathogen for the current pneumonia was resistant in vitro to previous nonstudy antibiotic therapy; known liver disease and total bilirubin > 5 times the upper limit of normal (ULN); or severe neutropenia (< 500 cells/mm³).

9.2.1.2 Results

9.2.1.2.1 Patient Disposition and Evaluability/Demographics

The evaluability/disposition of patients in Study 48A are summarized in Table 18 and Table 19.

Table 18. Summary of Patient Evaluability (Study 48A)

Population	Linezolid		Vancomycin	
	No.	%†	No.	%†
ITT Patients	203	100.0	193	100.0
MITT Patients	94	46.3	83	43.0
Clinically Evaluable Patients	108	53.2	96	49.7
Microbiologically Evaluable Patients	54	26.6	40	20.7

† Percentages based on ITT population.

ITT = Intent-to-Treat; MITT = Modified Intent-to-Treat

Table 19. Summary of Patient Disposition – ITT Patients (Study 48A)

Population	Linezolid N = 203		Vancomycin N = 193	
	No.	%	No.	%
Completed Treatment	142	70.0	125	64.8
Discontinued During Treatment	61	30.0	68	35.2
-Lack of Efficacy	10	4.9	11	5.7
-Death	14	6.9	17	8.8
-Adverse Event	9	4.4	14	7.3
-Ineligible but Started Study Medication	4	2.0	7	3.6
-Protocol Noncompliance	0	0	1	0.5
-Subject's Personal Request	3	1.5	2	1.0
-Other†	21	10.3	16	8.3

† Primarily due to isolation of gram-negative pathogens only.

ITT = Intent-to-Treat

Patients in both treatment groups were comparable at baseline with respect to age, vital signs, baseline APACHE II score, intubation status at baseline, pretreatment ventilator status, weight, sex, race, medical history, physical examination data, clinical signs and symptoms, and safety laboratory parameters. Approximately 69% of the patients were male, and the distribution of patient ages was approximately 20% <45 years, 25% 45-64 years, and 55% ≥65 years.

9.2.1.2.2 Clinical Cure Rates

An overview of the cure rates for patients with nosocomial pneumonia is presented in Table 20. The treatment groups were statistically equivalent with respect to the Sponsor's Assessment of Clinical Outcome for Clinically Evaluable patients (95% CI for difference = -14.9%, 11.3%).

Table 20. Clinical Cure Rates for Patients with Nosocomial Pneumonia (Study 48A)

Sponsor's Assessment of Clinical Outcome	Linezolid		Vancomycin†		95% CI
	n/N	%‡	n/N	%‡	
ITT Patients	86/161	53.4	74/142	52.1	-10.0, 12.6
MITT Patients	49/78	62.8	33/63	52.4	-5.9, 26.8
Clinically Evaluable Patients	71/107	66.4	62/91	68.1	-14.9, 11.3
Microbiologically Evaluable Patients	37/53	69.8	26/38	68.4	-17.9, 20.7

‡ Percentages are based on the total number of patients reporting, excluding indeterminate and missing.

ITT = Intent-to-Treat; MITT = Modified Intent-to-Treat; CI = confidence interval for difference

9.2.1.2.3 Pathogen Eradication Rates

Individual pathogen eradication rates are presented for the Microbiologically Evaluable population in patients with nosocomial pneumonia in Table 21.

Table 21. Pathogen Eradication Rates in Microbiologically Evaluable Patients With Nosocomial Pneumonia (Study 48A)

Pathogen	Linezolid		Vancomycin	
	n/N	%†	n/N	%†
<i>Streptococcus pneumoniae</i>	9/9	100.0	9/9	100.0
Penicillin intermediate‡	1/1	100.0	1/1	100.0
Penicillin-resistant‡	2/2	100.0	0	0
<i>Staphylococcus aureus</i>	25/41	61.0	15/23	65.2
Methicillin-resistant‡	15/23	65.2	7/9	77.8

† Percentages are based on the total number of patients reporting excluding indeterminate and missing.

‡ Data for resistant organisms are subsets of the pathogen total.

9.2.2 Conclusions

- Linezolid 600 mg twice daily is equivalent to vancomycin for the treatment of nosocomial pneumonia in adults (when both are administered with concomitant aztreonam or aminoglycoside for suspected gram-negative coverage). Linezolid cured 66.4% of the Clinically Evaluable patients versus 68.1% with vancomycin.
- The recommended duration of therapy is 10 to 14 days.
- Linezolid is comparable to vancomycin therapy in the eradication of *S pneumoniae* and *S aureus*.
- Linezolid effectively eradicated MRSA in nosocomial pneumonia.

10 SUMMARY OF EFFICACY DATA: SKIN AND SOFT TISSUE INFECTIONS

10.1 Uncomplicated Skin and Soft Tissue Infections: Studies 39A and 39

10.1.1 Clinical Methodology

10.1.1.1 Study Design

These randomized, double-blind, multicenter studies compared the efficacy, safety, and tolerance of linezolid and clarithromycin in the treatment of uncomplicated skin and soft

tissue infections. Each study consisted of four visits: a baseline/screening visit, a patient treatment evaluation visit on day 3 after treatment initiation, an EOT visit within 72 hours of the last dose of study medication, and an F-U visit 7 to 14 days (Study 39A) or 7 to 21 days (Study 39) after the EOT visit. Clinical and microbiologic assessments were performed at each visit; the TOC assessments were completed at the F-U visit. Patients who returned between 7 and 28 days after the last dose were included in the TOC assessment. Safety was evaluated throughout the study by physical examination, vital sign assessments, laboratory assessments, use of concomitant (noninvestigational) medications, and reporting of adverse events.

The only difference between the two studies were the locations of the investigational sites: patients in Study 39A were enrolled in North America and patients in Study 39 were enrolled in Europe, South Africa, Australia, and Latin America.

10.1.1.2 Study Drug Dosage Form and Dosage Regimen

- Linezolid oral tablets 400 mg twice daily for 7 to 14 consecutive days
- Clarithromycin oral tablets 250 mg twice daily for 7 to 14 consecutive days

10.1.1.3 Inclusion/Exclusion Criteria

Adult patients (at least 18 years of age) with suspected gram-positive uncomplicated skin and superficial skin structure infections, such as simple abscesses, impetiginous lesions, furuncles, carbuncles, cellulitis, erysipelas infections of intact skin, and mild burns, were eligible for enrollment in the study if they had an accessible infection site for Gram's stain and culture and at least two of the following symptoms: drainage/discharge, erythema, fluctuance, heat/localized warmth, pain/tenderness to palpation, or swelling/induration.

Patients were to be excluded for any of the following reasons: previous antibiotic treatment for more than 24 hours within 7 days of study entry (unless pathogen showed drug resistance, positive infection site culture was obtained, or treatment failed); abscesses that only needed surgical draining at the time of enrollment; a complicated skin and soft tissue infection that involved deeper soft tissue and/or may have required significant surgical intervention; diabetic foot ulcers, decubitus and ischemic ulcers; necrotizing fasciitis, gas gangrene, or burns on >10% of total body surface; an infection that had a high surgical incision cure rate; chronic medical conditions where inflammation could have been prominent for an extended period even after successful bacterial eradication; infections or conditions requiring concomitant antimicrobial or systemic corticosteroid therapy; infections of prosthetic materials; osteomyelitis; liver disease; neutropenia; pheochromocytoma; carcinoid syndrome; uncontrolled hypertension; or untreated hyperthyroidism.

10.1.2 Results

10.1.2.1 Patient Disposition and Evaluability/Demographics

Study 39A

The evaluability/disposition of patients in Study 39A are summarized in Table 22 and Table 23.

Table 22. Summary of Patient Evaluability (Study 39A)

Population	Linezolid		Clarithromycin	
	No.	%†	No.	%†
ITT Patients	382	100.0	371	100.0
MITT Patients	210	55.0	215	58.0
Clinically Evaluable Patients	314	82.2	309	83.3
Microbiologically Evaluable Patients	144	37.7	146	39.4

† Percentages based on ITT population.

ITT = Intent-to-Treat; MITT = Modified Intent-to-Treat

Table 23. Summary of Patient Disposition – ITT Patients (Study 39A)

Population	Linezolid N = 382		Clarithromycin N = 371	
	No.	%	No.	%
Completed Treatment	330	86.4	331	89.2
Discontinued During Treatment	52	13.6	40	10.8
-Lack of Efficacy	7	1.8	4	1.1
-Adverse Event	27	7.1	18	4.9
-Ineligible but Started Study Medication	1	0.3	0	0
-Protocol Noncompliance	4	1.0	1	0.3
-Subject's Personal Request	3	0.8	4	1.1
-Lost to Follow-Up	7	1.8	10	2.7
-Other†	3	0.8	3	0.8

† Not specified.

ITT = Intent-to-Treat

In general, patients in both treatment groups were comparable at baseline with respect to age, vital signs, weight, lesion size (length, width, and area), duration of infection, sex, race, medical history, physical examination data, diagnosis, primary site of infection, degree of involvement, clinical signs and symptoms, and safety laboratory parameters. Approximately

55% of the patients were male, and the distribution of patient ages was approximately 55% <45 years, 31% 45-64 years, and 15% ≥65 years.

Study 39

The evaluability/disposition of patients in Study 39 are summarized in Table 24 and Table 25.

Table 24. Summary of Patient Evaluability (Study 39)

Population	Linezolid		Clarithromycin	
	No.	%†	No.	%†
ITT Patients	166	100.0	166	100.0
MITT Patients	85	51.2	96	57.8
Clinically Evaluable Patients	127	76.5	124	74.7
Microbiologically Evaluable Patients	55	33.1	68	41.0

† Percentages based on ITT population.

ITT = Intent-to-Treat; MITT = Modified Intent-to-Treat

Table 25. Summary of Patient Disposition - ITT Patients (Study 39)

Population	Linezolid N = 166		Clarithromycin N = 166	
	No.	%	No.	%
Completed Treatment	146	88.0	153	92.2
Discontinued During Treatment	20	12.0	13	7.8
-Lack of Efficacy	2	1.2	3	1.8
-Adverse Event	4	2.4	2	1.2
-Ineligible but Started Study Medication	4	2.4	0	0
-Protocol Noncompliance	2	1.2	2	1.2
-Subject's Personal Request	1	0.6	3	1.8
-Lost to Follow-Up	5	3.0	2	1.2
-Other†	2	1.2	1	0.6

† Not specified.

ITT = Intent-to-Treat

In general, patients in both treatment groups were comparable at baseline with respect to age, vital signs, weight, lesion size (length, width, and area), duration of infection, sex, race, medical history, physical examination data, diagnosis, primary site of infection, degree of involvement, clinical signs and symptoms, and safety laboratory parameters. Approximately

56% of the patients were male, and the distribution of patient ages was approximately 61% <45 years, 30% 45-64 years, and 10% ≥65 years.

10.1.2.2 Clinical Cure Rates

An overview of the clinical cure rates for patients with uncomplicated skin and soft tissue infections is presented in Table 26. In both pivotal study 39A and supportive Study 39, the treatment groups were statistically equivalent with respect to the Sponsor's Assessment of Clinical Outcome for Clinically Evaluable patients (Study 39A 95% CI for difference = -0.7%, 9.2%; Study 39 95% CI for difference = -8.4%, 5.2%).

Table 26. Clinical Cure Rates for Patients with Uncomplicated Skin and Soft Tissue Infections (Studies 39A and 39)

Sponsor's Assessment of Clinical Outcome	Linezolid		Clarithromycin		95% CI
	n/N	% [†]	n/N	% [†]	
Pivotal Study 39A					
ITT Patients	290/343	84.5	268/323	83.0	-4.0, 7.2
MITT Patients	159/190	83.7	152/188	80.9	-4.9, 10.5
Clinically Evaluable Patients	283/310	91.3	262/301	87.0	-0.7, 9.2
Microbiologically Evaluable Patients	126/143	88.1	122/141	86.5	-6.2, 9.3
Supportive Study 39					
ITT Patients	130/149	87.2	135/149	90.6	-10.5, 3.8
MITT Patients	68/77	88.3	81/90	90.0	-11.2, 7.8
Clinically Evaluable Patients	113/124	91.1	114/123	92.7	-8.4, 5.2
Microbiologically Evaluable Patients	53/54	98.1	67/68	98.5	-5.0, 4.2

[†] Percentages are based on the total number of patients reporting, excluding indeterminate and missing.

ITT = Intent-to-Treat; MITT = Modified Intent-to-Treat; CI = confidence interval for difference

Clinical cure rates by diagnosis are summarized in Table 27. The cure rates were similar between treatment groups for all diagnostic categories.

Table 27. Clinical Cure Rates by Diagnosis for Clinically Evaluable Patients With Uncomplicated Skin and Soft Tissue Infections (Studies 39A and 39)

Diagnosis	Sponsor's Assessment of Clinical Outcome			
	Linezolid		Clarithromycin	
	n/N	%†	n/N	%†
Pivotal Study 39A				
Cellulitis	60/66	90.9	65/77	84.4
Infected Wound	44/47	93.6	28/30	93.3
Skin abscess	42/46	91.3	53/58	91.4
Folliculitis	23/26	88.5	14/17	82.4
Furuncle	26/26	100.0	17/19	89.5
Paronychia	22/25	88.0	16/18	88.9
Infected Bite	21/22	95.5	18/18	100.0
Other‡	45/52	86.5	51/64	79.7
Supportive Study 39				
Cellulitis	38/41	92.7	28/29	96.6
Infected Wound	9/9	100.0	11/12	91.7
Skin abscess	16/18	88.9	23/23	100.0
Folliculitis	2/2	100.0	2/3	66.7
Furuncle	16/17	94.1	11/11	100.0
Paronychia	2/2	100.0	4/5	80.0
Infected Bite	3/3	100.0	0	0
Other‡	27/32	84.4	35/40	87.5

† Percentages are based on the total number of patients reporting, excluding indeterminate and missing.

‡ Includes carbuncle, erysipelas, impetigo, infected surgical incision, skin ulcer, and other.

10.1.2.3 Pathogen Eradication Rates

Individual pathogen eradication rates are presented for the Microbiologically Evaluable population in Table 28.

Table 28. Pathogen Eradication Rates in Microbiologically Evaluable Patients With Uncomplicated Skin and Soft Tissue Infections (Studies 39A and 39)

Pathogen	Linezolid		Clarithromycin	
	n/N	%†	n/N	%†
Pivotal Study 39A				
<i>Staphylococcus aureus</i>	82/91	90.1	91/108	84.3
<i>Streptococcus agalactiae</i>	10/10	100.0	4/5	80.0
<i>Streptococcus pyogenes</i>	5/5	100.0	11/12	91.7
Other <i>Streptococcus</i> species‡	9/10	90.0	2/3	66.7
Supportive Study 39				
<i>Staphylococcus aureus</i>	38/39	97.4	51/53	96.2
<i>Streptococcus agalactiae</i>	1/1	100.0	0	0
<i>Streptococcus pyogenes</i>	6/6	100.0	7/7	100.0

† Percentages are based on the total number of patients reporting, excluding indeterminate and missing.

‡ Includes *S anginosus*, *S canis*, and *S intermedius*, *S mitis*, and *S sanguis*.

10.1.3 Pooled Pathogen Eradication Rates

Pathogen eradication rates for the uncomplicated skin and soft tissue infection studies (Studies 39A and 39) are presented in Table 17.

Table 29. Pooled Pathogen Eradication Rates in Microbiologically Evaluable Patients With Uncomplicated Skin and Soft Tissue Infection (Studies 39A and 39)

Pathogen	Linezolid		Clarithromycin	
	n/N	%†	n/N	%†
<i>Staphylococcus aureus</i>	120/130	92.3	142/161	88.2
<i>Streptococcus agalactiae</i>	11/11	100.0	4/5	80.0
<i>Streptococcus pyogenes</i>	11/11	100.0	18/19	94.7
Other <i>Streptococcus</i> species‡	9/10	90.0	2/3	66.7

† Percentages are based on the total number of patients reporting, excluding indeterminate and missing.

‡ Includes *S anginosus*, *S canis*, and *S intermedius*, *S mitis*, and *S sanguis*.

10.1.4 Conclusions

- Linezolid is equivalent to clarithromycin in the treatment of uncomplicated skin and soft tissue infections at oral doses of 400 mg twice daily. Linezolid cured 91.2% of the Clinically Evaluable patients versus 88.7% treated with clarithromycin.
- The recommended duration of therapy is 10 to 14 days.
- Linezolid effectively eradicated *S aureus*, *S agalactiae*, and *S pyogenes* at rates comparable to clarithromycin.

10.2 Complicated Skin and Soft Tissue Infections

10.2.1 Pivotal Study 55

10.2.1.1 Clinical Methodology

10.2.1.1.1 Study Design

This phase III, double-blind/double-dummy, comparator-controlled study was conducted in adult patients hospitalized with complicated skin and soft tissue infections. The study consisted of the following visit schedule: a baseline/screening visit, hospitalization phase (1 dose minimum), outpatient treatment with a Patient Treatment Evaluation visit every 6 days after discharge, an EOT visit within 72 hours of the last dose of study medication, and an F-U visit 15 to 21 days after the final dose of study medication. Clinical, microbiological, and economic assessments were performed at baseline, during patient hospitalization, at the switch from intravenous to oral treatment, after discharge while the patient continued on oral study medication, and at the EOT and F-U visits. Patients who returned between 12 and 28 days after the last dose of study medication were included in the TOC assessments. Safety was evaluated throughout the study by physical examination, vital sign assessments, laboratory assessments, and adverse events.

10.2.1.1.2 Study Drug Dosage Form and Dosage Regimen

- Linezolid IV 600 mg twice daily followed by oral linezolid 600 mg twice daily, alternating with placebo twice daily for 10 to 21 consecutive days
- Oxacillin sodium IV 2 g every 6 hours followed by oral dicloxacillin sodium 500 mg every 6 hours for 10 to 21 consecutive days

10.2.1.1.3 Inclusion/Exclusion Criteria

Hospitalized adult patients with a suspected gram-positive complicated skin and soft tissue infection that involved deeper soft tissue, or that required significant surgical intervention (such as a major abscess, infected ulcer, major burn, or deep and extensive cellulitis), and with at least two of the following: drainage/discharge, erythema, fluctuance, heat/localized warmth, pain/tenderness to palpation, swelling/induration; an accessible infection site for Gram's stain and culture; at least one of the following conditions considered to be pathogen-

related: fever, defined as body temperature $>37.5^{\circ}\text{C}$ (axillary); $>38^{\circ}\text{C}$ (orally); $>38.5^{\circ}\text{C}$ (tympanically); or $>39^{\circ}\text{C}$ (rectally), elevated total peripheral white blood cell count $>10,000/\text{mm}^3$, or $>15\%$ immature neutrophils (bands) regardless of total peripheral white blood cell count.

Patients were excluded for previous antibiotic treatment received for more than 24 hours within 7 days of study entry unless the pathogen showed drug resistance or the treatment failed (defined as no clinical improvement after 3 days of treatment); an uncomplicated skin and superficial skin structure infection (simple abscess, impetiginous lesion, furuncle, or superficial cellulitis); abscesses that only needed surgical draining at the time of patient enrollment; self-limited infections, such as isolated folliculitis or other infection that has a high surgical incision cure rate or furunculosis or carbunculosis that was not associated with a cellulitis at least 1 cm in radius; diabetic foot, decubitus, and ischemic ulcers, necrotizing fasciitis, gas gangrene, or burns greater than 20% of total body surface; superinfected eczema or other chronic medical conditions (ie, atopic dermatitis) where inflammation may be prominent for an extended period even after successful bacterial eradication; infections or conditions requiring concomitant antimicrobial (with the exception of aztreonam) or systemic corticosteroid treatment; infections complicated by the presence of prosthetic materials such as central venous catheters, permanent cardiac pacemaker battery packs, or those involving joint-replacement prostheses, etc, unless the prosthesis was removed; known osteomyelitis; known liver disease with total bilirubin >5 times ULN; known neutropenia (absolute neutrophil count <500 cells/ mm^3); unlikely to survive through the treatment period and evaluation (< 60 days).

10.2.1.2 Results

10.2.1.2.1 Patient Disposition and Evaluability/Demographics

The evaluability/disposition of patients in Study 55 are summarized in Table 30 and Table 31.

Table 30. Summary of Patient Evaluability (Study 55)

Population	Linezolid		Oxacillin/Dicloxacillin	
	No.	%†	No.	%†
ITT Patients	400	100.0	419	100.0
MITT Patients	212	53.0	219	52.3
Clinically Evaluable Patients	298	74.5	302	72.1
Microbiologically Evaluable Patients	143	35.8	151	36.0

† Percentages based on ITT population.

ITT = Intent-to-Treat; MITT = Modified Intent-to-Treat

Table 31. Summary of Patient Disposition – ITT Patients (Study 55)

Population	Linezolid N = 400		Oxacillin/Dicloxacillin N = 419	
	No.	%	No.	%
Completed Treatment	357	89.2	349	83.3
Discontinued During Treatment	43	10.8	70	16.7
-Lack of Efficacy	9	2.3	15	3.6
-Death	1	0.3	0	0
-Adverse Event	10	2.5	20	4.8
-Ineligible but Started Study Medication	4	1.0	3	0.7
-Protocol Noncompliance	3	0.8	5	1.2
-Subject's Personal Request	2	0.5	6	1.4
-Lost to Follow-Up	8	2.0	10	2.4
-Other	6	1.5	11	2.6

ITT = Intent-to-Treat

The treatment groups were comparable at baseline with respect to age, vital signs, weight, lesion size (length, width, and area), duration of infection, sex, race, medical history, physical examination data, diagnosis, primary site of infection, degree of involvement, clinical signs and symptoms, and safety laboratory parameters. Approximately 62% of the patients were male, and the distribution of patient ages was approximately 46% <45 years, 33% 45-64 years, and 21% ≥65 years.

10.2.1.2.2 Clinical Cure Rates

An overview of the clinical cure rates for patients with complicated skin and soft tissue infections is presented in Table 32. The treatment groups were statistically equivalent with respect to the Sponsor's Assessment of Clinical Outcome for Clinically Evaluable patients (95% CI for difference = -0.7%, 9.5%).

Table 32. Clinical Cure Rates for Patients with Complicated Skin and Soft Tissue Infections (Study 55)

Sponsor's Assessment of Clinical Outcome	Linezolid		Oxacillin/Dicloxacillin		95% CI
	n/N	% [†]	n/N	% [†]	
ITT Patients	279/328	85.1	272/354	76.8	2.4, 14.1
MITT Patients	144/173	83.2	138/184	75.0	-0.1, 16.6
Clinically Evaluable Patients	264/291	90.7	259/300	86.3	-0.7, 9.5
Microbiologically Evaluable Patients	126/140	90.0	130/151	86.1	-3.5, 11.3

[†] Percentages are based on the total number of patients reporting, excluding indeterminate and missing. ITT = Intent-to-Treat; MITT = Modified Intent-to-Treat; CI = confidence interval for difference

Clinical cure rates by diagnosis are summarized for Study 55 in Table 33. The cure rates were similar between treatment groups for all diagnostic categories.

Table 33. Clinical Cure Rates by Diagnosis for Clinically Evaluable Patients With Complicated Skin and Soft Tissue Infections (Study 55)

Diagnosis	Linezolid		Oxacillin/Dicloxacillin	
	n/N	%†	n/N	%†
Cellulitis	116/124	93.5	118/133	88.7
Skin abscess	36/39	92.3	36/44	81.8
Erysipelas	27/32	84.4	30/33	90.9
Infected Wound	17/20	85.0	22/27	81.5
Infected Surgical Incision	15/18	83.3	8/12	66.7
Skin ulcer	11/12	91.7	8/9	88.9
Infected Bite	4/5	80.0	2/3	66.7
Other	38/41	92.7	35/39	89.7

† Percentages are based on the total number of patients reporting excluding indeterminate and missing.

10.2.1.2.3 Pathogen Eradication Rates

Table 34 presents pathogen eradication rates in Microbiologically Evaluable patients with complicated skin and soft tissue infections.

Table 34. Pathogen Eradication Rates in Microbiologically Evaluable Patients With Complicated Skin and Soft Tissue Infections (Study 55)

Pathogen	Linezolid		Oxacillin/Dicloxacillin	
	n/N	%†	n/N	%†
<i>Staphylococcus aureus</i>	85/93	91.4	87/103	84.5
Methicillin-resistant§	2/3	66.7	0/2	0
<i>Streptococcus agalactiae</i>	7/7	100.0	4/6	66.7
<i>Streptococcus pyogenes</i>	23/29	79.3	27/32	84.4
Other <i>Streptococcus</i> spp‡	10/11	90.9	5/5	100.0

† Percentages are based on the total number of patients reporting, excluding indeterminate and missing.

§ Data for resistant organisms are subsets of the pathogen total.

‡ Includes *S anginosus*, *S bovis*, *S canis*, *S mitis*, and *S intermedius*.

10.2.2 Conclusions

- Linezolid is equivalent to comparators (vancomycin and oxacillin/dicloxacillin) in the treatment of complicated skin and soft tissue infections at doses of 600 mg twice daily IV/oral. Linezolid cured 89.1% of the Clinically Evaluable population versus 84.9% treated with the comparators.
- The recommended duration of therapy is 10 to 14 days.
- Linezolid effectively eradicated *S aureus* (including MRSA), *S agalactiae*, *S pyogenes*, and *S epidermidis* at rates comparable to comparators.

11 SUMMARY OF EFFICACY DATA: METHICILLIN-RESISTANT *STAPHYLOCOCCUS* SPECIES INFECTIONS (STUDY 31)

11.1 Clinical Methodology

11.1.1 Study Design

This phase III, randomized, open-label, comparator-controlled, multicenter study was conducted in order to support the pivotal trials; patients had to be at least 13 years of age with known or suspected methicillin-resistant *Staphylococcus* species infections. The study consisted of a baseline/screening visit, hospitalization during at least the first intravenous dose of study medication, outpatient or inpatient treatment evaluations every 6 days while on treatment after day 3, an EOT visit within 72 hours of the last dose of study medication, and a short-term follow-up (STFU) and long-term follow-up (LTFU) visit based on the type of infection. Clinical and microbiological assessments were performed throughout the study; the TOC assessments were completed at the STFU visit. Safety was evaluated throughout the study by physical examination, vital sign assessments, laboratory assessments, and adverse events.

11.1.2 Study Drug Dosage Form and Dosage Regimen

- Linezolid IV 600 mg twice daily followed by linezolid oral 600 mg twice daily for 7 to 28 consecutive days
- Vancomycin IV 1 g twice daily for 7 to 28 consecutive days

11.1.3 Inclusion/Exclusion Criteria

Hospitalized patients (including those in chronic care facilities), at least 13 years of age and 40 kg in weight were enrolled. Patients were also required to satisfy all of the following criteria: patients must have a known or suspected *Staphylococcus* infection as determined by laboratory findings consistent with *Staphylococcus* infection (eg, Gram's stain or culture

results) and have signs and symptoms of an active infection of pneumonia, skin and soft tissue infection, urinary tract infection, or bacteremia.

Patients were excluded from participation in the study for any of the following reasons: endocarditis; osteomyelitis or CNS infections; infected devices that could not be removed; absolute neutrophil count $< 500/\text{mm}^3$; known liver disease with total bilirubin > 5.0 times ULN; more than 24 hours of treatment with a potentially effective antibiotic within 48 hours of study entry, unless the therapy had failed or the pathogen showed drug resistance, with the exception of vancomycin; concurrent use of another investigational medication; an infection due to organisms known to be resistant to the study medications.

The original protocol limited eligibility to patients with cultures positive for MRSA or known MRSA carriers; however, due to the sponsor's interest in understanding what efficacy linezolid would have with invasive coagulase-negative staphylococci, this requirement was changed to include patients with known or suspected methicillin-resistant *Staphylococcus* species infections, as determined by laboratory findings consistent with such infections.

11.2 Results

11.2.1 Patient Disposition and Evaluability/Demographics

The evaluability/disposition of patients in Study 31 are summarized in Table 35 and Table 36.

Table 35. Summary of Patient Evaluability (Study 31)

Population	Linezolid		Vancomycin	
	No.	%†	No.	%†
ITT Patients	240	100.0	220	100.0
MITT Patients	157	65.4	144	65.5
Clinically Evaluable Patients	124	51.7	130	59.1
Microbiologically Evaluable Patients	64	26.7	70	31.8

† Percentages based on ITT population.

ITT = Intent-to-Treat; MITT = Modified Intent-to-Treat

Table 36. Summary of Patient Disposition – ITT Patients (Study 31)

Population	Linezolid N = 240		Vancomycin N = 220	
	No.	%	No.	%
Completed Treatment	162	67.5	151	68.6
Discontinued During Treatment	78	32.5	69	31.4
-Lack of Efficacy	7	2.9	3	1.4
-Death	16	6.7	13	5.9
-Adverse Event	9	3.8	7	3.2
-Ineligible, but Started Study Medication	32	13.3	38	17.3
-Protocol Noncompliance	2	0.8	2	0.9
-Subject's Personal Request	2	0.8	0	0
-Other†	10	4.2	6	2.7

† Not specified.

ITT = Intent-to-Treat

In general, patients in both treatment groups were comparable at baseline with respect to weight, race, sex, and geographic region. There was a statistically significant difference between treatment groups in age, with the linezolid group having a mean age of 63.9 years and the vancomycin group having a mean age of 59.8 years ($p = 0.016$). Patients were also comparable at baseline with respect to vital signs, lesion size (length, width, and area), duration of infection, medical history, physical examination data, diagnosis, primary site of infection, degree of involvement, clinical signs and symptoms, and safety laboratory parameters. Approximately 60% of the patients were male.

11.2.2 Clinical Cure Rates

11.2.2.1 Overall Clinical Cure Rates

An overview of the clinical cure rates for patients in Study 31 is presented in Table 37. (These results are derived from the total patient population; ie, those with known or suspected methicillin-resistant *Staphylococcus* species infections, including MRSA and coagulase-negative staphylococci.) The treatment groups were equivalent with respect to the Sponsor's Assessment of Clinical Outcome (95% CI for difference = -8.2%, 13.6%).

Table 37. Clinical Cure Rates for All Patients in Study 31

Sponsor's Assessment of Clinical Outcome	Linezolid		Vancomycin		95% CI
	n/N	%†	n/N	%†	
ITT Patients	109/192	56.8	93/169	55.0	-8.5, 12.0
MITT Patients	75/125	60.0	69/117	59.0	-11.4, 13.4
Clinically Evaluable Patients	94/122	77.0	87/117	74.4	-8.2, 13.6
Microbiologically Evaluable Patients	46/64	71.9	45/62	72.6	-16.3, 14.9

† Percentages are based on the total number of patients reporting, excluding indeterminate and missing. ITT = Intent-to-Treat; MITT = Modified Intent-to-Treat; CI = confidence interval for difference

11.2.2.2 Clinical Cure Rates for MRSA Infections

An overview of the clinical cure rates for patients in Study 31 with infections caused by MRSA only are presented in Table 38.

Table 38. Clinical Cure Rates for MRSA Patients in Study 31

Sponsor's Assessment of Clinical Outcome	Linezolid		Vancomycin	
	n/N	%†	n/N	%†
MITT Patients	59/98	60.2	53/85	62.4
Microbiologically Evaluable Patients	41/56	73.2	38/52	73.1

† Percentages are based on the total number of patients reporting, excluding indeterminate and missing.

MITT = Modified Intent-to-Treat

11.2.2.3 Clinical Cure Rates for MRSA Infections by Source of Infection

Table 39 summarizes the cure rates for the Sponsor's Assessment of Clinical Outcome for MRSA infections in Microbiologically Evaluable patients by source of infection.

Table 39. Clinical Cure Rates for Sponsor's Assessment of Clinical Outcome in the Microbiologically Evaluable Population by Source of MRSA Infection (Study 31)

Source of Infection	Linezolid		Vancomycin	
	n/N	%†	n/N	%†
All Sources	41/56	73.2	38/52	73.1
Pneumonia	9/12	75.0	12/16	75.0
Skin and soft tissue infection	27/34	79.4	22/30	73.3
Urinary tract infection	0/1	0	1/1	100.0
Other	3/6	50.0	2/3	66.7
Bacteremia of Unknown Source	2/3	66.7	1/2	50.0

† Number of assessed patients excludes those with indeterminate and missing outcomes.

11.2.3 Pathogen Eradication Rates

Individual pathogen eradication rates are presented for the Microbiologically Evaluable population in Table 40.

Table 40. Pathogen Eradication Rates in Microbiologically Evaluable Patients (Study 31)

Pathogen	Linezolid		Vancomycin	
	n/N	%†	n/N	%†
<i>Staphylococcus aureus</i> (methicillin-resistant)	34/56	60.7	36/57	63.2
Other <i>Staphylococcus</i> species‡	7/12	58.3	9/13	69.2

† Percentages are based on the total number of patients reporting, excluding indeterminate and missing.

‡ Includes *S auricularis*, *S epidermidis*, *S hemolyticus*, *S hominus*, and *S xylosum*.

12 SUMMARY OF EFFICACY DATA: METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* INFECTIONS

Table 41 summarizes the clinical cure rates in the Microbiologically Evaluable population for MRSA patients by study and diagnosis.

Table 41. Clinical Cure Rates for Microbiologically Evaluable MRSA Patients

Sponsor's Assessment of Clinical Outcome	Linezolid		Comparator*	
	n/N	%†	n/N	%†
Nosocomial Pneumonia				
Study 48A	15/23	65.2	7/9	77.8
Study 31	9/12	75.0	12/16	75.0
Complicated Skin and Soft Tissue Infections				
Study 55	2/3	66.7	1/2	50.0
Study 31	27/34	79.4	22/30	73.3

* Vancomycin in Studies 48A and 31; oxacillin/dicloxacillin in Study 55.

† Percentages are based on the total number of patients reporting, excluding indeterminate and missing.

The linezolid regimen was comparable to the comparator for both indications. Although clinical cure rates for MRSA infections were generally lower than those observed for methicillin-susceptible *S aureus*, it is likely that methicillin resistance served as a marker for the presence of extensive comorbidity in this patient population.

13 SUMMARY OF EFFICACY DATA: VANCOMYCIN-RESISTANT ENTEROCOCCAL INFECTIONS

13.1 Pivotal Study 54A

13.1.1 Clinical Methodology

13.1.1.1 Study Design

This phase III, randomized, double-blind, multicenter study was conducted in patients with infections caused by VRE. The study consisted of a baseline/screening visit; a treatment phase, including patient treatment evaluation visits on days 3, 6, 9, 15, and 21; an EOT visit within 72 hours of the last dose of study medication; and an F-U visit 15 to 21 days after the EOT visit. Patients with urinary tract infections returned for an F-U visit 7 to 10 days after EOT and an LTFU visit from 4 to 6 weeks after discontinuation of linezolid. Clinical and microbiological assessments were performed at each visit. Safety was evaluated throughout the study by physical examination, vital signs assessments, laboratory evaluations, and assessment of adverse events.

Study 54A was designed to test the superiority of the 600-mg dose of linezolid over the 200-mg dose of linezolid. The dose-comparison design was necessary, since at the time the study was designed and conducted there was no approved comparator for VRE bacteremia, and it would have been unethical to conduct a placebo-controlled trial. Based on animal models, efficacy was anticipated for the 200-mg dose because it produces blood levels above the MIC₉₀ for both *E faecium* and *E faecalis* for at least 40% of the dosing interval. A 400-mg dose was not used in this study because the interpatient variability of linezolid pharmacokinetics is such that it would have been difficult to determine the pharmacologic component for a difference between the 400- and 600-mg dose outcomes.

The design of Study 54A was the result of discussions with the FDA and was based on a planned enrollment of 500 patients (250 patients per treatment group). However, Pharmacia & Upjohn decided to terminate this study after 145 patients had been enrolled and treated in order to include this valuable experience in the NDA submission. The decision to terminate the study was a prospective decision and was not based on an interim analysis of the data. (After the termination of Study 54A, patients continued to be enrolled in extension Study 54, whose protocol was identical to Study 54A.. Interim data for Study 54 are included in the results section.)

13.1.1.2 Study Drug Dosage Form and Dosage Regimen

- Linezolid IV or oral 600 mg twice daily for 7 to 28 days
- Linezolid IV or oral 200 mg twice daily for 7 to 28 days

13.1.1.3 Inclusion/Exclusion Criteria

Male or female patients who were at least 13 years of age and weighed at least 40 kg with known VRE infections (eg, infections of the respiratory tract, urinary tract, peritoneum, or wounds, or VRE bacteremia of unknown source) were eligible for enrollment in the study if they had a VRE-positive culture of blood, urine, wound, abscess, respiratory secretions, or peritoneal or pleural fluid; an accessible site for Gram's stain and culture; signs and symptoms of an active infection, such as fever, chills, malaise, myalgia, or mental status changes; expected survival of 60 days; or signs and symptoms outlined for the following clinical syndromes:

- Skin and tissue infection required at least two of the following: drainage/discharge, erythema, fluctuance, heat/localized warmth, pain/tenderness to palpation, or swelling/induration.
- Urinary tract infection required one of the following symptoms (not required for patients unable to provide a history): dysuria, frequency, urgency, costovertebral angle tenderness, suprapubic pain, or a positive urine culture.

Patients were to be excluded from the study for any of the following reasons: females of child-bearing potential who were unable to take adequate contraceptive precautions, had a positive pregnancy test result within 24 hours prior to study entry, were otherwise known to be pregnant, or were currently breastfeeding an infant; endocarditis, osteomyelitis, or central nervous system (CNS) infections; infected devices that were not to be removed; gas gangrene or necrotizing fasciitis; known pheochromocytoma, carcinoid syndrome, untreated hyperthyroidism, or uncontrolled or untreated hypertension; previously enrolled in this or another linezolid study; hypersensitive to linezolid or one of its excipients; currently using another investigational medication; received more than 24 hours of a potentially effective antibiotic in the last 7 days prior to entry or since the last positive blood culture.

Prior to the enrollment of the first patient, the inclusion criteria were modified to allow patients to be enrolled with a single positive blood culture provided that they satisfied the other inclusion criteria (including the presence of signs and symptoms of active infection). Other changes to the inclusion/exclusion criteria were as follows:

- For UTI, the inclusion criterion for characteristic symptoms was conditional on the patient's ability to provide a history. Symptomatic patients were eligible for enrollment if the urine grew $\geq 10^3$ VRE CFU/mL. Asymptomatic patients were required to have $\geq 10^5$ VRE CFU/mL on urine culture.
- Gas gangrene/necrotizing fasciitis were added as exclusion criteria.

Originally, VRE bacteremia of unknown source was defined as two positive blood cultures drawn at least 8 hours apart. This definition was amended to include patients with two positive blood cultures drawn at least one hour apart, or alternatively, two positive blood cultures drawn concurrently from two different sites.

The protocol was also amended to include patients with positive VRE cultures within 96 hours of enrollment instead of the original 72 hour requirement.

13.1.2 Results

13.1.2.1 Patient Disposition and Evaluability/Demographics

The evaluability/disposition of patients in Study 54A are summarized in Table 42 and Table 43.

Table 42. Summary of Patient Evaluability (Studies 54A and 54)

Population	Linezolid 600 mg Twice Daily		Linezolid 200 mg Twice Daily	
	No.	%†	No.	%†
Study 54A				
ITT Patients	79	100.0	66	100.0
MITT Patients	69	87.3	58	87.9
Clinically Evaluable Patients	48	60.8	40	60.6
Microbiologically Evaluable Patients	36	45.6	29	43.9
Studies 54A & 54 Combined				
ITT Patients	113	100.0	114	100.0
MITT Patients	100	88.5	100	87.7
Clinically Evaluable Patients	73	64.6	65	57.0
Microbiologically Evaluable Patients	55	48.7	48	42.1

† Percentages based on ITT population.

ITT = Intent-to-Treat; MITT = Modified Intent-to-Treat

Table 43. Summary of Patient Disposition – ITT Patients (Studies 54A and 54)

Population	Linezolid 600 mg Twice Daily N = 79		Linezolid 200 mg Twice Daily N = 66	
	No.	%	No.	%
Study 54A				
Completed Treatment	60	75.9	50	75.8
Discontinued During Treatment	19	24.1	16	24.2
-Lack of Efficacy	0	0	2	3.0
-Death	6	7.6	5	7.6
-Adverse Event	6	7.6	3	4.5
-Ineligible but Started Study Medication	6	7.6	4	6.1
-Lost to Follow-Up	1	1.3	0	0
-Other†	0	0	2	3.0
Population	Linezolid 600 mg Twice Daily N = 113		Linezolid 200 mg Twice Daily N = 114	
	No.	%	No.	%
Studies 54A & 54 Combined				
Completed Treatment	88	77.9	80	70.2
Discontinued During Treatment	25	22.1	34	29.8
-Lack of Efficacy	0	0	3	2.6
-Death	8	7.1	12	10.5
-Adverse Event	7	6.2	6	5.3
-Ineligible but Started Study Medication	8	7.1	5	4.4
Protocol Noncompliance	0	0	2	1.8
Subject's Personal Request	1	0.9	1	0.9
-Lost to Follow-Up	1	0.9	0	0
-Other†	0	0	5	4.4

† Not specified.

ITT = Intent-to-Treat

There were no significant differences in age, weight, sex, and race between groups. Both treatment groups were comparable with respect to baseline characteristics. In Study 54A, approximately 46% of the patients were male, and the distribution of patient ages was approximately 15% <45 years, 28% 45-64 years, and 57% ≥65 years. In the combined Study 54A and 54, approximately 46% of the patients were male, and the distribution of patient ages was approximately 16% <45 years, 29% 45-64 years, and 55% ≥65 years.

13.1.2.2 Clinical Cure Rates

An overview of the clinical cure rates for patients in Study 54A and 54 is presented in Table 44. Unlike the other phase III studies, Study 54A was designed to test the superiority of a 600-mg twice-daily linezolid dose over a 200-mg twice-daily linezolid dose. The 600-mg twice-daily dose group had a higher cure rate than the 200-mg twice-daily dose group for the Sponsor's Assessment of Clinical Outcome in Clinically Evaluable patients (88.6% vs 73.7%; $p = 0.081$).

Table 44. Clinical Cure Rates for Patients in Studies 54A and 54

Sponsor's Assessment of Clinical Outcome	600 mg Twice Daily		200 mg Twice Daily	
	n/N	%†	n/N	%†
Study 54A				
ITT Patients	42/63	66.7	28/52	53.8
MITT Patients	40/55	72.7	28/47	59.6
Clinically Evaluable Patients	39/44	88.6	28/38	73.7
Microbiologically Evaluable Patients	30/35	85.7	22/29	75.9
Studies 54A & 54 Combined				
ITT Patients	60/92	65.2	46/88	52.3
MITT Patients	58/81	71.6	46/79	58.2
Clinically Evaluable Patients	57/68	83.8	44/60	73.3
Microbiologically Evaluable Patients	45/53	84.9	37/47	78.7

† Percentages are based on the total number of patients reporting, excluding indeterminate and missing.

ITT = Intent-to-Treat; MITT = Modified Intent-to-Treat; CI = confidence interval for difference

Clinical cure rates by pathogen for the Microbiologically Evaluable population are displayed in Table 45.

Table 45. Clinical Cure Rates (Sponsor's Assessment of Clinical Outcome) by Baseline Pathogen for Microbiologically Evaluable Patients in Study 54A

Baseline Pathogen	600 mg Twice Daily		200 mg Twice Daily	
	n/N	%†	n/N	%†
<i>Enterococcus avium</i> (vancomycin-resistant)	0	0	1/1	100.0
<i>Enterococcus faecalis</i>	3/4	75.0	3/4	75.0
Vancomycin susceptible§	1/2	50.0	3/4	75.0
Vancomycin resistant§	2/2	100.0	0	0
<i>Enterococcus faecium</i>	29/33	87.9	20/27	74.1
Vancomycin susceptible§	1/1	100.0	0	0
Vancomycin resistant§	28/32	87.5	18/25	72.0

† Percentages are based on the total number of patients reporting, excluding indeterminate and missing.

§ Data for susceptible and resistant organisms are subsets of the pathogen total.

13.1.2.3 Pathogen Eradication Rates

Individual pathogen eradication rates for the Microbiologically Evaluable population are shown in Table 46.

Table 46. Pathogen Eradication Rates for Microbiologically Evaluable Patients in Studies 54A and 54

Pathogen	Linezolid			
	600 mg Twice Daily		200 mg Twice Daily	
	n/N	%†	n/N	%†
Study 54A				
<i>Enterococcus avium</i> (vancomycin-resistant)	0	0	1/1	100.0
<i>Enterococcus faecalis</i>	3/4	75.0	3/4	75.0
Vancomycin-resistant‡	1/2	50.0	0	0
<i>Enterococcus faecium</i>	29/33	87.9	16/27	59.3
Vancomycin-resistant‡	28/32	87.5	15/25	60.0
Studies 54A & 54 Combined				
<i>Enterococcus avium</i> (vancomycin-resistant)	0	0	1/1	100.0
<i>Enterococcus faecalis</i>	5/7	71.4	4/5	80.0
Vancomycin-resistant‡	1/2	50.0	0	0
<i>Enterococcus faecium</i>	44/51	86.3	29/44	65.9
Vancomycin-resistant‡	43/50	86.0	28/42	66.7

† Percentages are based on the total number of patients reporting, excluding indeterminate and missing.

‡ Data for resistant organisms are subsets of the pathogen total.

13.2 Supportive Study 25 (Compassionate Use)

This is an ongoing, open-label, noncomparative trial of linezolid in patients infected with multidrug-resistant, gram-positive organisms for which no satisfactory alternative therapy is available. Evaluability criteria are similar to the controlled Study 54A. Adult patients are treated with linezolid 600 mg twice daily intravenously or orally for up to 21 days (or up to 3 months with approval by the P&U monitor). Patients weighing less than 40 kg (including infants older than 28 days) are treated with 10 mg/kg twice daily. Data for 230 patients in the P&U database before 30 June 1999 were included in this interim analysis.

13.2.1 Clinical Cure Rates

The majority of patients receiving linezolid through the compassionate use Study 25 (62.6%, 144/230) had VRE. Table 47 summarizes the clinical cure rates for patients with VRE in Study 25. The clinical cure rates were excellent and consistent with the results of the 600-mg twice-daily dose group in Studies 54A and 54.

Table 47. Clinical Cure Rates for Patients with VRE Infections (Study 25)

Sponsor's Assessment of Clinical Outcome	Linezolid	
	n/N	%†
Clinically Evaluable Patients	52/58	89.7

† Percentages are based on the total number of patients reporting excluding indeterminate and missing.

VRE = Vancomycin-resistant *Enterococcus*

13.2.2 Pathogen Eradication Rates

Pathogen eradication rates for Microbiologically Evaluable patients with VRE infections are displayed in Table 48.

Table 48. Pathogen Eradication Rates for Microbiologically Evaluable Patients with VRE Infections (Study 25)

Pathogen	Linezolid	
	n/N	%†
<i>Enterococcus faecalis</i>	9/9	100.0
<i>Enterococcus faecium</i>	55/64	85.9

† Percentages are based on the total number of patients reporting excluding indeterminate and missing.

VRE = Vancomycin-resistant *Enterococcus*

13.3 Clinical Cure Rates by Source of Infection: Studies 54A and 25

Table 49 presents a summary of clinical cure rates by source of infection and linezolid dose for Studies 54A and 25. While the numbers of patients with specific sources of VRE infection are small, the clinical cure rates by source of infection between the 600-mg twice-daily dose groups of Study 54A (VRE) and Study 25 (compassionate use) are generally comparable. Of note is the efficacy of 600-mg twice-daily linezolid therapy in the cure of deep tissue infections (bacteremia of unknown origin, peritonitis, intra-abdominal infections, those infections considered “not classified,” and pneumonia). For these infections, 87.9% (51/58) of the 600-mg twice daily dose group were clinical cures, compared with 66.7% (8/12) of the 200-mg twice-daily dose group.

Table 49. Cure Rates for Sponsor’s Assessment of Clinical Outcome in the Clinically Evaluable Population by Source of Infection (Studies 54A and 25)

Source of Infection	Linezolid 600 mg Twice Daily		Linezolid 200 mg Twice Daily
	Study 25*	Study 54A	Study 54A
	n/N (%)	n/N (%)	n/N (%)
All Sources	52/58 (89.6)	39/44 (88.6)	28/38 (73.7)
Bacteremia of unknown origin	10/12 (83.3)	6/9 (66.7)	2/2 (100.0)
Other	33/35 (94.3)	11/11 (100.0)	7/11 (63.6)
-Peritonitis†	11/12 (91.7)	1/1 (100.0)	3/6 (50.0)
-Intra-abdominal†	11/12 (91.7)	4/4 (100.0)	2/2 (100.0)
-Catheter-related†	9/9 (100.0)	3/3 (100.0)	1/1 (100.0)
-Not classified† ‡	2/2 (100.0)	3/3 (100.0)	1/2 (50.0)
Pneumonia	1/1 (100.0)	2/2 (100.0)	0
Skin and soft tissue	7/9 (77.8)	8/9 (88.9)	6/6 (100.0)
Urinary tract	1/1 (100.0)	12/13 (92.3)	13/19 (68.4)

* VRE patients only.

† Data for these sources of infections are subsets of “Other.”

‡ Includes sources of infection such as hepatic abscess, biliary sepsis, necrotic gall bladder, pericolonic abscess, and pancreatitis.

VRE = Vancomycin-resistant *Enterococcus*

13.4 Conclusions

- Linezolid 600 mg twice daily is effective for the treatment of a variety of infections caused by *Enterococcus* species, both sensitive and resistant strains.
- Linezolid 600 mg twice daily is effective for the treatment of infections caused by vancomycin-resistant *E faecium* or *E faecalis*, with a clinical cure rate of 89%.
- Treatment with linezolid IV/oral 600 mg twice daily results in an improved cure rate when compared with linezolid IV/oral 200 mg twice daily.
- A minimum recommended duration of therapy is 14 days. Refractory infections may require up to 28 days of therapy.

14 SUMMARY OF SAFETY DATA

The analyses of safety data (adverse events, laboratory assays, and vital signs) were all performed on the ITT population; ie, enrolled patients who received at least one dose of study medication.

Appendix B contains by-study adverse event and laboratory assay data for the seven comparator-controlled phase III studies, as well as for the dose-comparison study 54A.

14.1 Adverse Events in the Phase III Comparator-Controlled Studies

This section reviews the adverse event data that was gathered in the comparator-controlled phase III trials: Studies 31, 33, 39A, 39, 48A, 51, and 55. These studies evaluated the use of linezolid in community-acquired pneumonia, nosocomial pneumonia, skin and soft tissue infections (both complicated and uncomplicated), and methicillin-resistant *Staphylococcus* species infections. Comparators included oxacillin, dicloxacillin, clarithromycin, vancomycin, ceftriaxone, and cefpodoxime proxetil. Study 54A was excluded from this analysis because it was not a comparator-controlled trial and enrolled patients who were typically critically ill with significant comorbid diseases. Adverse event data for Study 54A are discussed in section 14.2.1.

14.1.1 Patient Population

14.1.1.1 Disposition

The total number of linezolid-treated patients was 2046 and the total number of comparator-treated patients was 2001. The proportion of reasons for the discontinuation of treatment of ITT patients are provided in Table 50. The percentages of patients who discontinued treatment were similar between the linezolid-treated patients (18.1%, 370/2046) and the patients who received comparator study medications (17.7%, 354/2001). The reasons for discontinuation were similar between the linezolid and comparator groups.

**Table 50. Phase III Primary Reasons for Discontinuation of Treatment – ITT Patients
(Studies 31, 33, 39A, 39, 48A, 51, and 55)**

Parameter	Linezolid N = 2046		Comparators N = 2001	
	n	%†	n	%†
Discontinued Patients	370	18.1	354	17.7
Lack of Efficacy	64	3.1	71	3.5
Death	37	1.8	34	1.7
Adverse Event (Serious)	30	1.5	32	1.6
Adverse Event (Nonserious)	68	3.3	47	2.3
Ineligible But Started Study Medication	58	2.8	63	3.1
Protocol Noncompliance	14	0.7	14	0.7
Subject's Personal Request	20	1.0	18	0.9
Lost to Follow-Up	29	1.4	31	1.5
Other	50	2.4	44	2.2

† Percentages are based on the total number of patients in each group.

14.1.1.2 Demographics

The demographic characteristics of patients in the linezolid and comparator groups are summarized in Table 51. The treatment populations were similar in the distribution of patients by age, sex, race, treatment indication, and region.

**Table 51. Phase III Demographics – ITT Patients
(Studies 31, 33, 39A, 39, 48A, 51, and 55)**

Parameter	Linezolid N = 2046		Comparators N = 2001	
	n	%†	n	%†
Age (years)				
<18	10	0.5	8	0.4
18 to 44	816	39.9	814	40.7
45 to 64	631	30.8	602	30.1
≥65	589	28.8	577	28.8
Sex				
Male	1212	59.2	1152	57.6
Female	834	40.8	849	42.4
Race				
White	1453	71.0	1421	71.0
Black	207	10.1	223	11.1
Asian or Pacific Islander	125	6.1	136	6.8
Other‡	261	12.8	221	11.0
Indication				
Pneumonia	908	44.4	874	43.7
Skin/Soft Tissue	1070	52.3	1064	53.2
Other	68	3.3	63	3.1
Region§				
North America	933	45.6	926	46.3
Latin America	343	16.8	321	16.0
Europe	652	31.9	635	31.7
Other	118	5.8	119	5.9

† Percentages are based on the total number of patients in each group. Percentages may not add to 100 due to rounding.

‡ The “Other” race category includes “Not allowed to ask,” “Mixed,” and “Missing” responses.

§ North America (US and Canada), Latin America (Mexico and South America), Europe (Europe, Israel, South Africa, and Australia), and Other.

14.1.1.3 Extent of Exposure

The extent of exposure for the linezolid and comparator groups is provided in Table 52. The mean duration of intravenous and oral treatment was similar in the linezolid and comparator groups, as was the total duration of treatment.

**Table 52. Phase III Extent of Exposure – ITT Patients
(Studies 31, 33, 39A, 39, 48A, 51, and 55)**

Parameter	Linezolid N = 2046		Comparators N = 2001	
	n	%†	n	%†
Days on IV Treatment†				
Total Reporting	1224		1198	
Mean ± SD	5.8 ± 4.1		6.7 ± 4.9	
Range	1 to 29		1 to 32	
Days on Oral Treatment†				
Total Reporting	1646		1451	
Mean ± SD	10.4 ± 4.1		10.7 ± 3.9	
Range	1 to 29		1 to 36	
Total Days on Treatment†				
Total Reporting	2031		1985	
Mean ± SD	11.6 ± 4.9		11.6 ± 4.8	
Range	1 to 31		1 to 46	

† Based on interval between start and stop dates: (stop-start) + 1. Exposure not calculated if stop date not recorded.

SD = Standard deviation

14.1.2 Adverse Event Summary

An overall summary of adverse events for the linezolid and comparator groups is presented in Table 53.

**Table 53. Phase III Overall Summary of Adverse Events – ITT Patients
(Studies 31, 33, 39A, 39, 48A, 51, and 55)**

Parameter	Linezolid N = 2046		Comparators N = 2001	
	n	%†	n	%†
Patients with at least one adverse event reported	1137	55.6	988	49.4
Patients with at least one drug-related adverse event reported	444	21.7	314	15.7
Patients with at least one serious adverse event reported	233	11.4	212	10.6
Treatment discontinued due to at least one adverse event	118	5.8	105	5.2
Treatment discontinued due to at least one drug-related adverse event	50	2.4	38	1.9
Patients who died	98	4.8	99	4.9

† Percentages are based on the number of patients reporting.

Table 53 shows that overall and drug-related adverse events were reported more frequently in linezolid-treated patients than in comparator-treated patients. Linezolid-treated patients also had slightly higher rates of serious adverse events and discontinuations due to adverse events (including discontinuations due to drug-related adverse events).

14.1.3 Overall Adverse Events

The data for adverse events within body systems that occurred in at least 2% of patients are presented in Table 54. The adverse event profile was comparable to those observed in the phase I and phase II studies. The most frequently reported adverse events were diarrhea (linezolid 8.3%, 170/2046; comparator 6.3%, 126/2001), headache (linezolid 6.5%, 134/2046; comparator 5.5%, 110/2001), and nausea (linezolid 6.2%, 127/2046; comparator 4.6%, 92/2001). There were four comparator-treated patients with *Clostridium difficile* colitis, as well as two with *C difficile* diarrhea and one with pseudomembranous colitis. One additional comparator-treated patient had evidence of *C difficile* in the stool, giving a total of 0.4% (8/2001) of comparator-treated patients with *C difficile* complications. For linezolid, only one patient had pseudomembranous colitis, while three patients had evidence of *C difficile* in the stool, giving 0.2% (4/2046) of linezolid-treated patients with *C difficile*-related complications.

**Table 54. Phase III Adverse Events in $\geq 2\%$ of Patients – ITT Patients
(Studies 31, 33, 39A, 39, 48A, 51, and 55)**

COSTART Body System MET	Linezolid N = 2046		Comparators N = 2001	
	n	%†	N	%†
Patients With None	909	44.4	1013	50.6
Patients With at Least One	1137	55.6	988	49.4
BODY				
Fever	33	1.6	42	2.1
Headache	134	6.5	110	5.5
Trauma	43	2.1	36	1.8
DIGESTIVE				
Constipation	44	2.2	42	2.1
Diarrhea	170	8.3	126	6.3
Nausea	127	6.2	92	4.6
Vomiting	75	3.7	41	2.0
NERVOUS				
Dizziness	41	2.0	38	1.9
Insomnia	52	2.5	35	1.7
SKIN				
Rash	40	2.0	44	2.2
UROGENITAL				
Infection Urinary Tract	43	2.1	27	1.3

† Percentages are based on the number of patients reporting. Patients are counted once per COSTART MET.

14.1.4 Drug-Related Adverse Events

An overall summary of drug-related adverse events that occurred in at least 1% of patients is presented in Table 55. The number of patients with drug-related adverse events was higher in the linezolid group (21.7%, 444/2046) than in the comparator group (15.7%, 314/2001). The percentage of patients with any given adverse event was low. There was no significant difference between the linezolid and comparator groups in the percentage of patients with any specific adverse event within a body system.

Table 55. Phase III Drug-Related[†] Adverse Events in $\geq 1\%$ of Patients – ITT Patients (Studies 31, 33, 39A, 39, 48A, 51, and 55)

COSTART Body System MET	Linezolid N = 2046		Comparators N = 2001	
	n	% [‡]	N	% [‡]
Patients With None	1602	78.3	1687	84.3
Patients With at Least One	444	21.7	314	15.7
BODY				
Headache	44	2.2	27	1.3
DIGESTIVE				
Diarrhea	89	4.3	65	3.2
Liver Function Tests Abnormal NOS	21	1.0	7	0.3
Nausea	69	3.4	46	2.3
Vomiting	23	1.1	8	0.4
SPECIAL SENSES				
Taste Alteration	24	1.2	14	0.7
UROGENITAL				
Moniliasis Vaginal	24	1.2	13	0.6

[†] Drug-related is defined as events specified as related or with relatedness not reported.

[‡] Percentages are based on the number of patients reporting. Patients are counted once per COSTART MET.

NOS = Not otherwise specified

14.1.5 Serious Adverse Events, Deaths, and Adverse Events Leading to Discontinuation of Study Medication

Serious adverse events are summarized in Table 56. There were no major differences between linezolid and comparator groups in the percentage of patients with serious adverse events by body system. The only serious adverse event which occurred in at least 1% of patients was pneumonia (linezolid 1.3%, 26/2046; comparator 1.2%, 24/2001).

**Table 56. Phase III Serious Adverse Events in $\geq 1\%$ of Patients – ITT Patients
(Studies 31, 33, 39A, 39, 48A, 51, and 55)**

COSTART Body System MET	Linezolid N = 2046		Comparators N = 2001	
	n	% [†]	n	% [†]
Patients With None	1813	88.6	1789	89.4
Patients With at Least One	233	11.4	212	10.6
RESPIRATORY				
Pneumonia	26	1.3	24	1.2

[†] Percentages are based on the number of patients reporting. Patients are counted once per COSTART MET.

The number of deaths was similar between groups: 4.8% (98/2046) of patients in the linezolid group died versus 4.9% (99/2001) of patients in the comparator group. No deaths were attributed to linezolid.

The percentage of patients who discontinued treatment because of adverse events was similar between groups: 5.8% (118/2046) for the linezolid group and 5.2% (105/2001) for the comparator group. There were no adverse events occurring in $\geq 1\%$ of the patients that resulted in the discontinuation of study medication.

14.1.6 Conclusions

- Linezolid is safe and well tolerated in the treatment of adults in doses up to and including 600 mg twice daily in trials up to 28 days.
- The occurrence of adverse events and drug-related adverse events were slightly higher in the linezolid group compared with the comparator group. The occurrence of serious adverse events, adverse events resulting in discontinuation of treatment, and deaths were comparable between groups.
- Adverse events were generally of mild to moderate intensity, of limited duration, and did not require study medication discontinuation.
- The most common ($\geq 2\%$) drug-related adverse events associated with linezolid were diarrhea (4.3%), nausea (3.4%), and headache (2.2%).

14.2 Adverse Events in Special Populations

Study 54A (VRE infections) was considered a special population study because it was not a comparator-controlled trial and enrolled patients who were typically critically ill with significant comorbid diseases. Other special populations that were evaluated included children with community-acquired pneumonia (Study 45), children with otitis media infections (Study 49), and patients in the compassionate use program (Study 25).

14.2.1 Study 54A

14.2.1.1 Adverse Event Summary/Overall Adverse Events

Patients in Study 54A experienced high rates of overall adverse events, serious adverse events, and deaths, which were all related to the severity of illness and comorbid conditions frequently seen in patients who are susceptible to infection with VRE. In fact, nearly a quarter (42/190) of all deaths reported for linezolid-treated patients across all phase III studies were seen in Study 54A, which is reflective of the severity of illness experienced by these patients. The proportion of patients experiencing at least one adverse event in the 200-mg twice-daily dose group (98.5%, 65/66) was higher than in the 600-mg twice-daily dose group (89.9%, 71/79).

14.2.1.2 Drug-Related Adverse Events

Drug-related adverse events occurring in $\geq 2\%$ of the patients are summarized in Table 57. Few drug-related adverse events occurred in greater than $\geq 2\%$ of the patients in either treatment group. Diarrhea, which occurred in 4.5% of the patients in the 200-mg twice-daily dose group, did not occur in the 600-mg twice-daily dose group.

Table 57. Drug-Related[†] Adverse Events in $\geq 2\%$ of Patients – ITT Patients (Study 54A)

COSTART Body System MET	Linezolid			
	600 mg Twice Daily N = 79		200 mg Twice Daily N = 66	
	n	% [‡]	n	% [‡]
Patients With None	59	74.7	52	78.8
Patients With at Least One	20	25.3	14	21.2
CARDIOVASCULAR				
Hypertension	1	1.3	2	3.0
DIGESTIVE				
Diarrhea	0	-	3	4.5
Incontinence Fecal	2	2.5	0	-
Vomiting	2	2.5	0	-
HEMIC AND LYMPHATIC				
Thrombocytopenia	3	3.8	1	1.5
SKIN				
Rash	2	2.5	2	3.0

[†] Drug-related is defined as events specified as related or with relatedness not reported.

[‡] Percentages are based on the number of patients reporting. Patients are counted once per COSTART MET.

Most of the drug-related adverse events in both treatment groups were classified as either mild or moderate, and the incidence of severe drug-related adverse events was comparable between treatment groups.

14.2.1.3 Serious Adverse Events, Deaths, and Adverse Events Leading to Discontinuation of Study Medication

The percentage of serious adverse events in $\geq 2\%$ of patients within body system are presented in Table 58. A higher percentage of patients experienced serious adverse events in the 200-mg twice-daily dose group (56.1%, 37/66) than in the 600-mg twice-daily dose group (50.6%, 40/79). The percentage of patients with serious adverse events within each body system was comparable between treatment groups.

Serious adverse events that were drug-related were reported for 6.1% (4/66) of the patients (six serious adverse events) in the 200-mg twice-daily dose group and for 5.1% (4/79) of the patients (four serious adverse events) in the 600-mg twice-daily dose group. The drug-related serious adverse events in the 200-mg twice-daily dose group were anemia, hypotension, bradycardia, hemorrhage, localized abdominal pain, and diarrhea. The drug-related serious adverse events in the 600-mg twice-daily dose group were thrombocytopenia, pancreatitis, leukopenia, and localized abdominal pain.

The most commonly occurring serious adverse events ($\geq 5\%$ of either treatment group) were sepsis and respiratory failure. Most serious adverse events in both treatment groups were rated as severe in intensity.

Table 58. Serious Adverse Events $\geq 2\%$ of Patients – ITT Patients (Study 54A)

COSTART Body System MET	Linezolid			
	600 mg Twice Daily N = 79		200 mg Twice Daily N = 66	
	n	%†	n	%†
Patients With None	39	49.4	29	43.9
Patients With at Least One	40	50.6	37	56.1
BODY				
Sepsis	5	6.3	4	6.1
Septic Shock	2	2.5	2	3.0
CARDIOVASCULAR				
Hemorrhage	0	-	3	4.5
Hypotension	3	3.8	2	3.0
DIGESTIVE				
Intestinal Perforation	2	2.5	0	-
Multiple Organ Failure	3	3.8	3	4.5
Vomiting	2	2.5	0	-
RESPIRATORY				
Dyspnea	0	-	3	4.5
Respiratory Failure	6	7.6	2	3.0
UROGENITAL				
Kidney Failure	3	3.8	1	1.5

† Percentages are based on the number of patients reporting. Patients are counted once per COSTART MET.

There was a higher percentage of deaths in the 200-mg twice-daily dose group (34.8%, 23/66) than in the 600-mg twice-daily dose group (24.1%, 19/79). None of the deaths were considered related to the study medication. Deaths were generally due to the patients' underlying illness. The most common ($\geq 2\%$ of either treatment group) adverse events associated with the cause of death in the 600- and 200-mg twice-daily dose groups were respiratory failure (7.6%, 6/79 and 4.5%, 3/66, respectively), sepsis (2.5%, 2/79 and 6.1%, 4/66, respectively), multiple organ failure (2.5%, 2/79 and 4.5%, 3/66, respectively), septic shock (1.3%, 1/79 and 3.0%, 2/66, respectively), kidney failure (3.8%, 3/79 and 0%, respectively), and dyspnea (0% and 3.0%, 2/66, respectively).

Drug-related adverse events causing discontinuation of study medication occurred in 6.3% (5/79) of the 600-mg twice-daily linezolid-treated patients and 3.0% (2/66) of the 200-mg twice-daily linezolid-treated patients. These events occurred most frequently in the cardiovascular and hemic and lymphatic body systems. There were no significant differences between treatment groups in frequencies of any drug-related adverse event by body system that resulted in study medication discontinuation.

Within body systems, there were no clinically important differences in the percentage of patients who had drug-related adverse events resulting in discontinuation of study medication between the groups.

14.2.1.4 Conclusions

- As expected, the patient population in Study 54A experienced high rates of overall adverse events, serious adverse events, and death.
- There did not appear to be any dose relationship to the occurrence of adverse events or death.
- Drug-related adverse events and adverse events (including drug-related) resulting in discontinuation were higher in the 600-mg twice-daily dose group than in the 200-mg twice-daily dose group.
- The percentages of patients who experienced adverse events, deaths, and serious adverse events were consistently higher in the 200-mg twice-daily dose group.

14.2.2 Pediatric Studies 45 and 49

Pediatric safety data is presented in section 15.4.

14.2.3 Study 25

Study 25 (compassionate use) is discussed in the Special Populations section because it is an open-label, uncontrolled trial for the treatment of patients with infections due to gram-positive bacteria who have no other available alternative treatment. The majority of patients in the trial are patients with VRE infections, as well as patients with MRSA infections who are unable to take vancomycin. Due to the severity of illness and frequent comorbid conditions, this population could be expected to have a high rate of adverse events, serious adverse events, and deaths.

In the interim report for this ongoing study, there were a total of 199 serious adverse events reported in 135 (58.7%) of 230 patients; in general, the serious adverse events were deemed to be related to the underlying diseases of the severely ill patients enrolled in this trial.

Ninety-eight (42.6%) of the 230 patients died either during the treatment or follow-up period. All of the deaths were attributed to complications of the underlying life-threatening illnesses of the patients, with most deaths due to sepsis (13.0%, 30/230) or multisystem organ failure (9.1%, 21/230).

Thirty-seven (16.1%) of the 230 patients had adverse events that resulted in discontinuation. Most of the adverse events that led to discontinuation from the trial were related to the underlying illnesses. Only 9 (3.9%) of the 230 enrolled patients discontinued the trial due to adverse events that the investigator judged to be related to the administration of linezolid. The primary drug-related adverse event that led to the discontinuation of linezolid was thrombocytopenia, occurring in 2.2% (5/230) of patients.

14.3 Safety Laboratory Data

In animal toxicology studies, linezolid produced hematopoietic and hepatic alterations that were time- and dose-dependent and were reversible after linezolid was withdrawn. These findings included moderate decreases in WBC, RBC, and platelet counts; and increases in alanine transaminase (ALT) values. In the phase I studies, hematologic changes were uncommon; 0/79 of subjects receiving low-dose linezolid (<1 g/day) and 1/41 (2.4%) subjects receiving high-dose linezolid (>1 g/day) was found to have a substantially abnormal hematocrit, platelet count, or RBC count. Phase I studies also documented elevated ALT in 2/79 (2.5%) low-dose and 4/41 (9.8%) high-dose linezolid subjects. These changes in laboratory safety variables were mild and reversible. Because linezolid is the first in a new class of antibiotics, it was extensively analyzed with respect to safety laboratory assays in the phase II and phase III clinical programs.

The following discussion of laboratory values for selected assays includes data from the pooled phase III comparator-controlled Studies 31, 33, 39A, 39, 48A, 51, and 55. (This dataset includes 45 patients from Study 33 whose laboratory assay data were inadvertently omitted from the NDA database.)

14.3.1 Mean Laboratory Assay Values

14.3.1.1 Hematology

Summary statistics for selected hematology assays are summarized in Table 59.

The mean WBC value and the mean neutrophil count values were elevated at baseline and decreased to within the normal range over the course of the studies, which was consistent with the resolution of infection. The findings were comparable between the linezolid group and the comparator group.

Elevations in platelet counts were seen after the start of the study, as expected with acute-phase reactions during infections. This elevation was within the normal range, and the mean platelet count remained within the normal range over the course of the studies for patients in both linezolid and comparator groups. This finding was comparable between groups.

The mean hemoglobin values at all time points remained within the normal range throughout the course of the studies for both the linezolid and comparator groups.

Table 59. Phase III Summary Statistics for Selected Hematology Assays – ITT Patients (Studies 31, 33, 39A, 39, 48A, 51, 55)

Assay	Mean ± Standard Deviation			
	Baseline	Treatment Days 1-7	Posttreatment Days 1-7	Posttreatment Days 15-21
WBC (x1000/mm ³)				
Linezolid	10.8 ± 6.1	8.4 ± 4.5	7.5 ± 3.6	7.6 ± 3.4
Comparators	10.5 ± 5.8	8.4 ± 4.1	7.9 ± 4.0	7.5 ± 3.2
Neutrophils (x1000/mm ³)				
Linezolid	7.9 ± 5.3	5.8 ± 4.1	4.9 ± 3.1	4.9 ± 3.0
Comparators	7.8 ± 5.0	5.8 ± 3.6	5.2 ± 3.7	4.7 ± 2.7
Platelet Count (x1000/mm ³)				
Linezolid	260 ± 102	290 ± 116	284 ± 121	292 ± 99
Comparators	264 ± 111	292 ± 116	312 ± 121	261 ± 94
Hemoglobin (g/dL)				
Linezolid	12.9 ± 2.2	12.7 ± 2.1	13.1 ± 1.9	13.0 ± 1.9
Comparators	12.9 ± 2.3	12.8 ± 2.1	13.1 ± 2.0	13.2 ± 1.9

14.3.1.2 Chemistry

Summary statistics for selected chemistry assays are summarized in Table 60.

Mean ALT values over time were comparable between the linezolid and comparator groups and remained normal over the course of the studies. Similarly, mean lipase and amylase values over time were comparable between the linezolid and comparator groups and remained normal over the course of the studies.

Table 60. Phase III Summary Statistics for Selected Chemistry Assays – ITT Patients (Studies 31, 33, 39A, 39, 48A, 51, 55)

Assay	Mean ± Standard Deviation			
	Baseline	Treatment Days 1-7	Posttreatment Days 1-7	Posttreatment Days 15-21
ALT (U/L)				
Linezolid	33.0 ± 59.9	38.4 ± 115.2	37.7 ± 60.7	28.4 ± 31.8
Comparators	34.4 ± 58.8	37.0 ± 74.4	35.1 ± 92.2	27.2 ± 29.4
Lipase (U/L)				
Linezolid	83.6 ± 85.1	96.5 ± 103.4	99.6 ± 99.4	88.6 ± 70.1
Comparators	90.5 ± 134.0	105.0 ± 120.9	105.6 ± 120.3	88.3 ± 73.5
Amylase (U/L)				
Linezolid	50.0 ± 36.7	54.9 ± 45.7	60.4 ± 31.8	58.5 ± 30.0
Comparators	52.9 ± 55.7	56.4 ± 39.5	61.5 ± 34.1	59.1 ± 32.9

14.3.2 Substantially Abnormal Laboratory Assay Values

Definitions of substantially abnormal laboratory assay values are provided in Table 61.

Table 61. Definitions of Substantially Abnormal Laboratory Assays

Laboratory Assay	Clinical Significance Criteria (criteria 1) for Normal Baseline	Clinical Significance Criteria when Baseline is Abnormal (criteria 2)
Hemoglobin	<75% of LLN	< 75% of BL (if BL > ULN) < 90% of BL (if BL < LLN)
Hematocrit	<75% of LLN	< 75% of BL (if BL > ULN) < 90% of BL (if BL < LLN)
Red Blood Cells	<75% of LLN	< 75% of BL (if BL > ULN) < 90% of BL (if BL < LLN)
Platelets	<75% of LLN	<75% of BL
White Blood Cells	<75% of LLN	<75% of BL
Neutrophils (abs)	<0.5 LLN	<0.5 x BL
Total bilirubin	>2 x ULN	>1.5 x BL
Aspartate Aminotransferase	>2 x ULN	>2 x BL
Alanine Aminotransferase	>2 x ULN	>2 x BL
Amylase	>2 x ULN	>2 x BL
Lipase	>2 x ULN	>2 x BL
Creatine kinase	>2 x ULN	>2 x BL

BL = Baseline

LLN = Lower Limit of Normal

ULN = Upper Limit of Normal

A patient was considered abnormal at baseline if the baseline value was outside the laboratory reference range. For patients normal at baseline, postbaseline values were evaluated by criteria 1 to determine substantially abnormal values. For patients abnormal at baseline, both the conditions given by criteria 1 and criteria 2 must have been met by postbaseline values to classify them as substantially abnormal values.

14.3.2.1 Hematology

The percentage of patients with substantially abnormal hematology values for selected assays are provided in Table 62. There were no clinically important differences between the linezolid and comparator groups in this analysis.

Table 62. Phase III Substantially Abnormal Values (Corrected for Baseline Abnormalities) for Selected Hematology Assays – ITT Patients (Studies 31, 33, 39A, 39, 48A, 51, and 55)

Laboratory Assay	Linezolid		Comparators	
	n/N	%	n/N	%
WBC (x 1000/mm ³)	33/2020	1.6	21/1974	1.1
Neutrophils (x 1000/mm ³)	15/1954	0.8	17/1909	0.9
Platelet Count (x 1000/mm ³)	48/2010	2.4	30/1966	1.5
RBC (x 10 ⁶ /mm ³)	83/2019	4.1	73/1973	3.7
Hemoglobin (g/dL)	110/2020	5.4	95/1974	4.8
Hematocrit (%)	78/2016	3.9	65/1973	3.3

n = Total number of patients with a substantially abnormal value.

N = Total number of patients with at least one observation of the given laboratory parameter while on study.

14.3.2.2 Chemistry

The percentages of patients with substantially abnormal chemistry laboratory values for selected assays are provided in Table 63. There were no clinically important differences between the linezolid and comparator groups in this analysis.

Table 63. Phase III Substantially Abnormal Values (Corrected for Baseline Abnormalities) for Selected Chemistry Assays – ITT Patients (Studies 31, 33, 39A, 39, 48A, 51, and 55)

Laboratory Assay	Linezolid		Comparators	
	n/N	%	n/N	%
Total bilirubin (mg/dL)	14/2021	0.7	16/1981	0.8
Creatine kinase (U/L)	103/2017	5.1	65/1976	3.3
ALT (U/L)	145/1959	7.4	139/1919	7.2
AST (U/L)	80/1959	4.1	102/1920	5.3
Lipase (U/L)	79/2018	3.9	74/1976	3.7
Amylase (U/L)	36/2024	1.8	30/1983	1.5

n = Total number of patients with a substantially abnormal value.

N = Total number of patients with at least one observation of the given laboratory parameter while on study.

14.3.3 Additional Analyses Laboratory Assay Values

In addition to the data presented in sections 14.3.1 and 14.3.2 above, additional analyses were performed for selected hematology and serum chemistry laboratory assays in order to

examine more closely any potential for hematopoietic, hepatic, or pancreatic toxicity of linezolid. Analyses included adjusted differences calculations, logistic regression, baseline distribution plots, cumulative percentages, population time plots, and an in-depth review of each of the outlier patients; ie, those with the worst assay values. Assays analyzed included WBC count, neutrophil count, platelet count, RBC count, hemoglobin value, hematocrit value, ALT value, AST value, and amylase value. These analyses were submitted to the FDA as part of the 4-month safety update report.

The analyses demonstrate that there is no increased hematopoietic, hepatic, or pancreatic toxicity risk in linezolid-treated patients in these selected parameters, compared with patients treated with a wide variety of currently marketed and commonly prescribed antibiotics.

14.3.4 Conclusions

- Preclinical and phase I testing highlighted potential laboratory complications associated with linezolid therapy. The evaluation of phase II and III laboratory data revealed that linezolid does not have a substantial clinical effect on safety laboratory values at recommended doses of up to and including 600 mg twice daily for up to 28 days.
- In phase I studies, abnormal hematology values were uncommon in linezolid-treated subjects and, together with ALT elevations, occurred mainly at doses of >1g/day and generally were normal at F-U.
- Mean hematologic and hepatic parameters remained within normal ranges over the course of the studies for both linezolid and comparators.
- The percentages of patients with substantially abnormal hematologic and hepatic laboratory values were similar between the linezolid and comparator groups in phase III comparator-controlled studies.
- Changes seen in safety laboratory parameters were generally reversible after completion of therapy.
- Changes seen in safety laboratory values were generally not clinically significant nor did they require medication discontinuation.

14.4 QTc Data

QTc intervals were further investigated using data collected from three different phase I safety/tolerance studies (Studies 02, 15, and 16). Thirty-six subjects were evaluated: 18 received multiple doses of linezolid 625 mg, 2 received multiple doses of linezolid 750 mg, and 16 received placebo. These studies and subjects were chosen for analysis as they represent the highest and longest exposure data in a controlled setting with ECG and linezolid plasma concentration data. The times of the postdosing QTc interval recordings were at or near the C_{max} for linezolid.

The mean ΔQTc interval value was -0.82 ± 12.5 msec for placebo-treated subjects and 0.89 ± 13.5 msec for linezolid-treated subjects. Individual ΔQTc interval values were small and

variable among both placebo- and linezolid-treated subjects. All QTc intervals values were less than 440 msec (the maximum value was 435 msec for a placebo-treated subject and 439 msec for a linezolid-treated subject). Linezolid plasma concentrations did not correlate with Δ QTc ($r^2 = 0.0038$, $p = 0.71$).

In conclusion, no linezolid-related effects on the QTc interval in humans have been observed.

14.5 Drug-Drug Interactions

14.5.1 Potential MAO Interactions

Preclinical animal data indicated that linezolid exerts a mild, reversible inhibition of MAO. To further explore the potential for MAO interactions between linezolid and other commonly used medications, phase I studies examined the potential MAO interactions of linezolid. Additionally, adverse event data from phase II and III studies were examined for patients who took certain classes of concomitant noninvestigational medications (NIMs) known to have the potential for potentiating MAOI effects.

14.5.1.1 Phase I Studies

Phase I studies assessed the effect of concomitant administration with linezolid and tyramine, pseudoephedrine, phenylpropanolamine, or dextromethorphan hydrobromide.

- Very high doses of tyramine (≥ 100 mg) taken concomitantly with linezolid were required to raise systolic blood pressure ≥ 30 mm Hg (typical high-tyramine foods contain 1 to 2 mg tyramine per portion.). No effect was detected with tyramine dosing in ranges of normal dietary intake (< 100 mg per meal).
- Coadministration of pseudoephedrine or phenylpropanolamine with linezolid did produce slight elevations of blood pressure in healthy volunteers, which were within the range of blood pressure fluctuations seen with normal daily activity.
- There was no apparent interaction between linezolid and dextromethorphan.

14.5.1.2 Phase II Studies

14.5.1.2.1 Adult Patients

In phase II studies, 247 out of 867 linezolid-treated patients received medications that could potentially interact with MAO. A comparative analysis was done to determine the possible effect of linezolid in patients taking concomitant MAO-interacting drugs, compared with those not taking such agents. Although there were increased incidences of certain adverse events, the results were not consistent with an MAO interaction. Too few patients took potential MAOI-interacting drugs to make a reasonable assessment of any MAOI effect.

Overall, the potential of linezolid to interact with MAO-interacting drugs appeared to be low in the phase II studies. As a result of this analysis, patients who were taking MAOI-interacting drugs were permitted to be recruited in the phase III clinical program.

14.5.1.2.2 Pediatric Patients

In the uncontrolled phase II pediatric studies, 56 of 143 patients treated with linezolid received medications that potentially interact with MAO. Five of these 56 patients had potentially MAOI-related adverse events. Four of these events were fever (expected in this patient population) and one was mild restlessness.

14.5.1.3 Phase III Studies

In phase III studies, 30.9% (632/2046) of patients treated with linezolid also received medications that potentially interact with MAO (Table 64). In comparison, 30.3% (605/1999) patients treated with comparator drugs were also on MAO-interacting agents.

In both linezolid and comparator groups, the incidence of potential MAOI-related adverse events was generally higher in those that also took MAO-interacting drugs compared with those that did not. Among patients who did not receive MAO-interacting drugs, the incidence of adverse events were generally comparable between linezolid and the comparator groups.

Among the patient population that received MAO-interacting drugs, the overall incidence of adverse events was relatively low and none resulted in the discontinuation of study medication. In general, the incidence of potential MAOI-related events was similar between patients in the linezolid group as compared with patients in the comparator group. Adverse events potentially related to MAOI effect were generally of mild to moderate intensity.

Hypertension was observed more often in patients treated with linezolid and MAO-interacting drugs than in patients treated with comparator and MAO-interacting drugs (2.1% vs 0.8%).

**Table 64. Phase III Monoamine Oxidase Interactions – ITT Patients
(Studies 31, 33, 39A, 39, 48A, 51, and 55)**

COSTART Body System MET	All Linezolid		All Comparators	
	NOT ON MAOI-interacting NIMs* N = 1414	ON MAOI-interacting NIMs N = 632	NOT ON MAOI-interacting NIMs N = 1394	ON MAOI-interacting NIMs N = 605
	n (%)	n (%)	n (%)	n (%)
CARDIOVASCULAR				
Arrhythmia	4 (0.3)	21 (3.3)	10 (0.7)	14 (2.3)
Bradycardia	3 (0.2)	4 (0.6)	3 (0.2)	3 (0.5)
Hypertension	22 (1.6)	13 (2.1)	4 (0.3)	5 (0.8)
Hyperthermia, Diaphoresis, or Flushing	26 (1.8)	30 (4.7)	31 (2.2)	28 (4.6)
Hypotension or Shock	4 (0.3)	18 (2.8)	8 (0.6)	16 (2.6)
Palpitation or Tachycardia	6 (0.4)	9 (1.4)	4 (0.3)	9 (1.5)
NERVOUS				
Confusion, Sedation, Delirium, or CNS Depression	13 (0.9)	11 (1.7)	15 (1.1)	6 (1.0)
Restlessness, Tremor, or Myoclonus	3 (0.2)	1 (0.2)	2 (0.1)	4 (0.7)

* NIMs = Non Investigational Medications

14.5.2 Other Potential Linezolid Drug Interaction Evaluations

Phase I studies evaluated the potential drug–drug interaction of linezolid use in conjunction with companion antibiotics to treat possible coexisting gram-negative infections. In vitro studies indicate that linezolid is neither a substrate for, nor an inhibitor of, all major human hepatic cytochrome P450 isoforms. In addition, a phase I study was done to evaluate the potential for linezolid interaction in vivo with CYP2C9, using warfarin as the substrate. There were no drug–drug interactions noted between linezolid and aztreonam, gentamicin, or cytochrome P450 substrates.

14.5.3 Conclusions: Potential Drug-Drug Interactions

- Linezolid has no drug–drug interactions with aztreonam or gentamicin.
- Linezolid has no drug–drug interaction with dextromethorphan.
- Linezolid has no drug–drug interaction with warfarin or cytochrome substrates.

- Although linezolid has a mild potential for MAO inhibition, in recommended doses of 600 mg twice daily, more than 100 mg of oral tyramine was required to induce clinically significant blood pressure changes, thus, no food restrictions are required.
- Concomitant use of pseudoephedrine or phenylpropanolamine led to slight increases in blood pressure, which were within normal blood pressure fluctuation in healthy subjects.
- In evaluation of phase III data, the incidence of adverse events when linezolid or comparators were used with potential MAO-interacting drugs were similar, except for a small increase in the percentage of patients with hypertension (2.1% for linezolid versus 0.8% for all comparators). None of these events led to study medication discontinuation. It is not clear that any of these adverse events could be attributed to an MAOI effect.
- The overall risk of MAO interaction with linezolid therapy appears to be small and does not routinely lead to discontinuation of study medication.

14.6 Drug-Demographic And Drug-Disease Interactions

14.6.1 Age and Sex

In the phase I studies, no significant differences have been found between young and elderly subjects. Females have a slightly lower (~20%) clearance than males, but this difference is not believed to be clinically relevant with regard to either safety or efficacy. The weight-adjusted clearance in children is higher than that observed in adults.

Data from the phase I, II, and III studies show that the incidence of drug-related adverse events does not appear to be affected by the age of the patient. When drug-related adverse event data were examined by sex, urogenital complaints were more common in females, but these differences were also seen in the comparator groups and likely reflect the incidence of vaginal yeast infections. When laboratory data are examined by age and sex, linezolid has no effect on laboratory values.

14.6.2 Race

Data from the phase I, II, and III studies show that the incidence of drug-related adverse events or abnormal laboratory results does not appear to be affected by the race of the patient, although the majority of the patients evaluated have been white.

14.6.3 Renal or Hepatic Impairment

With either renal or mild to moderate hepatic dysfunction, no linezolid dosage adjustments are required.

In patients undergoing dialysis, the dose should be given after a dialysis session, as hemodialysis is a source of elimination of linezolid (approximately 30% of a dose was eliminated in a 3-hour dialysis session beginning 3 hours after the dose of linezolid was administered).

The two primary metabolites of linezolid have been found to accumulate in the plasma of subjects with severe renal impairment or with end-stage renal disease who are being maintained on hemodialysis. This accumulation is higher than in subjects with normal or moderately impaired renal function. The safety of these two metabolites at accumulated levels has not been established in patients with severe renal impairment. Like linezolid, the two metabolites are dialyzable.

No data are available for those patients with concomitant hepatic and renal failure. No data are available for patients who are undergoing continuous ambulatory peritoneal dialysis or other methods of renal dialysis.

14.7 In Utero Exposure

Women of childbearing potential were allowed to participate in most of the linezolid studies if they were not pregnant and were not at risk of becoming pregnant. Despite this, three linezolid-treated patients were found to be pregnant after enrolling. Two patients had spontaneous abortions with no maternal complications. One patient delivered a healthy infant on September 22, 1999. No other data are available regarding the use of linezolid during pregnancy.

14.8 Overdosage

Overdose was defined as patients who received ≥ 2400 mg/day. No reports of linezolid overdose were received in the phase III trials.

14.9 Drug Abuse

Based on the preclinical studies and the phase I, II, and III clinical studies, there is no evidence to suggest that linezolid has the potential for abuse. There are no underlying pharmacological mechanisms, or neural or behavioral signs and symptoms, that suggest that linezolid would induce drug-seeking behaviour. There have been no known reports of drug abuse or drug dependence associated with the use of linezolid in the clinical trials.

14.10 Long-Term Safety

The compassionate use program (Study 25) includes uncontrolled data from 47 patients who were treated with linezolid for more than 28 days. The maximum duration of treatment as of the 30 June 1999 database cutoff date was 163 days. Twenty-four of the 47 patients (51.1%) reported serious adverse events. Body systems with an incidence of adverse events $>5\%$ were the following: body as a whole (17.0%, 8/47), cardiovascular system (14.9%, 7/47), digestive system (19.1%, 9/47), hemic and lymphatic system (8.5%, 4/47), and respiratory system (8.5%, 4/47).

The phase II and III trials were designed for less than 28 days of linezolid therapy, thus no long-term exposure data are available from controlled studies.

15 PEDIATRIC USE

15.1 Background

Infections due to gram-positive organisms, including staphylococci, streptococci, and enterococci, continue to cause significant morbidity and mortality in children. In addition, the incidence and proportion of nosocomial infections in children caused by these gram-positive organisms is increasing, especially from *S aureus*, coagulase-negative staphylococci, and enterococci. These infections are of epidemiological and clinical importance because of their capacity to cause serious and life-threatening disease in debilitated as well as healthy children. Antimicrobial resistance is a significant problem and is of increasing importance in both nosocomial and community-acquired infections caused by these gram-positive pathogens. Of particular concern to children are MRSA, PRSP, and, more recently, VRE. Therapeutic options in children are severely limited by unacceptable safety margins in children for currently available antibiotics targeting these resistant organisms or challenges encountered from being restricted to an intravenous route of administration. The development of gram-positive agents with new mechanisms of action, oral bioavailability, and acceptable safety profiles would provide an important advance to current therapies for the treatment of serious infections in children.

Addressing this unmet medical need, Pharmacia & Upjohn has embarked on an extensive pediatric drug development program for linezolid. This has included the development of intravenous sterile solution, oral tablet, and oral suspension formulations for use in children. Phase I studies included pharmacokinetics in children aged 3 months to 16 years, sensory taste tests for the oral suspension formulation, and a planned pharmacokinetics study in neonates, including premature neonates. Phase II studies in children were initiated at the same time as the initiation of the phase III program in adults. The phase II program included two uncontrolled studies examining the safety, efficacy, and pharmacokinetics of linezolid for the treatment of children hospitalized with community acquired pneumonia, and acute otitis media. A phase III program for children is currently being planned and will include a double-blind comparator-controlled study in skin and soft tissue infections, and an open-label study comparing linezolid to vancomycin for resistant pathogens (both planned for initiation in 2000). This brochure will present the highlights of the linezolid pediatric program.

15.2 Pharmacokinetics in Children

The pharmacokinetics of linezolid in pediatric patients (aged 3 months to 16 years) was determined in a single-dose intravenous study (Study 28) involving 43 subjects who received a dose of 1.5 mg/kg; 14 additional subjects received a dose of 10 mg/kg. At a dose of 1.5 mg/kg, the weight-adjusted clearance values averaged about 6 mL/min/kg and ranged from 1.4 to 12.7 mL/min/kg. This was a higher clearance than observed in adults (range between 1 and 3 mL/min/kg). At a dose of 10 mg/kg, peak plasma concentrations (C_{max}) in children were similar to those in adults after a 625-mg dose.

Based on this preliminary phase I data, it was determined that further pharmacokinetic analysis would need to be conducted in pediatric patients in the phase II program. In these studies, a dose similar to the recommended adult dose on a milligram per kilogram basis; ie, 10 mg/kg twice daily up to a maximum dose of 600 mg, was selected. Taking the pharmacokinetics into consideration, the trials were designed for pediatric patients with infections primarily due to *S pneumoniae*, while collecting additional samples for pharmacokinetic analysis.

A total of 360 linezolid concentrations from 135 patients enrolled in the two phase II studies (Studies 45 and 49) were available for the analysis, which used population pharmacokinetics modelling. In children under 5 years of age, clearance adjusted by body weight was inversely proportional to age, with younger age groups demonstrating increased clearance. However, children 5 years of age and older receiving a 10-mg/kg oral dose demonstrated similar weight-adjusted clearance, weight-adjusted volume of distribution, and half-life compared with adults receiving a 625-mg oral dose.

For patients less than 5 years of age, further pharmacokinetic analysis is being planned. Population pharmacokinetics will be investigated in a comparison study of linezolid and vancomycin in pediatric patients, aged birth to 5 years, with infections due to resistant pathogens. For this study, a linezolid dose of 10 mg/kg three times daily has been selected, based on the observed increased clearance of linezolid in this age group. In addition, a separate analysis of pharmacokinetics in neonates, including premature neonates, is being planned.

15.3 Phase II Pediatric Efficacy Information

15.3.1 Pneumonia (Study 45)

This non-randomized, open-label, multicenter study was designed to demonstrate the efficacy, safety, tolerance, and pharmacokinetics of linezolid in pediatric patients aged 12 onths to 17 years hospitalized with community-acquired pneumonia. A total of 79 pediatric patients were enrolled into the study. Patients received 10 mg/kg (up to 600 mg) twice daily. Patients initially received linezolid intravenously but could be switched to oral suspension at the discretion of the investigator. Linezolid (intravenous and oral) was to be administered for 7 to 14 days, although patients could receive treatment for up to 28 days.

15.3.1.1 Clinical Cure Rates

An overview of the clinical cure rates for pediatric patients hospitalized with community-acquired pneumonia is presented in Table 65. These data are consistent with the findings observed in the controlled clinical trials (Studies 51 and 33) in adults with community-acquired pneumonia.

Table 65. Clinical Cure Rates for Pediatric Patients with Community-Acquired Pneumonia (Study 45)

Sponsor's Assessment of Clinical Outcome	Linezolid	
	n/N	%†
ITT Patients	63/67	94.0
Clinically Evaluable Patients	61/64	95.3
Microbiologically Evaluable Patients	6/6	100.0

† Percentages are based on the total number of patients reporting excluding indeterminate and missing.

ITT = Intent-to-Treat

15.3.1.2 Pathogen Eradication Rates

Individual pathogen eradication rates for the Microbiologically Evaluable population are displayed in Table 66.

Table 66. Pathogen Eradication Rates for Microbiologically Evaluable Pediatric Patients with Community-Acquired Pneumonia (Study 45)

Pathogen	Linezolid	
	n/N	%†
<i>Streptococcus pneumoniae</i>	5/5	100.0
Penicillin-resistant‡	2/2	100.0
<i>Streptococcus pyogenes</i>	1/1	100.0

† Percentages are based on the total number of patients reporting excluding indeterminate and missing.

‡ Data for resistant organisms are subsets of the pathogen total

15.3.2 Otitis Media (Study 49)

This non-randomized, open-label, multicenter study was designed to demonstrate the efficacy, safety, tolerance, and pharmacokinetics of linezolid therapy in pediatric patients aged 12 months to 6 years with acute otitis media. A total of 65 pediatric patients were enrolled into the study. Patients received oral linezolid 10 mg/kg (up to 600 mg) twice daily. Linezolid was to be administered for 7 to 10 days.

In the Clinically Evaluable population, the success rate (ie, cured plus improved) for the Sponsor's Assessment of Clinical Outcome was 69.1% (38/55).

Among Microbiologically Evaluable patients, success rates for acute otitis media secondary to *S pneumoniae*, *S pyogenes*, *S epidermidis*, or gram-negative fastidious bacteria (*H influenzae*, *H parainfluenzae*, and *M catarrhalis*) at F-U were 84.6% (11/13), 75.0%

(3/4), 50.0% (1/2), and 50.0% (5/10), respectively. Of the 13 *S pneumoniae* pathogens isolated in middle ear infections, eight were susceptible to penicillin, whereas five were penicillin non-susceptible.

For Microbiologically Evaluable patients <2 years of age, the success rate for Sponsor's Clinical Outcome by Pathogen (all pathogens) was 42.9% (6/14), whereas the success rate of those ≥ 2 years was 93.3% (14/15). Success rates were greater in the ≥ 2 years of age population regardless of the pathogen isolated from the middle ear fluid sample.

15.4 Phase II Pediatric Safety Information

Pediatric safety information contains pooled adverse event data from Study 45 (community-acquired pneumonia) and Study 49 (acute otitis media); a total of 143 patients were treated in these two studies. Study 45 utilized both intravenous and oral routes of administration, whereas in Study 49, linezolid was only administered orally.

15.4.1 Overall Adverse Events

In these non comparator-controlled studies, 55.9% (80/143) of pediatric patients experienced one or more adverse events, of which 20.3% (29/143) were reported as drug-related.

Adverse events resulted in the discontinuation of treatment with study medication in 3.5% (5/143) of patients, all of whom were enrolled in Study 45. Of these patients, 2.8% (4/143) discontinued treatment due to drug-related adverse events. Serious adverse events were experienced by 3.5% (5/143) of patients, of whom four out of five were enrolled in Study 45.

The most common ($\geq 5\%$ of patients) adverse events in pediatric patients occurred in the digestive and skin body systems, including diarrhea (16.8%, 24/143), vomiting (11.9%, 17/143), and loose stools (5.6%, 8/143). In addition, rash occurred in 11.2% (16/143) of patients.

Of the 16 patients with rash, 7 were classified as diaper rash (2 of them drug-related). Of the remaining 9 patients, one was reported to be a viral rash; two had no further descriptors as to location or type of rash; three were reported with locations (buttocks, arms, legs, face, and neck) but the investigator added no further descriptors; one was reported as "excoriated, erythematous papules on the face and neck," not considered drug-related; one was described as "papular, nonpruritic on upper chest and back," considered drug-related; and one was reported as "red, maculopapular, and nonpruritic" without a location (in the comment section, the investigator goes on to report that this rash appeared several hours after the first dose of linezolid and the mother felt that it was related to the soap used by the hospital).

15.4.2 Drug-Related Adverse Events

Drug-related adverse events that occurred in greater than 1% of pediatric patients are presented in Table 67. Overall, 20.3% (29/143) of the patients experienced one or more adverse events that were considered to be drug related. The majority of patients had events associated with the digestive system, and the most common adverse event was diarrhea in

9.1% (13/143) of all patients. No other adverse event occurred in $\geq 5\%$ of the patients in these studies.

Three patients (all from Study 45) had neutropenia reported as a drug-related adverse event. Two of the events were not considered serious, while one was considered a serious adverse event (see section 15.4.3). One of the two nonserious drug-related adverse events was in a 1-year-old female with consolidated right upper lobe pneumonia. This patient had a baseline neutrophil count of 4.5×10^3 cells/ μL (local laboratory measurement), which declined to 1.2×10^3 cells/ μL on day 3 and 1.0×10^3 cells/ μL at the EOT visit. The neutropenia had resolved (7.8×10^3 cells/ μL , local laboratory measurement) by the F-U visit and the pneumonia was considered cured. The second reported nonserious drug-related adverse event was in an 18-month-old male with consolidated left lobar pneumonia. This patient received 9 days of linezolid and was considered cured. He developed neutropenia at EOT. He had a baseline neutrophil count of 16.5×10^3 cells/ μL (local laboratory measurement), which declined to 2.8×10^3 cells/ μL on day 3 and 0.8×10^3 cells/ μL at EOT. The neutropenia had resolved (1.7×10^3 cells/ μL) by the F-U visit and the pneumonia was considered cured.

Table 67. Pediatric Studies – Drug-Related Adverse Events in $>1\%$ of Patients – ITT Patients (Studies 45 and 49)

COSTART Body System MET	Linezolid N = 143	
	n	% [†]
Patients With None	114	79.7
Patients With at Least One	29	20.3
DIGESTIVE		
Diarrhea	13	9.1
Loose Stools NEC	5	3.5
Vomiting	6	4.2
HEMIC AND LYMPHATIC		
Neutropenia	3	2.1
SKIN		
Rash	4	2.8

[†] Percentages are based on the number of patients reporting. Patients are counted once per COSTART MET
NEC = Not elsewhere classified

15.4.3 Serious Adverse Events, Deaths, and Adverse Events Leading to Discontinuation of Study Medication

The percentage of serious adverse events in the pediatric studies was 3.5% (5/143). Four of these five serious adverse events occurred in Study 45, including vomiting, pneumothorax, convulsions, and neutropenia. The neutropenia was reported as a serious drug-related adverse event within 3 days of starting linezolid in a 2-year-old patient with a diagnosis of bronchiolitis. The patient only received 3 days of linezolid. The neutropenia resolved with the resolution of the underlying illness. The only laboratory values available were at EOT when the neutrophil count 0.6×10^3 cells/ μL , which declined to 0.5×10^3 cells/ μL on posttreatment day 6. The neutropenia had resolved (2.7×10^3 cells/ μL) by the F-U visit and the bronchiolitis had resolved.

One serious adverse event (bronchiolitis) occurred in Study 49 and resolved after 7 days with no residual effects. This event was not considered drug related. There were no deaths reported in these studies.

Five of 143 patients (3.5%) discontinued due to adverse events, including diarrhea and vomiting, generalized abdominal pain and rash, sepsis, otitis media, and neutropenia. All of the patients were from Study 45. With the exception of otitis media, all of the adverse events leading to discontinuation were considered drug-related.

15.4.4 Conclusions

- Linezolid is safe and well tolerated in children in doses of up to 10 mg/kg twice daily.
- The most commonly reported adverse events in children were diarrhea, loose stools, vomiting, and rash. These were generally mild to moderate in intensity.
- In these uncontrolled trials, linezolid has a cure rate greater than 95% for children hospitalized with community acquired pneumonia.
- In these uncontrolled trials, linezolid was effective in eradicating *S pneumoniae* in hospital-acquired pneumonia and acute otitis media.
- Although neutropenia was reported in these uncontrolled studies, the relationship to linezolid is unclear.

16 BENEFIT/RISK RELATIONSHIP AND CONCLUSIONS

16.1 Introduction

With the increasing incidence of resistant gram-positive bacterial infections in the United States, new antibiotic development has now become urgent. The oxazolidinones represent a novel class of antibiotics with activity against these organisms, and linezolid is the first member of the class to complete phase III testing. Linezolid disrupts bacterial protein synthesis by preventing the formation of the ribosomal initiation complex through a unique

mechanism of action. Based on extensive preclinical and clinical experience, linezolid's antibacterial activity has been shown to be unaffected by previously described mechanisms of antibiotic resistance. Its antimicrobial spectrum of activity is most similar to vancomycin, although linezolid also has some activity against gram-negative bacteria of the respiratory tract (eg, *Haemophilus influenzae* and *Moraxella catarrhalis*).

In vitro, linezolid is highly active against routine gram-positive bacteria as measured by the minimum inhibitory concentrations necessary to inhibit 90% of isolates (MIC₉₀). The MIC₉₀ for both methicillin-susceptible *Staphylococcus aureus* (MSSA) and methicillin-resistant *S aureus* (MRSA) is <4 µg/mL. It is even more active against *Staphylococcus epidermidis* and other coagulase-negative staphylococci, with an MIC₉₀ of <2 µg/mL. Linezolid is also highly active against streptococci, including *Streptococcus pyogenes*, *Streptococcus agalactiae*, and drug-resistant *Streptococcus pneumoniae* (MIC₉₀, <2 µg/mL.). Finally, linezolid has excellent in vitro activity against vancomycin-resistant *Enterococcus* (VRE), including *Enterococcus faecium*, *Enterococcus faecalis*, and other *Enterococcus* spp.

In comparator-controlled phase III trials, linezolid has been shown to be equivalent to the drugs of choice for community and hospital-acquired pneumonia and complicated and uncomplicated skin and soft tissue infections. Clinical evidence also shows that it is active against MRSA and vancomycin-resistant *E faecium* across a variety of clinical indications.

As a member of the first new class of antibiotics in the last 30 years, linezolid is an important addition to the anti-infective pharmacopoeia. Its benefits and risks are discussed below.

16.2 Benefits

Linezolid's clinical and microbiologic efficacy were demonstrated in seven phase III trials in which it was compared with well-established antibiotics, such as second- and third-generation cephalosporins, penicillinase-resistant penicillins, vancomycin, and macrolides. Compared with cefpodoxime and ceftriaxone, linezolid was equally effective for the outpatient and inpatient treatment of community-acquired pneumonia. Compared with oxacillin, dicloxacillin, and clarithromycin, linezolid was equally effective for the treatment of complicated and uncomplicated skin and soft tissue infections. Linezolid was also as effective as vancomycin for the treatment of MRSA infections, including infections complicated by secondary bacteremia. In combination with aztreonam or aminoglycosides, linezolid was as effective as vancomycin for the treatment of nosocomial pneumonia. Finally, linezolid was also clinically effective for VRE infections, as shown by the results of a phase III dose-comparison trial. Linezolid's clinical activity against VRE was further substantiated by uncontrolled efficacy data in the compassionate-use program.

The phase III data also demonstrated linezolid's microbiologic efficacy. All of the phase III comparator-controlled studies showed that linezolid successfully eradicated bacterial pathogens at rates equivalent to comparator antibiotics. Organisms successfully eradicated by linezolid included *S pneumoniae* (including PRSP), *S pyogenes*, *S agalactiae*, MSSA, MRSA, *S epidermidis*, and other coagulase-negative staphylococci. Results from the dose-comparison trial showed that linezolid was microbiologically effective against VRE.

Although data were limited, linezolid also demonstrated clinical and microbiological activity against *H influenzae*.

In an uncontrolled phase II trial, linezolid showed promising efficacy in the treatment of pediatric pneumonia. Given the increasing prevalence of drug-resistant pneumococci in children, including recently described isolates exhibiting vancomycin tolerance, linezolid may prove to be an important therapeutic option for pediatric respiratory tract diseases.

Because linezolid is rapidly and completely absorbed via the gastrointestinal tract and since cross-resistance with conventional antibiotics has not been observed, it is the first antibiotic with reliable oral activity against MRSA. Since the 1980s, when methicillin resistance became widely endemic in US hospitals, vancomycin has been the only uniformly effective treatment for MRSA. Heretofore, patients infected with this common, highly resistant organism were often forced to endure prolonged therapeutic courses of intravenous vancomycin. Prolonged intravenous therapy, however, places patients at risk for both mechanical and infectious complications of vascular catheterization (eg, bleeding, pneumothorax, and catheter-related sepsis). Linezolid's demonstrated activity against MRSA, as well as its 100% bioavailability, may obviate lengthy courses of intravenous vancomycin therapy in many patients.

Furthermore, Pharmacia & Upjohn is aware of a number of patients who were infected with MRSA and yet intolerant of vancomycin. As such, linezolid offers a new therapeutic alternative for these patients for whom no alternative may currently exist. Although the prevalence of vancomycin intolerance has not been studied extensively, it has been well described, accounting for nearly 18% of all requests for compassionate-use linezolid. Other patients have received compassionate-use linezolid because they were infected with MSSA but lacked intravenous access due to a variety of underlying medical conditions, such as extensive body burns. Linezolid has the benefit of addressing all of these unmet medical needs: (1) a consistently reliable antibiotic with activity against MRSA, (2) a consistently reliable antibiotic with gram-positive activity for patients who are allergic to, or intolerant of, vancomycin, and (3) a consistently reliable antibiotic with 100% oral bioavailability for patients who lack intravenous access.

Until recently, MRSA was essentially considered a nosocomial organism. However, recent data now suggest that methicillin resistance is no longer confined to hospitals. A number of recent reports have documented that MRSA is being increasingly recovered from the community. The increased prevalence of MRSA in the community has led to the suggestion that initial therapeutic strategies for presumed *S aureus* infections may need to be reconsidered. Compounding the problem of increasing methicillin resistance is that resistance to other non- β -lactam antibiotics has also increased. Typically, many strains of MRSA are resistant to macrolides, clindamycin, and trimethoprim and, frequently, resistant to quinolones and gentamicin. In fact, many isolates of MRSA and methicillin-resistant coagulase-negative staphylococci are now resistant to all currently marketed antibiotics, except vancomycin, which must be given intravenously. Oral linezolid offers physicians the benefit of treating patients with uncomplicated community-acquired MRSA infections as outpatients. Two trials have demonstrated linezolid's effectiveness in treating uncomplicated

skin and soft tissue infections on an outpatient basis. Two other trials have demonstrated linezolid's effectiveness in treating patients with complicated skin and soft tissue infections due to MRSA. Linezolid offers an alternative to vancomycin for those MRSA-infected patients who do not require (or no longer require) intravenous therapy.

Coincident with the increased prevalence of gram-positive bacterial infections over the past 20 years, the use of vancomycin has increased dramatically. With the recent emergence of VRE and glycopeptide-intermediate *S aureus*, the Centers for Disease Control and Prevention (CDC) has now called for the prudent use of vancomycin in order to limit the development of further resistance. Antibiotic resistance, however, may be considered as two discrete phenomena. First is the induction, or acquisition, of resistance. If a random, spontaneous mutation occurs in the presence of an antibiotic and that mutation confers resistance to the ambient antibiotic, then that gene will tend to increase in prevalence as long as the applied antibiotic remains in the environment. Most antibiotic resistance, however, does not occur *de novo*. Resistant bacteria are generally transmitted from person to person by the hands of health-care workers and fomites. Since the dissemination of resistance factors is facilitated in antibiotic-rich environments like hospitals, patients are at a high risk of acquiring resistant bacterial infections as long as they remain hospitalized. Furthermore, patients who must be hospitalized for prolonged periods of time in order to receive intravenous antibiotics, such as vancomycin, are at high risk of becoming colonized with resistant bacteria (eg, VRE). Once colonized, or infected, these patients may then further serve as reservoirs of resistant bacteria. An antibiotic such as linezolid, which is as active orally as it is intravenously, may facilitate early discharge of hospitalized patients. As such, linezolid may have two theoretical benefits: (1) it may prevent patients from being secondarily infected or colonized with resistant bacterial infections, and (2) it may facilitate discharge of colonized/infected patients from an environment where dissemination of antibiotic resistance occurs.

Linezolid also has a number of highly favorable pharmacokinetic characteristics. Plasma levels are equally high irrespective of the route of administration, and linezolid's half life permits twice-daily dosing. Furthermore, absorption is unaffected by food, and the adult dose of linezolid need not be adjusted based on age or sex. Patients with underlying renal or hepatic disease may also safely receive the full adult dose of linezolid. For children and patients with difficulty swallowing, linezolid is also available as an oral suspension.

Finally, linezolid is neither a substrate for, nor an inhibitor or an inducer of, the major human cytochrome P-450 isoforms. Consequently, cytochrome P-450 mediated drug-drug interactions are not anticipated. Preclinical data have shown that linezolid is a weak potential monoamine oxidase inhibitor (MAOI), but classic MAOI events were not recognized in the phase III trials.

16.3 Risks

Relative to comparators, the integrated phase III data showed that linezolid was associated with slightly higher percentages of adverse events and drug-related adverse events. In the

patients treated with linezolid, the most common adverse events were diarrhea (8.3%), headache (6.5%), and nausea (6.2%). In patients treated with comparators, the most common adverse events were diarrhea (6.3%), headache (5.5%), and nausea (4.6%). These adverse events were usually mild to moderate in intensity, rarely required discontinuation of linezolid, and resolved after completion of therapy or withdrawal of the medication. No other adverse events occurred in • 5% of patients who were treated with linezolid. Like other antibiotics, linezolid may also cause mucocutaneous candidiasis or *Clostridium difficile* diarrhea, presumably due to ecological shifts in the human microflora.

Rates of serious adverse events, adverse events resulting in the discontinuation of study medication, and deaths were similar between linezolid and the comparators. No single drug-related adverse event accounted for $\geq 1\%$ of the discontinuations in patients who received linezolid therapy.

Laboratory abnormalities were also associated with linezolid during the phase III trials, but these were qualitatively and quantitatively similar to those observed with the comparators.

16.4 Conclusions

Based on over 4000 patient observations from randomized controlled clinical trials, linezolid's efficacy has been demonstrated to be equivalent to those of the current drugs of choice for the treatment of community-acquired and nosocomial pneumonia, as well as complicated and uncomplicated skin and soft tissue infections. Linezolid has also demonstrated clinical efficacy against MRSA and vancomycin-resistant *Enterococcus faecium* in a variety of indications. Overall, linezolid is well tolerated when administered either orally or intravenously. The most common side effects are mild to moderate in intensity and quickly subside upon completion of therapy or withdrawal of the medication. Laboratory abnormalities were qualitatively and quantitatively similar between linezolid and comparators. Table 68 summarizes the benefits and risks of linezolid.

Table 68. Benefits and Risks of Linezolid

BENEFITS
<ul style="list-style-type: none"> • New class of synthetic antibiotic • Unique mechanism of action: lack of cross-resistance with conventional antibiotics • Broad, gram-positive spectrum of activity including resistant strains • Demonstrated clinical and microbiologic efficacy for the treatment of: <ul style="list-style-type: none"> • Community-acquired pneumonia • Hospital acquired pneumonia • Complicated skin and soft tissue infections • Uncomplicated skin and soft tissue infections • Infections due to methicillin-resistant <i>Staphylococcus aureus</i> (MRSA) and vancomycin-resistant <i>Enterococcus</i> (VRE) • Therapeutic alternative for vancomycin allergic/intolerant patients • 100% oral bioavailability (equivalent to intravenous) • Infection control (theoretical) • Dosing convenience • No adult dosage adjustments • Lack of interaction with cytochrome P-450 system • Available as an oral suspension for children and adults with dysphagia
RISKS
<ul style="list-style-type: none"> • Adverse events: <ul style="list-style-type: none"> • Gastrointestinal (diarrhea, nausea) • Headache • Mucocutaneous candidiasis/<i>Clostridium difficile</i> diarrhea • Abnormal liver function tests • Infrequent hematological suppression • Drug interaction: weak monoamine oxidase inhibitor

In conclusion, the benefits of linezolid, administered at doses of 400 mg or 600 mg twice daily to adult patients, far outweigh the risks associated with its use. Linezolid represents an excellent choice for the treatment of gram-positive infections, particularly when there is a risk of resistance.